/VOLUME 35 APRIL 1970 NUMBER 4 JOCEAH

THE JOURNAL OF Organic Chemistry

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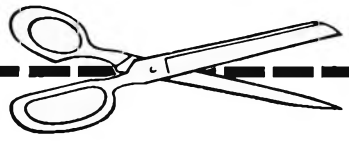

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Published monthly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second-class postage paid at Easton, Pa.

Production Staff: Manager, Editorial Production, CHARLES R. BERTSCH; Production Editor, EILEEN SEGAL; Assistant Editor, FERN S. JACKSON; Editorial Assistant, ANDREW J. D'AMELIO.

Advertising Office: Reinhold Publishing Corporation, 600 Summer St., Stamford, Conn. 06904

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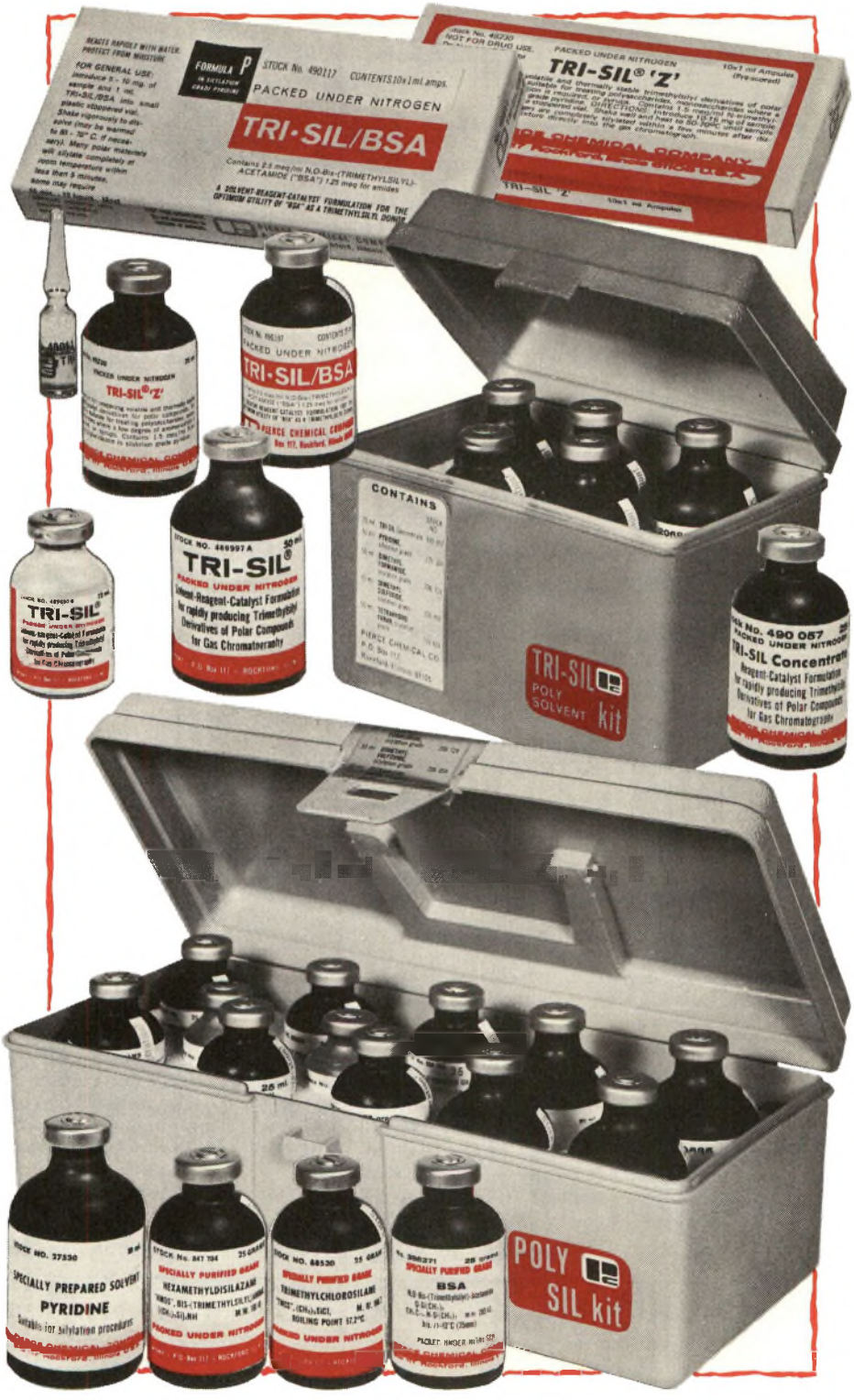

THE JOURNAL OF Organic Chemistry®

VOLUME 35, NUMBER 4 APRIL 1970

NOTES

AUTHOR INDEX

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Papers in which the primary interest lies in the implications of new compounds for medicinal, polymer, agricultural, or analytical chemistry are generally considered to be published most appropriately in specialized journals, together with information on evaluation with respect to the original reason for synthesis. Papers that deal with synthesis of new compounds by established methods and that are primarily of value as a part of the permanent chemical literature are in general more suitable for specialized journals dealing with a specific class of compounds; for compilations of data, the *Journal of Chemical and Engineering Data* may be appropriate.

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

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THE JOURNAL OF Organic Chemistry®

VOLUME 35, NUMBER 4

APRIL 1970

The Chemistry of Indenothiophenes. II. 4H-Indeno[1,2-*b*]thiophene and 8H-Indeno[1,2-*c*]thiophene

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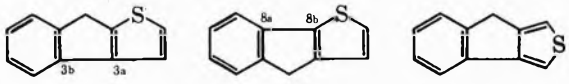
Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506

Received August 6, 1969

The syntheses of 4H-indeno[1,2-*b*]thiophene (**2**) and 8H-indeno[1,2-*c*]thiophene (**3**) are described. Upon metalation with *n*-butyllithium and treatment with Dry Ice, the former yields exclusively 4H-indeno[1,2-*b*]thiophene-4-carboxylic acid (**13**), while the latter gives 8H-indeno[1,2-*c*]thiophene-8-carboxylic acid (**14**, 38%), 8H-indeno[1,2-*c*]thiophene-1-carboxylic acid (**15**, 14%), and 8H-indeno[1,2-*c*]thiophene-3-carboxylic acid (**16**, 48%). These results are discussed in terms of the mode of fusion of the thiophene nucleus and direct bridging between the benzene and thiophene rings.

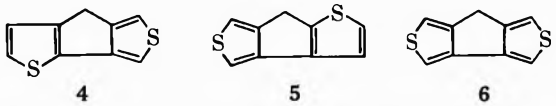
An earlier paper[2] concerning the chemistry of indenothiophenes described the synthesis and metalation of 8H-indeno[2,1-*b*]thiophene (**1**). In this paper we wish to report the syntheses and metalative properties of 4H-indeno[1,2-*b*]thiophene (**2**) and 8H-indeno[1,2-*c*]-thiophene (**3**).



1 **2** **3**

Interest in these and similar systems has been stimulated by recent reports of studies dealing with competitive metalation between hydrogen atoms attached to thiophene rings and those in methylene groups attached to thiophene rings.[3]

Janssen and DeJong[3b] have reported the metalation of three cyclopentadithiophenes,[4] **4**, **5**, and **6**, in both ether

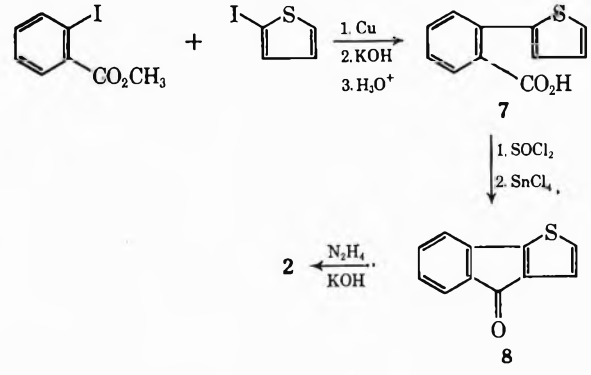


4 **5** **6**

and cyclohexylamine solution, using *n*-butyllithium and lithium cyclohexylamide as base. A study of the ultraviolet spectra of these anions led to the conclusion that the negative charge resides in the central ring of each system. However, compounds derived from these anions have not yet been reported to verify these assignments.

Synthesis of 4H-Indeno[1,2-*b*]thiophene (2).—Initial attempts to synthesize **2** *via* the phosphorus pentasulfide ring closure of 2-formylmethyl-1-indanone dimethyl acetal were unfruitful. Since reaction of the pyrrolidine enamine of 1-indanone with bromoacetaldehyde dimethyl acetal gave, depending on the vigor of the reaction conditions, either unchanged enamine or 1-indanone, this approach was abandoned. The actual synthetic sequence used to prepare **2** is shown in Scheme I.

SCHEME I



Modification of the procedure of Chow and coworkers[5] using Ullmann coupling of methyl *o*-iodobenzoate and 2-iodothiophene gave a mixture from which methyl 2-thienylbenzoate was obtained. Saponification of this methyl ester afforded *o*-2-thienylbenzoic acid (**7**) in an overall yield of 32%. Cyclization of **7** was accomplished *via* the acid chloride using stannic chloride to give 4H-indeno[1,2-*b*]thiophen-4-one (**8**) in 78% yield. Wolff–Kishner reduction of **8** afforded **2** in 68% yield.

(1) NDEA Fellow, 1967–1969.

(2) D. W. H. MacDowell and T. B. Patrick, *J. Org. Chem.*, **32**, 2441 (1967).

(3) (a) O. Meth-Cohn and S. Gronowitz, *Acta Chem. Scand.*, **20**, 1733 (1966); (b) M. J. Janssen and J. DeJong, *Rec. Trav. Chim. Pays-Bas*, **86**, 1246 (1967); (c) J. Skramstad, *Acta Chem. Scand.*, **23**, 703 (1969).

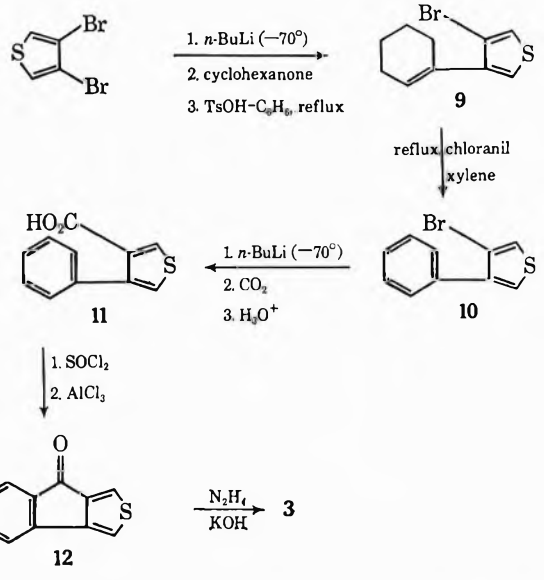
(4) A. Kraak, A. W. Wiersema, P. Jordens, and H. Wynberg, *Tetrahedron*, **24**, 3381 (1968).

(5) A. W. Chow, N. M. Hall, J. R. E. Hoover, M. M. Dolan, and R. J. Ferlauto, *J. Med. Chem.*, **9**, 551 (1966).

The reduced compound **2** is a white, crystalline solid with a strong odor resembling that of fluorene.

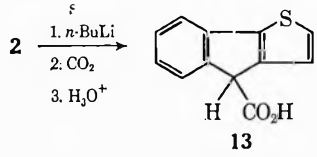
Synthesis of 8H-Indeno[1,2-*c*]thiophene (3).—Preliminary attempts to form this system by utilizing the Hinsberg condensation of diethyl thiodiglycolate with indan-1,2,3-trione following the procedure of Wynberg[6] were unsuccessful, and afforded only recovered indan-1,2,3-trione and thiodiglycolic acid. The successful synthesis of **3** is outlined in Scheme II.

Scheme II



Halogen–metal interchange in 3,4-dibromothiophene provided the best method of obtaining the precursor acid, 3-phenylthiophene-4-carboxylic acid (**11**). Treatment of 4-bromo-3-thienyllithium with cyclohexanone at −70° afforded the corresponding cyclohexanol, which was dehydrated by means of *p*-toluenesulfonic acid in refluxing benzene to yield 3-bromo-4-(1-cyclohexenyl)thiophene (**9**) in 86% yield. Dehydrogenation of **9** with chloranil in refluxing xylene for 10 hr provided optimum conditions for the preparation of 3-bromo-4-phenylthiophene (**10**). In contrast to work reported by Szmuszkovicz[7] and Gronowitz,[8] it was found that the use of benzene or chlorobenzene as a solvent in this dehydrogenation was unsatisfactory. The bromide obtained in this manner had a dark red color, and careful purification by sublimation or column chromatography over alumina was necessary to ensure good results in the conversion into **11**. Halogen–metal exchange in **10** at −70°, followed by carbonation, gave yields of 3-phenylthiophene-4-carboxylic acid (**11**) of 76–84%. Ring closure of **11** *via* the acid chloride proceeded under the influence of aluminum chloride in carbon disulfide solution for 24 hr to produce 8H-indeno-[1,2-*c*]thiophen-8-one (**12**) in 82–91% yield. Wolff–Kishner reduction of **12** produced **3** in 60% yield. 8H-Indeno[1,2-*c*]thiophene (**3**) is a white, crystalline solid possessing an odor resembling that of fluorene. Gronowitz[9] has reported the use of a mixture of lithium aluminum hydride and aluminum chloride to reduce 1,2,4,6-tetramethyl-7H-cyclopenta[1,2-*c*:3,4-*c*′]dithiophen-7-one to 1,3,4,6-tetramethyl-7H-cyclopenta[1,2-*c*:3,4-*c*′]-dithiophene in 92% yield. However, reduction of **12** under the same conditions produced only 30–40% **3** after purification by column chromatography. Further elution with more polar solvents produced a quantity of resinous material, the identity of which was not further investigated. Lowering the relative amounts of lithium aluminum hydride to aluminum chloride[10] produced a 55:45 mixture of **3** and the corresponding alcohol (by nmr). It is noteworthy that both 2- and 3-benzoylthiophene are reduced to the corresponding benzyl compounds in greater than 90% yields under the same conditions that produced the mixture of alcohol and **3** from **12**.

Metalation Experiments.—It was previously reported[2] that metalation of **1** with *n*-butyllithium in ether solution occurred exclusively at the methylene bridge; no metalation on the thiophene ring was detected. Treatment of **2** with slightly more than 1 equiv of ethereal *n*-butyllithium followed by carbonation, work-up as in the case of **1**,[2] and examination of the nmr spectrum of the crude product revealed an aromatic absorption at τ 2.0–3.0 and a singlet for the methine proton at τ 5.20. The absence of any absorption at τ 5.20–10.0 indicated that metalation had occurred exclusively at the methylene bridge of **2**.



13

The nmr spectrum of the crude product obtained by similar treatment of **3** with 1 equiv of ethereal *n*-butyllithium followed by work-up as described for **2** revealed bands at τ 1.25 (m), 2.2–3.0 (m, aromatic), 5.17 (s), 6.08 (s), and 6.28 (s). On the basis of previous work,[2] the singlet at τ 5.17 is assigned to the methine hydrogen of 8H-indeno[1,2-*c*]thiophene-8-carboxylic acid (**14**). The singlet at τ 6.08 is assigned to the methylene hydrogens of 8H-indeno[1,2-*c*]thiophene-1-carboxylic acid (**15**), which are shifted downfield owing to the inductive effect of the neighboring carboxyl group. The multiplet at τ 1.25 and the singlet at τ 6.28 are assigned to the C_4 hydrogen and methylene hydrogens, respectively, of the 8H-indeno[1,2-*c*]thiophene-3-carboxylic acid (**16**). The relative amounts of these products formed in the metalation–carbonation reaction are 38% **14**, 14% **15**, and 48% **16**. These values were determined by weighing the paper under the curves traced out in the recording of the nmr spectrum, and are the average of three experiments.

The acid **16** was isolated in pure form through fractional crystallization of a mixture of acids from benzene–hexane. The assignment of the C_4 hydrogen at τ 1.25 is based on an examination of molecular models. The proximity of the neighboring carboxyl group to the C_4 hydrogen allows it to exert a negative anisotropic effect on the C_4 hydrogen, causing it to absorb at lower field than the other aromatic hydrogens. This assign-

(6) H. Wynberg and H. J. Kooreman, *J. Amer. Chem. Soc.*, **87**, 1739 (1965).

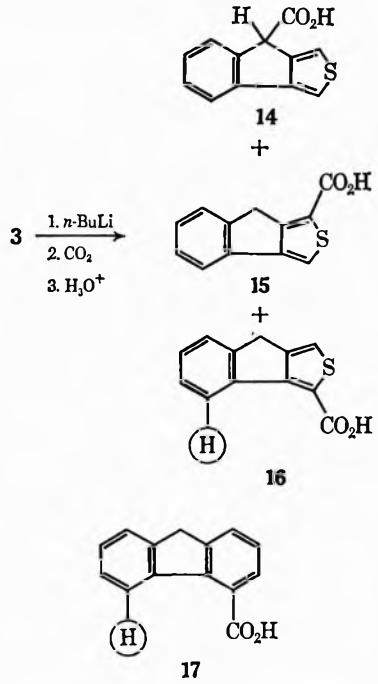
(7) L. F. Fieser and J. Szmuszkovicz, *ibid.*, **70**, 3352 (1948); J. Szmuszkovicz and E. J. Modest, *ibid.*, **72**, 571 (1950).

(8) S. Gronowitz and N. Gjos, *Acta Chem. Scand.*, **21**, 2823 (1967).

(9) S. Gronowitz, J. E. Skramstad and B. Eriksson, *Ark. Kemi*, **28**, 99 (1967).

(10) R. F. Nystrom and C. R. A. Berger, *J. Amer. Chem. Soc.*, **80**, 2896 (1958).

ment was confirmed by examination of the nmr spectrum of fluorene-4-carboxylic acid (**17**), whose spectrum reveals a multiplet at τ 1.50 of the same character as the C_4 hydrogen in **16**.



Discussion

The differences in metalative properties of **1**, **2**, and **3** may be rationalized in the following manner: The 3a–3b bridge in **1** and the 8a–8b bridge in **2**, respectively, along with the b fusion of the thiophene ring, convey to these molecules a formal similarity to fluorene and indene. Thus an anion generated at the methylene bridge in **1** and **2** is delocalized extensively, which causes the methylene hydrogens to become more acidic than those on the α position of the thiophene ring. However, c fusion of the thiophene ring in **3** causes considerable loss of delocalization for the anion formed at the methylene bridge when compared with that in **1** and **2**. This is indicated by the formation of substantial amounts of additional products, **15** and **16**, upon carbonation of the metalation product of **3**. Furthermore, it allows the thiophene C_3 hydrogen to become slightly more acidic than the methylene hydrogen and provides an excellent example of the less extensive electron delocalization across the 3,4 bond in thiophene[11] compared with that in the 2,3 bond.

These results are in qualitative agreement with the pK_a values calculated for the methylene bridge hydrogens of **1**, **2**, and fluorene by simple Hückel molecular orbital theory.[12] See Table I.

The formal resemblance of **1** and **2** to fluorene is reflected in the comparable calculated pK_a values. Consequently, it is not unexpected to find that metalation of **1** and **2** occurs exclusively at their respective methylene bridges. However, the pK_a value calculated for **3** suggests that the hydrogens on its methylene bridge are somewhat less acidic than those in **1** and **2** and is in qualitative agreement with the observed lower degree of metalation of the methylene bridge of **3**.

TABLE I

	τ (CH_2)	Calcd pK_a[a]
Fluorene	6.19	25
1	6.20	24
2	6.39	25
3	6.30	27

[a] Reference 12.

Experimental Section[13]

4H-Indeno[1,2-*b*]thiophen-4-one (8).—To a three-necked, 500-ml flask, fitted with a calcium chloride drying tube and containing *o*-(2-thienyl)benzoic acid[5] (**7**, 13.97 g, 0.0685 mol) dissolved in dry benzene (140 ml) and dry N,N-dimethylformamide (3.5 ml) was added thionyl chloride (7.0 ml). The solution was heated at reflux for 2 hr and cooled, and the benzene evaporated. The brown residue was kept under nitrogen and was freed from the last traces of thionyl chloride by treatment with four successive portions of dry benzene, followed by evaporation of each portion of benzene. Final evaporation of the benzene left the acid chloride as a brown oil, ir (neat) 1770 cm^{-1} (acid chloride C=O).

A solution of the acid chloride obtained above in dry benzene (100 ml) was added to a three-necked, 500-ml flask protected by a calcium chloride drying tube and cooled to −2°. A solution of stannic chloride (9.8 ml) in dry benzene (40 ml) was added at such a rate as to keep the temperature at 4°. After addition was completed, the dark mixture was stirred for 10 min at 4° and for a further 10 min without external cooling.

The dark mixture was poured onto a slurry of ice (400 ml) and 1 *M* hydrochloric acid (200 ml) and was stirred well. The layers were separated and the aqueous layer was extracted with benzene (500 ml) in three portions. The benzene solution was washed twice with water, three times with 1 *M* sodium hydroxide (75 ml), three times with water, and twice with brine, dried ($MgSO_4$), and concentrated to leave 9.84 g (78%) of orange solid, mp 99–101°. Sublimation at 95–97° (0.6–1.1 mm) afforded an analytical sample: mp 101° (lit.[14] mp 99°); uv max (95% C_2H_5OH) 255 mμ (ε 36,500), 264 (39,600), and 294 (5850); ir (KBr) 1710 cm^{-1} (ketone C=O); nmr ($CDCl_3$) τ 2.2–3.1 (m, 6, $C_{11}H_6OS$).

Anal. Calcd for $C_{11}H_6OS$: C, 70.94; H, 3.25; S, 17.22. Found: C, 70.78; H, 3.31; S, 17.22.

4H-Indeno[1,2-*b*]thiophene (2).—4H-Indeno[1,2-*b*]thiophen-4-one (**8**, 0.50 g, 2.69 mmol) was mixed with 95% hydrazine (1.1 ml), potassium hydroxide (0.50 g), and diethylene glycol (5 ml) at 45° (oil-bath temperture) in a three-necked, 100-ml flask fitted with a condenser arranged for downward distillation. The mixture was heated to 195° over a 1-hr period and maintained at this temperature for 0.5 hr. The reaction mixture was cooled, water (20 ml) was added, and the mixture was distilled. This procedure was repeated until 80 ml of distillate had collected. The distillate was extracted with three portions of ether. The combined ether solutions were washed twice with water and twice with brine, dried ($MgSO_4$), and concentrated to leave 320 mg (68%) of white solid, mp 66–68°. An analytical sample was obtained by sublimation at 60–65° (1.0 mm): mp 68–69°; uv max (95% C_2H_5OH) 225 mμ (ε 6640), 232 (5800), 265 (sh, 8760), 238 (16,300), 299 (16,200), and 304 (11,900); ir (KBr) 750 cm^{-1}; nmr ($CDCl_3$) τ 2.4–3.0 (m, 6, $C_{10}H_6S$) and 6.39 (s, 2, $C_6H_4CH_2C_4H_2S$).

(11) S. Gronowitz in "Organosulfur Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1967, p 124.

(12) T. B. Patrick, Ph.D. Dissertation, West Virginia University, Morgantown, 1967. The pK_a values are based on the π energy differences between the anion and its conjugate acid as outlined in A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, Inc., New York, N. Y., 1961, Chapter 14. These values were calculated using simple Hückel zero-order approximations on an IBM 7040 computer. The only sulfur parameters used were $h(s) = 1.0\ \beta_{cc}$, $hc(s) = 0.1\ \beta_{cc}$, and $Kc\text{-}s = 0.7\ \beta_{cc}$ following R. Zahradnik, Advan. Heterocycl. Chem., **5**, 58 (1965).

(13) All temperature readings are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Nuclear magnetic resonance spectra were recorded on a Varian HA-60 spectrometer using tetramethylsilane as an internal standard (τ 10) and solvents as specified. The ultraviolet spectra were determined in 95% ethanol on a Bausch and Lomb 505 spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrometer.

(14) Y. Poirier and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 1062 (1966).

Anal. Calcd for $C_{11}H_8S$: C, 76.69; H, 4.68; S, 18.62. Found: C, 76.89; 4.58; S, 18.70.

4H-Indeno[1,2-*b*]thiophene-4-carboxylic Acid (13).—A 250-ml, three-necked flask fitted with a reflux condenser, calcium chloride drying tube, and pressure-equalizing addition funnel was flame dried under nitrogen. To a solution of **2** (0.500 g, 2.90 mmol) (homogeneous by tlc) dissolved in anhydrous ether (30 ml) and contained in this flask was added ethereal 0.92 *M* *n*-butyllithium[15] (3.3 ml, 3.04 mmol). The resulting solution was then refluxed for 30 min, during which time it changed from yellow to orange-red in color. Refluxing was stopped and the reaction was quenched by adding *ca.* 10 g of freshly chipped Dry Ice. Several minutes after the vigorous reaction had subsided, water (25 ml) was added and the layers were separated. The aqueous layer was washed with three portions of ether and the combined ether washings were back washed with one portion of water. The combined aqueous portions were cooled, acidified with 1 *M* hydrochloric acid (7 ml), and extracted with three portions of ether. The ether solutions were washed with two portions of water and two portions of brine, dried ($MgSO_4$), and evaporated to leave 0.329 g (53%) of acid.

Evaporation of the neutral ether layer left 0.209 g of unchanged starting material.

An analytical sample of the acid was obtained by recrystallization from benzene: mp 212–213°; ir (KBr) 1690 cm^{-1} (acid C=O); nmr (acetone-d_6) τ 2.2–3.0 (m, 6, $C_{10}H_6S$), 3.6 (broad mound, 1, CO_2H), and 5.24 (s, 1, methine).

Anal. Calcd for $C_{12}H_8O_2S$: C, 66.65; H, 3.73; S, 14.83. Found: C, 66.32; H, 3.65; S, 15.03.

Methyl 4H-Indeno[1,2-*b*]thiophene-4-carboxylate.—An ethereal solution of diazomethane (9 ml, 0.107 g, 2.54 mmol) prepared from *p*-toluenesulfonylmethylnitrosamide was added to 4H-indeno[1,2-*b*]thiophene-4-carboxylic acid (**13**, 0.254 g, 1.23 mmol) dissolved in ether (25 ml). After nitrogen evolution had ceased, the solution was allowed to stand for 30 min and was diluted with an additional volume of ether (25 ml). The ether solution was washed with three 10-ml portions of dilute sodium hydroxide, three times with water, and twice with brine, dried ($MgSO_4$), and concentrated to leave 0.237 g (84%) of green oil which solidified on standing. Sublimation at 70–73° (0.10–0.15 mm) followed by careful recrystallization from hexane afforded an analytical sample: mp 72.5–73°; ir (KBr) 1725 cm^{-1} (ester C=O); nmr ($CDCl_3$) τ 2.25–2.40 (m, 6, $C_{10}H_6S$), 5.30 (s, 1, methine), and 6.27 (s, 3, OCH_3).

Anal. Calcd for $C_{13}H_{10}O_2S$: C, 67.80; H, 4.38; S, 13.96. Found: C, 67.97; H, 4.52; S, 13.83.

3-Bromo-4-(1-cyclohexenyl)thiophene (9).—An ethereal solution of 1.5 *M* *n*-butyllithium (226 ml, 0.338 mol) was added to a three-necked, 1-l. flask, fitted with a calcium chloride drying tube, which had been flame dried under nitrogen. The solution was cooled to −70° and a solution of 3,4-dibromothiophene (75.0 g, 0.310 mol) in anhydrous ether (90 ml) was added over an 8-min period. After the solution had been stirred for 7 min, a solution of freshly distilled cyclohexanone (30.4 g, 0.310 mol) in anhydrous ether (55 ml) was added rapidly. The resulting mixture was allowed to stir at −70° for 10 min and then for another 10 hr after removal of the cooling bath.

The yellow ethereal solution was cooled below room temperature and was acidified with 2 *M* hydrochloric acid (225 ml). The ether layer was washed with water (100 ml), saturated sodium bicarbonate solution (100 ml), twice with water, and twice with brine and dried ($MgSO_4$).

Concentration left the crude alcohol, which was dissolved in benzene (100 ml) and dehydrated by refluxing it for 3 hr with a catalytic amount of *p*-toluenesulfonic acid. The benzene solution was cooled, diluted with an equal volume of ether (emulsion prevention), washed twice with water and twice with brine, dried ($MgSO_4$), and distilled to give 64.7 g (86%) of product: bp 87–97° (0.2 mm); $n^{25}D$ 1.6011; nmr ($CDCl_3$) τ 2.80 (d, 1, J = 4 Hz, H-2), 3.0 (d, 1, J = 4 Hz, H-5), 4.05–4.20 (m, 1, vinyl), 7.60–7.90 (m, 4 allylic CH_2), and 8.17–8.40 (m, 4, aliphatic CH_2).

Anal. Calcd for $C_{10}H_{11}BrS$: C, 49.40; H, 4.56; Br, 32.87; S, 13.18. Found: C, 49.52; H, 4.59; Br, 32.86; S, 13.35.

3-Bromo-4-phenylthiophene (10).—2,3,5,6-Tetrachlorobenzoquinone (66.6 g, 0.271 mol, purified by one recrystallization from benzene) was dissolved in refluxing anhydrous xylene (380 ml) contained in a three-necked, 1-l. flask under anhydrous conditions. After addition of a solution of 3-bromo-4-(1-cyclohexenyl)thiophene (**9**, 32.0 g, 0.132 mol) over a 5-min period, the reaction mixture was heated under reflux for 10 hr (caution, acidic fumes). The dark red solution was cooled below room temperature in an ice bath, which resulted in the formation of a voluminous amount of solid. The solid was separated by filtration and the filter cake was washed with small portions of cold xylene. The filtrate was washed with 20-ml portions of 2 *M* sodium hydroxide until the washings were clear (eight washings are required), twice with water, and twice with brine, dried ($MgSO_4$), and concentrated to give 31.2 g of red solid which was dissolved in a minimum amount of benzene and chromatographed on a 4.45 cm × 48 cm column containing 640 g of unactivated Alcoa F-20 alumina. The column was eluted with 6 l. of hexane. Concentration of eluent left 23.0 g (72%) of white solid, mp 62–68°. Recrystallization from methanol afforded an analytical sample: mp 69–70°; nmr ($CDCl_3$) τ 2.65 (s, 5, C_6H_5), 2.73 (d, 1, J = 3.5 Hz), and 2.85 (d, 1, J = 3.5 Hz).

Anal. Calcd for $C_{10}H_7BrS$: C, 50.22; H, 2.95; Br, 33.42; S, 13.14. Found: C, 50.09; H, 2.95; Br, 33.57; S, 13.27.

4-Phenylthiophene-3-carboxylic Acid (11).—To a three-necked, 100-ml flask under an atmosphere of dry nitrogen was added ethereal 2.11 *M* *n*-butyllithium (10.9 ml, 0.023 mol). This solution was cooled to −70° and 3-bromo-4-phenylthiophene (**10**, 5.0 g, 0.021 mol) in anhydrous ether (35 ml) was added over a 5-min period. The mixture was allowed to stir for 10 min at −70° before a large excess of Dry Ice was added cautiously through Gooch tubing. The mixture was allowed to warm to room temperature and water (35 ml) was added. The aqueous layer was separated and was washed twice with ether. The combined ether layers were washed once with water. The combined aqueous layers were cooled and acidified with 1 *M* hydrochloric acid (28 ml, pH 2). The precipitated acid was filtered, washed with mall portions of cold water, and dried to give 3.6 g (84%) of white solid, mp 203–206°.

Recrystallization from methanol offered an analytical sample, mp 206–208°. In subsequent runs more satisfactory recrystallization from benzene occurred: ir (KBr) 1675 cm^{-1} (acid C=O); nmr (DMSO-d_6) τ 1.78 (d, 1, J = 3.5 Hz, H-2), 2.57 (d, 1, J = 3.50 Hz, H-5), and 2.63 (s, 5, C_6H_5).

Anal. Calcd for $C_{11}H_8O_2S$: C, 64.69; H, 3.95; S, 15.70. Found: C, 64.46; H, 4.07; S, 15.98.

8H-Indeno[1,2-*c*]thiophen-8-one (12).—To a hot suspension of 4-phenylthiophene-3-carboxylic acid (**11**, 12.6 g, 0.0616 mol) in dry benzene (164 ml) was added thionyl chloride (5.05 ml). The mixture was allowed to reflux for 2 hr, during which time the white suspension dissolved to give a pale yellow solution. Removal of benzene left the crude acid chloride, which was treated in a manner identical with that used to prepare the acid chloride of **7**, ir (neat) 1770 cm^{-1} (acid chloride C=O).

A solution of the crude acid chloride obtained above in reagent carbon disulfide (100 ml) was added over a 5-min period to a suspension of aluminum chloride (18.75 g, 0.141 mol) and reagent carbon disulfide (240 ml) contained in a three-necked, 1-l. flask under anhydrous conditions. The resulting brown mixture was heated under reflux for 24 hr and was then cooled and poured onto a mixture of 1 *M* hydrochloric acid (75 ml) and ice with stirring. The carbon disulfide layer was separated and evaporated, and the residue was dissolved in ether. The aqueous phase was extracted twice with ether. The combined ether layers were washed once with water and twice with brine, dried, ($MgSO_4$), and concentrated to leave 8.9 g (91%) of yellow solid, mp 88–90°.

An analytical sample was prepared by recrystallization from ethanol followed by sublimation at 80° (0.1 mm): mp 90–90.5°; uv max (95% C_2H_5OH) 256 mμ (sh, ε 48,000) and 263.5 (60,900); ir (KBr) 1720 cm^{-1} (ketone C=O); nmr ($CDCl_3$) τ 2.35 (d, 1, J = 2 Hz, H-1), 2.99 (d, 1, J = 2 Hz, H-3), and 2.5–2.9 (m, 4, C_6H_4).

Anal. Calcd for $C_{11}H_6OS$: C, 70.94; H, 3.25; S, 17.22. Found: C, 70.71; H, 3.14; S, 17.46.

8H-Indeno[1,2-*c*]thiophene (3).—The apparatus was assembled as described for **2** with a three-necked, 500-ml flask. 8H-Indeno[1,2-*c*]thiophen-8-one (**12**, 5.13 g, 0.0276 mol), potassium hydroxide (5.13 g), 95% hydrazine (10.25 ml), and diethylene glycol (51 ml) were mixed at 45° (oil-bath temperature). Over a 30-min period the mixture was heated to 200° which was maintained for 45 min. The mixture was cooled, water (100-

(15) The *n*-butyllithium used in these carbonation reactions was analyzed by the double-titration method: H. Gilman and R. Jones, *Org. Reactions*, **6**, 339 (1951).

ml portions) was added, and the mixture was distilled until 800 ml of distillate had been collected. The distillate was extracted with three portions of ether. The ether extracts were washed three times with water and twice with brine, dried ($MgSO_4$), and concentrated to leave 2.85 g (60%) of tan solid, mp 88–92°. This solid was dissolved in a minimum amount of benzene and chromatographed on a 1.58 × 28.5 cm column packed with unactivated Alcoa F-20 alumina. Elution with 1 l. of hexane followed by concentration left 2.06 g of white solid, mp 90–92°. Recrystallization of a small sample from methanol afforded an analytical sample: mp 92–93°; uv max (95% C_2H_5OH) 230 mμ (ε 5630), 238 (8300), 264.5 (16,000), 273 (16,700) 280 (sh, 7100), 287 (8,600), and 299 (13,410); nmr ($CDCl_3$) τ 2.30–3.05 (m, 6, $C_{10}H_6S$) and 6.30 (s, 2, $C_6H_4CH_2C_4H_2S$).

Anal. Calcd for $C_{11}H_8S$: C, 76.69; H, 4.68; S, 18.62. Found: C, 76.53; H, 4.62; S, 18.78.

8H-Indeno[1,2-*c*]thiophene-3-carboxylic Acid (16).—A 100-ml, three-necked flask fitted with a calcium chloride drying tube, reflux condenser, and pressure-equalizing addition funnel was flame dried under a stream of nitrogen. To a solution of **3** (0.50 g, 2.90 mmol, homogeneous by tlc) dissolved in anhydrous ether (30 ml) was added ethereal 1.26 *M* *n*-butyllithium[15] (2.30 ml, 2.90 mmol). The solution turned dark red immediately upon addition of the *n*-butyllithium and was refluxed for 30 min. Refluxing was stopped and the reaction was quenched with *ca.* 10 g of freshly chipped Dry Ice. Several minutes after the vigorous reaction had subsided, water (20 ml) was added and the layers were separated. The aqueous layer was washed with four portions of ether and the ether solutions were back washed with one portion of water. The aqueous layers were combined, cooled, acidified with 1 *M* hydrochloric acid, and extracted with three portions of ether. The ether solution was washed with two portions of water and two portions of brine, dried ($MgSO_4$), and evaporated to leave 0.28 g (45%) of acidic material.

The neutral ether solution was evaporated to yield 0.10 g of unchanged starting material.

An analytical sample of **16** was obtained by recrystallization from benzene–hexane of a sample obtained in a similar experiment: mp 209–210° dec; ir (KBr) 1640 cm^{-1} (acid C=O); nmr (acetone-*d*) τ 1.25 (m, 1, H-4), 2.20–2.65 (m, 4, $C_{10}H_4S$), and 6.30 (s, 2, $C_6H_3CH_2C_4HS$).

Anal. Calcd for $C_{12}H_8O_2S$: C, 66.65; H, 3.73; S, 14.83. Found: C, 66.79; H, 3.78; S, 14.68.

Fluorene-4-carboxylic Acid (17).—Fluorenone-4-carboxylic acid (5 g) was reduced in the manner described by Weisburger and Weisburger:[16] yield 57%; mp 192–193° (lit.[16] mp 191–192°); ir (KBr) 1680 cm^{-1} (acid C=O); nmr ($CDCl_3$) τ −3.2 (s, 1, CO_2H), 1.5 (m, 1, H-4), 2.0–2.7 (m, 6, $C_{12}H_6$), and 6.10 (s, $C_{12}H_6CH_2$).

Anal. Calcd for $C_{14}H_{10}O_2$: C, 79.61; H, 4.77. Found: C, 79.82; H, 4.83.

Registry No.—**2**, 7260-71-1; **3**, 7260-70-0; **8**, 5706-08-1; **9**, 23062-40-0; **10**, 23062-41-1; **11**, 23062-42-2; **12**, 23062-43-3; **13**, 23062-44-4; **13** methyl ester, 23062-45-5; **16**, 23062-46-6; **17**, 6954-55-8.

Acknowledgment.—The authors wish to thank Mr. Robert Smith, Mr. Donald Wieland, and Kiyoshi Yamauchi for recording the nmr spectra.

(16) E. K. Weisburger and J. H. Weisburger, *J. Org. Chem.*, **20**, 1396 (1955).

Azepinoindoles. IV.[1] 1,2,3,4,5,10-Hexahydroazepino[3,4-*b*]indole and 1,2,3,4,5,10-Hexahydroazepino[2,3-*b*]indole

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Received August 11, 1969

The selective preparation of both 3,4,5,10-tetrahydroazepino[3,4-*b*]indol-1(2H)-one (**5**) and 3,4,5,10-tetrahydroazepino[2,3-*b*]indol-2(1H)-one (**14**) from 1,2,3,4-tetrahydrocarbazol-1-one *via* the Beckmann rearrangement is described. Rapid air oxidation of the initial product derived from the lithium aluminum hydride reduction of **14** gave 2,3,4,5-tetrahydroazepino[2,3-*b*]indol-5a(1H)-ol (**17**). The proof of structure **17** and some of its interesting chemistry is discussed.

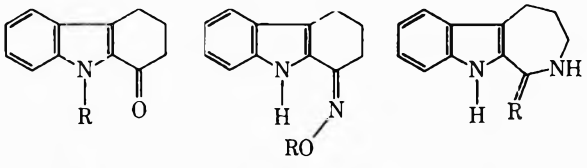
Recently,[2] we reported the selective preparation of 3,4,5,6-tetrahydroazepino[4,3-*b*]indol-1(2H)-one and 3,4,5,6-tetrahydroazepino[3,2-*b*]indol-2(1H)-one *via* the Beckmann rearrangements of the oxime and tosyloxy oxime of 1,2,3,4-tetrahydrocarbazol-4-one with polyphosphoric acid and deactivated alumina, respectively. Concurrent with this study we investigated the preparation and chemistry of 3,4,5,10-tetrahydroazepino[3,4-*b*]indol-1(2H)-one (**5**) and 3,4,5,10-tetrahydroazepino-[2,3-*b*]indol-2(1H)-one (**14**). The latter investigation is the subject of the present discussion.

The reaction of 1,2,3,4-tetrahydrocarbazol-1-one (**1**)[3] with hydroxylamine (Chart I) gave a mixture of oximes **3** and **7** which could be separated by silica gel chromatography. Both oximes underwent a facile rearrangement in polyphosphoric acid to give the same lactam **5** in 73–85% yield.[4] This compound **5** was also obtained by the reaction of **1** with sodium azide in polyphosphoric acid.[5] Positive identification of **5** was supplied by its characteristic uv spectrum and by its lithium aluminum hydride reduction to **6**, which had previously been reported in the literature[6] and had an nmr singlet at δ 4.00 for the C-1 protons. Alkylation of **5** with triethyloxonium fluoroborate[7] gave the expected imino ether **11**, which reacted with amines to give amidines such as **12** and **13**.[8]

Since it was apparent that in polyphosphoric acid, analogous to our previous results,[2] oxime **7** was undergoing a facile isomerization to **3** prior to Beckmann rearrangement, we employed the method of Craig and Naik[9] for the preparation of **14**. Oximes **3** and **7** were converted into the corresponding tosyloxy derivatives **4** and **8** with *p*-toluenesulfonyl chloride in pyridine. Rearrangement of **4** with neutral alumina, which had been deactivated with 1% water, gave **5** in 81% yield. The analogous rearrangement of **8** on alumina which had been deactivated with 0.5% water gave the iso-

(1) Part III: J. B. Hester, Jr., *J. Org. Chem.*, **32**, 4095 (1967).
(2) J. B. Hester, Jr., *ibid.*, **32**, 3804 (1967).
(3) S. Coffee, *Rec. Trav. Chim. Pays-Bas*, **42**, 528 (1923).
(4) H.-J. Teuber, D. Cornelius, and U. Wolcke, *Justus Liebigs Ann. Chem.*, **696**, 116 (1966), have reported the preparation of **5** by the Beckmann rearrangement of **1** oxime in polyphosphoric acid under conditions similar to ours.
(5) N. J. Doorenbos and R. E. Havranek, *J. Org. Chem.*, **30**, 2474 (1965).
(6) S. Morosawa, *Bull. Soc. Chem. Jap.*, **33**, 1113 (1960).
(7) H. Meerwein, *Org. Syn.*, **46**, 113 (1966).
(8) R. E. Benson and T. L. Cairns, *J. Amer. Chem. Soc.*, **70**, 2115 (1948).
(9) J. C. Craig and A. R. Naik, *ibid.*, **84**, 3410 (1962).

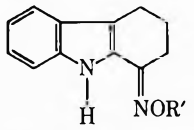
CHART I



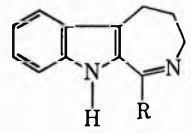
1, R = H
2, R = CH_3

3, R = H
4, R = p-$C_7H_7SO_2$

5, R = O
6, R = H_2

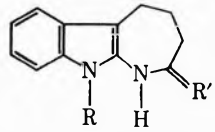


7, R = H; R′ = H
8, R = H; R′ = p-$C_7H_7SO_2$
9, R = CH_3; R′ = H
10, R = CH_3; R′ = p-$C_7H_7SO_2$



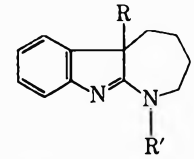
11, R = OEt
12, R = $NHCH_2CH_2NEt_2$

13, R = N

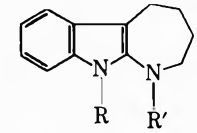


14, R = H; R′ = O
15, R = H; R′ = H_2
16, R = CH_3; R′ = O

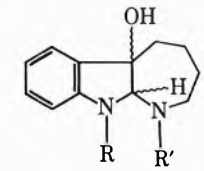
CHART II



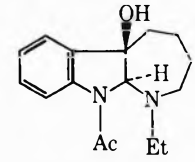
17, R = OH; R′ = H
20, R = R′ = H
21, R = OAc; R′ = H
22, R = OAc; R′ = Ac
23, R = OH; R′ = Et
24, R = H; R′ = Et



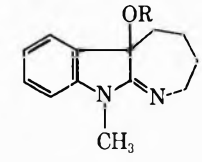
25, R = H; R′ = Ac
26, R = Et; R′ = Ac
27, R = Ac; R′ = Ac
28, R = Ac; R′ = Et
29, R = CH_3; R′ = Et
30, R = CH_3; R′ = Ac



31, R = Et; R′ = Ac
32, R = Ac; R′ = Ac
33, R = CH_3; R′ = Ac



34



35, R = H
36, R = Ac

meric lactam **14**, uncontaminated by **5**, in 25% yield. In this reaction, the low yield of **14** compared with that of **5** and the necessity of using a more active alumina catalyst for the rearrangement of **8** than for **4** are consistent with the view[2,10] that aryl migration in this case is more difficult than alkyl migration. The probable explanation for this phenomenon assumes that a highly strained intermediate would be required for aryl migration; however, the electronic interaction of the oxime with the indole nucleus is undoubtedly a contributing factor.

Lithium aluminum hydride reduction of **14** followed by isolation of the product by crystallization from methanol resulted in a 71% yield of the alcohol **17** (Chart II). Strong support for structure **17** was provided by the similarity of its uv absorption with that of an analogous product [λ_{max} (EtOH) 224 mμ (ϵ 20,000), 280 (13,800), 289 (13,500), and 317 (6600)] obtained by air oxidation of 3-methyl-2-piperidinoindole.[11] The presence of an alcohol function was suggested by the ir and mass spectra. Compound **17** formed stable, crystalline salts with both hydrochloric and hydrobromic acids. The nmr spectrum of these salts was interesting in that the C-2 protons were strongly deshielded by the amidine system and formed the AB portion of an ABXY spin system.[12] For the hydrochloride, assignment of the axial configuration to the downfield (δ 4.12) proton was based on its apparent ($J \cong 10$ Hz) coupling with the C-3 axial proton; the C-2 equatorial proton was found at δ 3.49 and had an apparent coupling ($J \cong 5$ Hz) with the C-3 equatorial proton. When the C-2 protons were replaced by deuterium, the assigned nmr peaks were absent.[13] Confirmation of structure **17** was accomplished by an X-ray crystallographic study[14] of **17** hydrobromide using the heavy atom method with least-squares refinement of the initial trial structure. The final R factor was 0.169.

Support for the view that **17** was formed by air oxidation of an initially formed amine **15** was provided by the isolation of a stable hydrochloride salt **20** and acetamide **25**[15a] from the reactions of the lithium aluminum hydride reduction product of **14** with hydrogen chloride and acetic anhydride, respectively, before exposure to air. Assignment of structure **20** rather than the double-bond tautomer (1,2,3,4,5,10-hexahydroazepino[2,3-*b*]indole hydrochloride) to the hydrochloride was based on the ir spectrum which had the characteristic C=N$^+$ band at 1680 cm^{-1} and analogy to a similar product obtained from 3-methyl-2-piperidinoindole.[11,15b]

The reaction of **17** with acetic anhydride in pyridine yielded a mixture of the mono- and diacetyl derivatives **21** and **22**, which was separated by silica gel chromatography. Structure **21** was supported by the ester band at 1750 cm^{-1} in the ir, the C-methyl peak at δ 2.10 in the nmr, and peaks in the mass spectrum corresponding to the loss of CH_3CO (*m/e* 201), CH_3COO (*m/e* 185), and CH_3OOH (*m/e* 184) from the molecular ion (*m/e* 244); peaks in the mass spectrum corresponding to loss of 17 or 18 mass units from the molecular ion were not observed. Compound **22** had ir bands at 1745 and 1670 cm^{-1} for the ester and amide functions. In the mass spectrum the major fragmen-

(10) See R. Huisgen, J. Witte, and I. Ugi, *Chem. Ber.*, **90**, 1844 (1957); P. A. S. Smith in "Molecular Rearrangements," Part I, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, Chapter 8.

(11) T. Hino, M. Nakagawa, T. Wakatsuki, K. Ogawa, and S. Yamada, *Tetrahedron*, **23**, 1441 (1967).

(12) The chemical shifts presented for this discussion are based on first-order approximations.

(13) These and subsequent nmr assignments are consistent with the molecular configuration in which the azepine ring assumes a chair conformation with N-1 and C-2, -5a and -10a approximately coplanar. Support for this conformation in solution is provided by the uv spectrum, which suggests a high degree of π-orbital overlap in the amidine system; in the crystalline hydrobromide salt this conformation was demonstrated by X-ray diffraction studies.

(14) D. J. Duchamp, unpublished results.

(15) (a) Contrast this result to the work of J. Kebrle and K. Hoffmann, *Helv. Chim. Acta*, **39**, 116 (1956), which suggests that the reaction of 2-aminoindole with acetic anhydride to give 1-acetyl-2-acetamidoindole occurs *via* initial acylation of the indole nitrogen. (b) See A. R. Katritzky and J. M. Lagowski, *Advan. Heterocycl. Chem.*, **2**, 23 (1963).

tation corresponded to loss of ketene (*m/e* 244) from the molecular ion (*m/e* 286) with further fragmentation being similar to that of **21**; minor peaks of *m/e* 226 and 227 corresponded to loss of CH_3COOH and CH_3COO from the molecular ion. The nmr spectrum of **22** had singlets at δ 2.59 and 2.08 which were assigned to the amide and ester acetyl groups, respectively. In addition this spectrum offered an interesting example of the strong deshielding exerted by an amide on the adjacent equatorial proton.[2,16] The quartet at δ 4.95 was assigned to the C-2 equatorial proton based on its apparent coupling ($J \cong 7$ Hz) with the C-3 equatorial proton; the quartet at δ 3.21 had an apparent coupling ($J \cong 10$ Hz) with the C-3 axial proton and was thus assigned to the C-2 axial proton. Both C-2 proton absorptions had the expected geminal coupling constant ($J = -15$ Hz). This assignment was supported by a spin-decoupling experiment. Substitution of deuterium for the C-2 protons of **22** to give **18** was effected by acylating the product **19** derived from the lithium aluminum deuteride reduction of **14**. The nmr peaks assigned to the C-2 protons of **22** were absent in the spectrum of **18**.

Brief treatment with 1 equiv of sodium hydroxide in ethanol at ambient temperature converted **22** into the original alcohol **17**. Lithium aluminum hydride reduction of **22** gave a mixture of **17** and a new alcohol **23**. The latter compound **23** was also obtained in 75% yield from the lithium aluminum hydride reduction of **25**. The uv spectrum of **23** was similar to that of **17**; the presence of the hydroxyl and ethyl moieties was demonstrated by the nmr and mass spectra.

Catalytic hydrogenation of **21** with a palladium catalyst in acetic anhydride gave **25** as the only isolable product. An explanation for this transformation assumes either (a) initial reduction of the amidine double bond followed by elimination of acetic acid and acylation of the resulting amine **15** or (b) hydrogenolysis of the acetoxy moiety to give **15**, which could subsequently undergo acylation by the acetic anhydride. This transformation thus offers strong chemical support for the gross structure of oxidation product **17**.

Catalytic hydrogenation of **17** in acetic anhydride with a palladium catalyst gave a complex mixture of products from which four crystalline materials, **26**, **31**, **32**, and **34**, were isolated by silica gel chromatography. Compound **26** was characterized by its typical indole chromophore in the uv, the amide band at 1675 cm^{-1}, and the absence of NH and OH absorption in the ir and the characteristic N–Et and $CH_3(C{=}O)N$ absorptions in the nmr. The nmr hextet at δ 4.73, assigned to the C-2 equatorial proton, was characteristic of the deshielding effect of an adjacent amide and thus established the location of the acetamide function (N-1).

The alcohol **31** was characterized by its OH and amide carbonyl bands in the ir, its typical indoline chromophore in the uv, and the peak at *m/e* 256 in the mass spectrum, which represented loss of water from the molecular ion (*m/e* 274). The nmr demonstrated that **31** was a mixture of *cis* and *trans* epimers. In particular the C-10a proton was represented by two singlets at δ 6.09 and 5.34 which had an area ratio of 6:5. The exchangeable hydroxyl protons were represented by singlets at δ 3.83 and δ 3.48. This interpretation was justified by the clean, acid-catalyzed conversion of **31** into **26** in 78% yield.

Assignment of structure **32** was based on the uv spectrum, which suggested an oxindole-type chromophore, the ir spectrum, which had OH and amide carbonyl absorption, and the mass spectrum, which had peaks corresponding to the successive loss of water (*m/e* 270) and two molecules of ketene (*m/e* 229 and 186) from the molecular ion (*m/e* 288). The nmr spectrum had singlets at δ 6.69 and 5.98 with an area ratio of 5:2, which were assigned to the C-10a proton, and thus indicated that this material was also a mixture of *cis* and *trans* isomers. Singlets at δ 2.03 and 2.18 were assigned to the acetamide moieties of the major isomer. Assignment of the downfield multiplet, δ 8.17, to the C-9 aromatic proton was based on the reported deshielding of the *ortho* proton by the amide carbonyl of *ortho*-monosubstituted N-phenylamides.[17] The acid-catalyzed dehydration of **32** gave the new diacetyl indole **27** in 92% yield. Support for structure **27** was derived from spectral data and from its facile conversion into **25** with sodium in ethanol.

Compound **34** was an isomer of **31** which had an oxindole chromophore in the uv spectrum and bands corresponding to OH and amide carbonyl absorption in the ir spectrum. In the mass spectrum the major fragmentation pathway was represented by peaks at *m/e* 245 and 203 which corresponded to successive loss of ethyl and ketene from the molecular ion (*m/e* 274). Minor peaks at *m/e* 259 and 256 corresponded to loss of methyl and water from the molecular ion. The nmr spectrum confirmed the presence of N-ethyl and N-acetyl groups; it had a sharp singlet at δ 4.85 for the C-10a proton and a broad singlet at δ 3.3 for the exchangeable hydroxyl proton. There was no indication of an isomer mixture, as had been observed for **31** and **32**. The low-field multiplet at δ 8.21, assigned to the C-9 proton, supported the N-10 acetamide assignment. Acid-catalyzed dehydration of **34** gave the noncrystalline indole **28**, which had an ir ($CHCl_3$) band at 1685 cm^{-1} for the amide carbonyl but no absorption attributable to a hydroxyl group. Further characterization of this compound was not attempted. Ethanolysis of **28** with sodium ethoxide in ethanol followed by isolation of the product by crystallization from methanol–ethyl acetate gave the alcohol **23**, presumably by air oxidation of the initially formed product. Acidification of **28** with anhydrous hydrogen chloride followed by crystallization of the salt from methanol–ethyl acetate gave **24**. This compound had the characteristic $C{=}N^+$ absorption at 1675 cm^{-1} in the ir; in the nmr spectrum the C-5a proton was represented by a quartet at δ 4.17.

The facile autoxidations of **15** and its N-1 alkyl derivatives (*viz.* **25**(**28**) → **23**) and the unusual behavior of the oxidation product **17** toward catalytic hydrogenation in acetic anhydride made it of interest to investigate the effect of alkylation at N-10 on these reactions. For this purpose **1** was alkylated with

(16) Numerous examples of this effect have now been reported, *e.g.*, (a) H. Paulsen and K. Todt, *Chem. Ber.*, **100**, 3385 (1967); (b) R. A. Johnson, *J. Org. Chem.*, **33**, 3627 (1968); (c) D. M. Lynch and W. Cole, *ibid.*, **31**, 3337 (1966).

(17) (a) R. F. C. Brown, L. Radom, S. Sternhell, and I. D. Rae, *Can. J. Chem.*, **46**, 2577 (1968); (b) M. Zanger, W. W. Simons, and A. R. Gennaro, *J. Org. Chem*, **33**, 3673 (1968); (c) A. Ribera and M. Rico, *Tetrahedron Lett.*, 535 (1968); (d) K. Nagarajan, M. D. Nair, and P. M. Pillai, *Tetrahedron*, **23**, 1683 (1967).

dimethyl sulfate to give **2**, which was subsequently converted into the oxime **9**[18] and tosyloxy oxime **10**. Beckmann rearrangement of **10** on neutral alumina which had been deactivated with 0.4% water gave a 23% yield of **16**, which was uncontaminated by the isomeric lactam. Lithium aluminum hydride reduction of **16** followed by the usual work-up in air gave a 71% yield of the autoxidation product **35**. Support for structure **35** was obtained from the ir spectrum, which had bands at 3180 and 1665 cm^{-1} for OH and C=N, respectively, and the nmr spectrum, which had a broad singlet at δ 5.82 for the exchangeable hydroxyl proton and quartets at δ 3.39 and 4.14, assigned to the C-2 equatorial and axial protons, respectively.

Catalytic reduction of **35** in acetic anhydride with a 10% palladium on carbon catalyst gave a mixture of four compounds, **29**, **30**, **33**, and **36**, which was separated by chromatography. Compound **29** was an oil which had no NH or OH absorption in the ir spectrum; it was characterized as its crystalline hydrochloride salt. Support for structure **29** was provided by the mass spectrum, which had peaks at *m/e* 213 and 199 corresponding to loss of methyl and ethyl radicals from the molecular ion of the free base (*m/e* 228) and by the nmr spectrum of the salt, which had peaks attributable to the N-methyl and N-ethyl groups. The ir spectrum of the hydrochloride had a strong band at 1640 cm^{-1} ($C=N^+$) and no absorption attributable to ^+NH, which suggests that salt formation occurs by protonation at C-5a rather than on nitrogen. It should also be noted that **29**, a 1,10-dialkyl derivative of **15**, was relatively stable to autoxidation and could be handled in air without appreciable degradation.

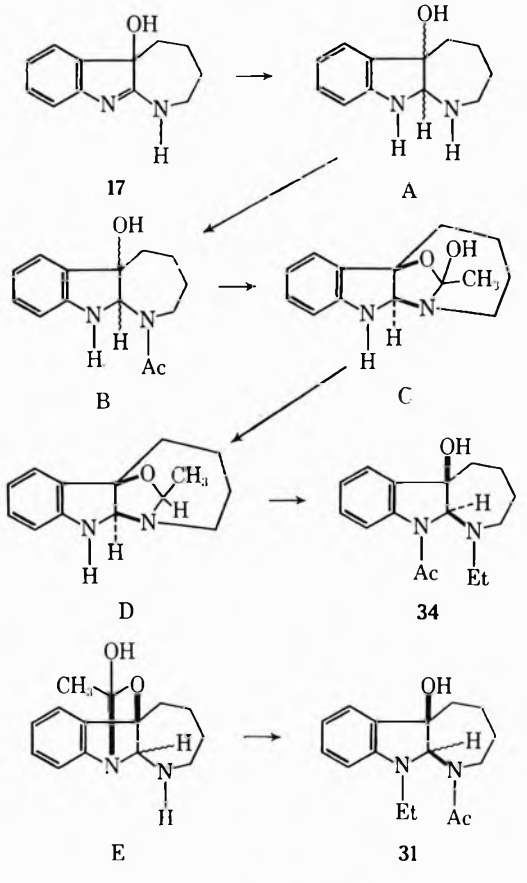
Structure **33** was suggested by the high-resolution mass spectrum, which had a peak at *m/e* 242.1429 corresponding to loss of water from the molecular ion (*m/e* 260.1514). The hydroxyl and amide assignments were supported by ir bands at 3280 and 1615 cm^{-1}; the indoline chromophore appeared in the uv spectrum. The nmr spectrum had a pair of singlets at δ 5.85 and 5.20 with an area ratio of 8.5:6 which were assigned to the C-10a proton; the N-methyl and acetamide moieties were also represented by pairs of singlets which suggested that **33** was a mixture of *cis* and *trans* isomers. This view was confirmed by the facile, acid-catalyzed conversion of **33** into the indole **30**, which had also been isolated from the hydrogenation mixture. Support for the latter structure (**30**) was derived from the typical indole chromophore in the uv spectrum, the peak corresponding to loss of CH_3CO (*m/e* 199) from the molecular ion (*m/e* 242) in the mass spectrum, the amide band at 1670 cm^{-1} in the ir spectrum, and the C-methyl and N-methyl singlets as well as the characteristic hextet at δ 4.56 for the C-2 equatorial proton in the nmr spectrum.

Assignment of structure **36** was based on the ester and C=N bands at 1740 and 1675 cm^{-1} in the ir spectrum, the characteristic uv chromophore, the C-methyl and N-methyl singlets at δ 2.04 and 3.13 in the nmr spectrum, and the molecular ion at *m/e* 258.1369 in the high-resolution mass spectrum.

With regard to the autoxidation of **15** and its N-monoalkylated derivatives, we suggest that, analogous to other known samples,[2,19] the reaction proceeds *via* a radical mechanism, initiated by homolytic cleavage of the N–H bond of the amine. The resulting allylic radical could react with oxygen or hydroperoxide radical at C-5a to give a hydroperoxide intermediate. Further reaction of this hydroperoxide with a second molecule of the amine (*viz.*, **15**) would give the observed product, **17**. Support for this mechanism is derived from the fact that the N,N′-dialkyl derivative **29** is stable to this type of autoxidation.

A mechanistic interpretation of the products obtained from the catalytic reduction of **17** and **35** in acetic anhydride is illustrated in Scheme I for compound **17**.

SCHEME I



We suggest that the reaction is initiated by reduction of the amidine double bond to give a *cis–trans* mixture of alcohols (A). Acylation of A can then occur at either or both nitrogens; monoacylation at N-1 would give B. In this case, when the hydroxyl and acetamide groups are *cis* to each other (*trans* ring junction), an interaction can occur to give the oxazolidine intermediate C. This type of interaction is general for molecules containing similarly positioned functional groups[20] and has been specifically invoked to explain the N → O acyl-transfer reaction.[21] Of importance to this discussion is the fact that the formation of C would destroy the resonance stabilization of the amide function and would thus make it susceptible to catalytic reduction. Precedent for the reduction of C

(18) V. I. Shvedov, L. B. Altukhova, E. K. Komissarora, and A. N. Grenev, *Chem. Heterocycl. Compounds*, **1**, 241 (1965).

(19) (a) H. I. X. Mager and W. B. Bevends, *Rec. Trav. Chim. Pays-Bas*, **84**, 1329 (1965). (b) See A. G. Davies, "Organic Peroxides," Butterworth and Co. Ltd., London, 1961, p 27–31.

(20) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, Inc., New York, N. Y., 1966, Chapter 1.

(21) E. E. vanTamelen, *J. Amer. Chem. Soc.*, **73**, 5773 (1951).

to oxazolidine D may be found in the catalytic reduction of rhetsinine to rhetsine,[22] which undoubtedly proceeds by way of a similar intermediate; catalytic reduction of oxazolidines such as D to amino alcohols has been reported.[23] In this case the reduction of D followed by acylation of the remaining nitrogen would give **34**, which, if this mechanism is correct, must have the stereochemistry shown. Monoacylation of A at N-10 followed by the acyl–alcohol interaction just described would give the oxazolidine intermediate E. In this case, however, formation of the oxazolidine would not be dictated by the stereochemistry of the ring junction; both isomers could be formed. Reduction of E could thus lead to a mixture of the *cis* and *trans* isomers of **31**, which was the observed result. Both diacetylation of A and monoacetylation of *cis*-B could give **32**, which would therefore be expected to be a *cis–trans* mixture. The observed predominance of one isomer in this case suggests that the latter route may be more important. In view of the observed facile dehydration of the C-5a alcohols, it is probable that the indoles (*viz.*, **26**) obtained from the hydrogenation reaction mixtures are the result of dehydration of the corresponding alcohol either during the reaction or during the work-up procedure.

Experimental Section[24]

***syn*-3,4-Dihydrocarbazol-1(2H)-one Oxime (3) and *anti*-3,4-Dihydrocarbazol-1(2H)-one Oxime (7).**—A mixture of **1** (330.0 g, 1.783 mol), hydroxylamine hydrochloride (187 g), NaOAc (242 g), EtOH (6.5 l.), and water (1.62 l.) was refluxed under N_2 for 7 hr, cooled, and allowed to stand at ambient temperature for 18 hr. Concentration of the solution *in vacuo* gave a solid residue which was collected by filtration, washed with water, and dried. Chromatography of this solid on silica gel (16 kg) with 30% EtOAc–70% Skellysolve B separated the isomers. The first material eluted from the column was crystallized from ether–Skellysolve B to give 157.4 g of **7**, mp 134–143°. An analytical sample was obtained: mp 129–136°; uv (EtOH) λ_{max} 205 mμ (ε 22,900), 244 (13,750), 304 (22,850), and 311 (inflection, 22,300); ir (Nujol) 3440, 3320, 3200 (NH and OH), and 1630 cm^{-1} (C=N).

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.24; H, 6.19; N, 14.16.

The second material eluted from the column was crystallized from EtOAc–Skellysolve B to give 145 g of **3**, mp 155–165°. An analytical sample was obtained: mp 175.5–176.5°; uv (EtOH) λ_{max} 206 mμ (ε 21,650), 244 (16,600), 306 (21,750), and 313 (inflection, 21,350); ir (Nujol) 3460, 3420, 3120, 3010 (NH and OH), and 1635 cm^{-1} (C=N).

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.58; H, 5.98; N, 14.12.

3,4,5,10-Tetrahydroazepino[3,4-*b*]indol-1(2H)-one (5). A.—A stirred mixture of **7** (9.95 g, 0.0497 mol) and polyphosphoric acid (300 g) was heated under N_2 at 110–120° for 10 min, cooled, and poured into a mixture of crushed ice and water. The resulting solid was collected by filtration, washed with water, dried, and recrystallized from CH_2Cl_2–MeOH to give 7.22 g (72.5%) of **5**, mp 222–228°. An analytical sample was obtained: mp 228–229° [lit.[4] mp 224–227°]; uv (EtOH) end absorption, λ_{max} 229 mμ (ε 25,550) and 298 (17,250); ir (Nujol) 3270, 3200 (NH), and 1625 cm^{-1} (C=O).

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.72; H, 6.22; N, 13.96.

B.—In the manner described in A, the reaction of compound **3** (14.1 g, 0.0704 mol) with polyphosphoric acid (424 g) gave 12.0 g (85%) of **5**, mp 221–224°.

C.—A stirred mixture of **1** (6.5 g, 0.0351 mol) in polyphosphoric acid (200 g) was warmed to 50–60° and treated during 20 min with sodium azide (2.97 g, 0.0457 mol). Heating was continued for 3 hr, after which the mixture was poured into ice-water. The product was extracted with CH_2Cl_2; the extract was washed with water, dried ($MgSO_4$), and concentrated. Chromatography of the residue on silica gel (500 g) with EtOAc gave 1.73 g of recovered **1**, mp 168–169.5° (lit.[3] mp 169–170°), and 1.47 g (21%) of **5**, mp 222–230°.

D.—A solution of **3** (10.0 g, 0.05 mol) in pyridine (250 ml) was cooled in an ice bath, treated with *p*-toluenesulfonyl chloride (10.5 g, 0.0552 mol), and allowed to stand at ambient temperature for 18 hr. It was then treated with water and concentrated *in vacuo*. The resulting crystalline product was collected by filtration, washed with water, and dried to give 17.3 g of **4**, mp 132–135° dec. A solution of **4** (9.00 g) in benzene was adsorbed on a column of neutral alumina (600 g) which had been deactivated with 1% water. The column was treated successively with benzene (1 l.), 50% benzene–50% $CHCl_3$ (2 l.), and $CHCl_3$ (1.5 l.); the product was eluted with 20% MeOH–80% $CHCl_3$ and crystallized from CH_2Cl_2–MeOH to give 3.01 g, mp 228–229.5°, and 1.21 g, mp 220–224°, of **5**. In these experiments **5** was identified at least by ir ($CHCl_3$) comparison with the authentic sample. The melting-point discrepancies were due to the appearance of two polymorphic crystalline forms.

1,2,3,4,5,10-Hexahydroazepino[3,4-*b*]indole (6).—Compound **5** (2.00 g, 0.01 mol) was added under N_2 to a stirred, ice-cold suspension of $LiAlH_4$ (2.0 g) in tetrahydrofuran (150 ml). The resulting mixture was warmed to ambient temperature during 5 hr and refluxed for 10.75 hr. It was then cooled in an ice bath and treated successively with water (2 ml), 15% NaOH (2 ml), and water (6 ml). This mixture was filtered and the filtrate was concentrated to give a solid which was recrystallized from MeOH–EtOAc to yield 1.35 g (72.5%) of **6**, mp 212–214°. An analytical sample was obtained: mp 212.5–214.5°; uv (EtOH) λ_{max} 225 mμ (ε 33,850), 284 (7500), 291 (6900), and 276 (inflection, 6650); nmr [$(CD_3)_2NCDO$] δ 4.00 (s, 2, C-1).

Anal. Calcd for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 76.98; H, 7.84; N, 14.96.

1-Ethoxy-3,4,5,10-tetrahydroazepino[3,4-*b*]indole (11).—A solution of triethyloxonium fluoroborate, prepared from boron trifluoride etherate (4.06 ml) and epichlorohydrin (1.88 ml), in CH_2Cl_2 (10 ml), was added to a stirred suspension of **5** (3.00 g, 0.015 mol) in CH_2Cl_2 (250 ml) at 10–15°. This mixture was allowed to stand at ambient temperature for 18 hr and the solid complex was collected by filtration and treated with cold, dilute K_2CO_3. The product was extracted with CH_2Cl_2; the extract was washed with water, dried (K_2CO_3), and concentrated. Crystallization of the residue from EtOAc–Skellysolve B gave 1.65 g (48.3%) of **11**: mp 122.5–124°; uv (EtOH) λ_{max} 208 mμ (ε 20,750), 231 (24,500), and 300 (17,950); ir (Nujol) 3130, 3070 (NH), and 1650 cm^{-1} (C=N).

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.85; H, 7.27; N, 12.26.

1-{[2-(Diethylamino)ethyl]amino}-3,4,5,10-tetrahydroazepino-[3,4-*b*]indole (12).—A mixture of **11** (4.56 g, 0.02 mol), N,N-diethylethylenediamine (14 g), *p*-toluenesulfonic acid (800 mg), and benzene (200 ml) was refluxed under N_2 for 15 hr. During the inital stages of the reaction the ethanol–water azeotrope was distilled from the mixture through a small, helix-packed column. The cooled reaction mixture was poured into water and the product was extracted with ether. The ether extract was washed with water and brine, dried (K_2CO_3), and concentrated. Crystallization of the residue from EtOAc–Skellysolve B yielded 4.37 g, mp 143.5–145°, and 0.848 g, mp 141.5–143.5° (87.7%), of **12**. An analytical sample was obtained: mp 144.5–145.5°;

(22) I. J. Pachter and G. Suld, *J. Org. Chem.*, **25**, 1680 (1960).

(23) (a) E. Gil-Av, *J. Amer. Chem. Soc.*, **74**, 1346 (1952); (b) A. C. Cope and E. M. Hancock, *ibid.*, **64**, 1503 (1942); (c) M. Senkus, *ibid.*, **67**, 1515 (1945).

(24) Melting points were taken in capillary tubes and are corrected. Ultraviolet spectra were determined on a Cary Model 14 spectrophotometer, ir spectra on a Perkin-Elmer Model 421 spectrophotometer, mass spectra at 70 eV on an Atlas Model CH-4 spectrometer, high-resolution mass spectra on a Consolidated Electronics Model 21-110 spectrometer, and nmr spectra on a Varian Model A-60A spectrometer. Nmr peaks are recorded in parts per million downfield from tetramethylsilane. In general, only those nmr peaks which are either necessary for the structure proof or are readily assignable to a specific proton or group of protons are reported; the integrated spectra are, however, in all cases in agreement with the assigned structures. Skellysolve B is a commercial hexane, bp 60–70°, made by Skelly Oil Co., Kansas City, Mo. Darco G-60 is an activated carbon prepared by Atlas Chemical Industries, Inc., Wilmington 99, Del. Celite is a filter aid manufactured by Johns–Manville, New York, N. Y. The alumina used for chromatography was obtained from M. Woelm, Eschwege, Germany, and the silica gel from E. Merck AG, Darmstadt, Germany.

uv (EtOH) λ_{max} 207 mμ (ε 22,850), 238 (21,100), and 307.5 (20,450).

Anal. Calcd for $C_{18}H_{26}N_4$: C, 72.44; H, 8.78; N, 18.78. Found: C, 72.45; H, 9.00; N, 18.61.

3,4,5,10-Tetrahydro-1-piperidinoazepino[3,4-*b*]indole Hydrochloride Dihydrate (13).—Compound **11** (5.75 g, 0.0252 mol) was added to a cold, stirred mixture of sulfuric acid (0.63 ml) and piperidine (63 ml) and the resulting mixture was refluxed under N_2 for 36 hr and poured into ice–water. The resulting mixture was treated with 1.5 ml of 50% aqueous NaOH and extracted with ether; the ether extract was washed with brine, dried (K_2CO_3), and concentrated. The residue was chromatographed on silica gel (1.1 kg); the product was eluted with 2% acetic acid–methanol as the acetic acid salt. A solution of this material in water was made alkaline with 50% aqueous NaOH, and the solid which precipitated was collected by filtration, washed with water, and dried. A suspension of this material in EtOAc was acidified with methanolic hydrogen chloride. The resulting salt was recrystallized from water to give 2.04 g, mp 225–237° (softening at 136°), and 0.285 g, mp 230–239° (softening at 130°), of **13**. An analytical sample was obtained: mp 150–153° dec; uv (EtOH) λ_{max} 208 mμ (ε 25,750), 241 (15,340), and 315 (20,750).

Anal. Calcd for $C_{17}H_{21}N_3 \cdot HCl \cdot 2H_2O$: C, 60.08; H, 7.71; N, 12.36; Cl, 10.43; H_2O, 10.60. Found: C, 60.46; H, 7.83; N, 12.43; Cl, 10.53; H_2O, 10.46.

3,4,5,10-Tetrahydroazepino[2,3-*b*]indol-2(1H)-one (14).—A solution of **7** (157.4 g, 0.788 mol) in pyridine (3.5 l.) was cooled in an ice bath under N_2 and treated with *p*-toluenesulfonyl chloride (172 g). This mixture was kept at ambient temperature for 18 hr and poured into ice–water. The resulting crystalline product was collected by filtration, washed with water, dried, and recrystallized from benzene to give 258.2 g of **8**, mp 165.5–167° dec. A solution of this material in benzene was absorbed on a column of neutral alumina (16 kg) which had been deactivated with 0.5% water. The column was then treated successively with benzene (20 l.), 20% $CHCl_3$–80% benzene (28 l.), and $CHCl_3$ (63 l.). During this procedure some unreacted **8** was eluted from the column. The product was eluted from the column with mixtures of MeOH (20–40%) and $CHCl_3$; it was crystallized from CH_2Cl_2–MeOH to give 39.6 g (25.2%) of **14**, mp 200–206° dec. The analytical sample was crystallized from MeOH–EtOAc: mp 205.5–206.5°; uv (EtOH) end absorption, λ_{max} 321 mμ (ε 28,400) and 299 (13,850) and inflections at 218 (21,550), 273 (7100), and 285, (11,000); ir (Nujol) 3410, 3370, 3270, 3170 (NH), and 1680 cm^{-1} (C=O); nmr [$(CD_3)_2NCDO$] δ 2.1 (m, 2, C-4) and 2.7 (m, 4, C-3, C-5); mass spectrum *m/e* (rel intensity) 200 (100) and 145 (90.7).

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.90; H, 5.61; N, 14.28.

2,3,4,5-Tetrahydroazepino[2,3-*b*]indol-5a(1H)-ol (17). A.—Compound **14** (12.7 g, 0.0634 mol) was added under N_2 to an ice-cold, stirred suspension of $LiAlH_4$ (13 g) in tetrahydrofuran (1300 ml). The resulting mixture was refluxed for 15 hr, cooled in an ice bath, and treated successively with water (13 ml), 15% aqueous NaOH (13 ml), and water (39 ml). This mixture was stirred for a few minutes and filtered. The filtrate was concentrated *in vacuo*. A solution of the residue in MeOH was stored at 0° for 2 days and crystallized to give 4.80 g, mp 252.5–253.5° dec, 2.99 g, mp 248.5–250° dec, and 1.30 g, mp 247–248.5° dec (70.8%), of **17**. An analytical sample was obtained: mp 255–259.5°; uv (EtOH) λ_{max} 223 mμ (ε 23,060), 280 (10,030), 290 (9270), and 319 (4300); ir (Nujol) 3270, 3230, 3180, 3120 (NH and OH), and 1640 cm^{-1} (C=N); mass spectrum *m/e* (rel intensity) 202 (100), 185 (7), 173 (44), 146 (13), and 145 (12); pK_a' (60% EtOH) 6.9.

Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.82; H, 6.99; N, 13.64.

B.—A stirred mixture of **22** (100 mg, 0.350 mmol) and absolute ethanol (10 ml), under N_2, was treated with 0.320 ml of 1.113 *N* NaOH, and the resulting solution was kept at ambient temperature for 50 min and poured into ice water. This mixture was extracted with CH_2Cl_2. The extract was dried (K_2CO_3) and concentrated *in vacuo*. Crystallization of the residue from MeOH gave 28 mg of **17**, mp 250.5–254.5° dec. Recrystallization from MeOH gave material, mp 252–253.5° dec, which was identical with authentic **17** by comparison of the ir and uv spectra.

The hydrochloride of **17** was prepared by acidifying a solution of **17** in MeOH with methanolic hydrogen chloride. The analytical sample was crystallized from MeOH: mp 229.5–230.5° dec; uv (EtOH) λ_{max} 221 mμ (ε 19,650), 224 (19,700), 269 (5700), 278 (5550), 299 (4200), and 293 (inflection, 4150); ir (Nujol) 3170, 3060, 3010 (NH and OH) and 1685 cm^{-1} (C=N$^+$); nmr (D_2O) δ 4.12 (q, 1, $J_{gem} \cong -14$ Hz, $J_{a,a} \cong 10$ Hz, C-2 axial) and 3.49 (q, 1, $J_{gem} = -14$ Hz, $J_{e,e} = 5$ Hz, C-2 equatorial).

Anal. Calcd for $C_{12}H_{15}ClN_2O$: C, 60.37; H, 6.33; Cl, 14.86; N, 11.74. Found: C, 60.44; H, 6.63; Cl, 15.00; N, 11.52.

The hydrobromide of **17** was prepared by acidifying a methanolic solution of **17** with methanolic hydrogenbromide. The salt was crystallized from MeOH–EtOAc, mp 205.5–206.5° dec.

Anal. Calcd for $C_{12}H_{15}BrN_2O$: C, 50.89; H, 5.34; Br, 28.22; N, 9.90. Found: C, 50.82; H, 5.47; Br, 28.23; N, 10.14.

1-Acetyl-1,2,3,4,5,10-hexahydroazepino[2,3-*b*]indole (25). A.—Compound **14** (5.05 g, 0.0252 mol) was added under N_2 to an ice-cold, stirred suspension of $LiAlH_4$ (5.0 g) in tetrahydrofuran (350 ml). The resulting mixture was refluxed for 18 hr, cooled in an ice bath, and treated successively with water (5 ml), 15% aqueous NaOH (5 ml), and water (15 ml). This mixture was stirred under N_2 for 1 hr and filtered. The filtrate was treated with pyridine (100 ml) and acetic anhydride (10 ml) and concentrated to a volume of 100 ml *in vacuo*. This solution was treated with additional acetic anhydride (10 ml), kept under N_2 at ambient temperature for 18 hr, and concentrated *in vacuo*. The residue was stirred with water for several hours, and the crystalline product was collected by filtration, washed with water, dried, and recrystallized from EtOAc to give 1.55 g (26.9%) of **25**, mp 194.5–196.5°. A small second crop, 0.121 g, mp 193.5–194.5°, was obtained by concentrating the mother liquor. An analytical sample was obtained: mp 193°; uv (EtOH) λ_{max} 223 mμ (ε 37,050), 285 (8800), 289.5 (8400), and 275 (inflection, 9350); ir (Nujol) 3180 (NH) and 1640 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 228 (100), 186 (65.7), 185 (64.5), 158 (17.8), 157 (35.3), and 130 (28); nmr [$(CD_3)_2SO$] δ 1.72 (m, 4, C-3,4), 1.98 (s, 3, CH_3CO), 2.74 (m, 2, C-5), 3.65 (m, 2, C-2), 7.25 (m, 4, C-6–9), and 11.2 (s, 1, NH).

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.39; H, 7.14; N, 12.37.

B.—A mixture of **21** (1.00 g, 4.09 mmol), 10% palladium on carbon (0.5 g), and acetic anhydride (100 ml) was hydrogenated at an intial pressure of 30 psi for 8 hr and filtered through Celite. The filtrate was concentrated *in vacuo*. A solution of the residue in xylene was concentrated *in vacuo* to remove last traces of acetic anhydride. This residue was crystallized from EtOAc to give 0.362 g of **25**, mp 192–193.5°.

C.—Compound **27** (81 mg, 0.30 mmol) was added under N_2 to a solution of sodium (10 mg) in absolute ethanol (3 ml). The resulting solution was stirred for 44 min at ambient temperature and poured into water. The solid produet was collected by filtration, washed with water, dried, and recrystallized from EtOAc to give 53 mg (77%) of **25**, mp 192–193.5°.

The products from B and C were identified by mixture melting point and ir, uv, and nmr comparison with the authentic sample.

1,2,3,4,5,5a-Hexahydrcazepino[2,3-*b*]indole Hydrochloride (20).—Compound **14** (1.00 g, 5.00 mmol) was added under N_2 to an ice-cold, stirred suspension of $LiAlH_4$ (1.0 g) in tetrahydrofuran (100 ml). The resulting mixture was refluxed for 18 hr, cooled in an ice bath, and treated successively with water (1 ml), 15% aqueous NaOH (1 ml), and water (3 ml). This mixture was filtered into a flask containing methanolic hydrogen chloride. The resulting solution was concentrated *in vacuo*. A solution of the residue in water was decolorized with Darco G-60 and concentrated *in vacuo*. Water was removed from the resulting material by the addition of absolute ethanol twice with concentration after each addition. The resulting crystalline product was recrystallized from EtOH–EtOAc and then from MeOH–EtOAc to give 0.362 g (32.5%) of **20**, mp 254–257° dec. An analytical sample was obtained: mp 253.5–255.5°; uv (EtOH) λ_{max} 215 mμ (ε 18,000) and 273 (10,150) and inflections at 265 (9550), 269 (9900), and 280 (7400); ir (Nujol) 3000, 2780, 2720 (NH), and 1680 cm^{-1} (C=N$^+$); nmr (D_2O) δ 3.68 (m, 2, C-2), and 7.38 (m, 4, C-6–9).

Anal. Calcd for $C_{12}H_{15}ClN_2$: C, 64.71; H, 6.79; Cl, 15.92; N, 12.58. Found: C, 64.65; H, 6.90; Cl, 16.08; N, 12.54.

1-Acetyl-2,3,4,5-tetrahydroazepino[2,3-*b*]indol-5a(1H)-ol Acetate Ester (22) and 2,3,4,5-Tetrahydroazepino[2,3-*b*]indol-5a-(1H)-ol Acetate Ester (21).—A stirred mixture of **17** (1.02 g, 5.05 mmol), acetic anhydride (3 ml), and pyridine (50 ml) was kept at ambient temperature in the dark under N_2 for 18 hr and concentrated *in vacuo*. A solution of the residue in xylene was

concentrated *in vacuo* to remove last traces of pyridine and acetic anhydride. The residue was chromatographed on silica gel (50 g). The first compound was eluted with 40% EtOAc–60% cyclohexane and was crystallized from EtOAc–Skellysolve B to give 0.377 g (26.1%) of **22**, mp 127.5–128.5°. An analytical sample was obtained: mp 127.5–129°; uv (CH_2Cl_2) λ_{max} ~230 mμ (ε 20,100), 287 (8310), 297 (9720), and 309 (9410); ir (Nujol) 1745 [$CH_3(C{=}O)O$] and 1670 cm^{-1} [$CH_3(C{=}O)N$]; mass spectrum *m/e* (rel intensity) 286 (51), 244 (100), 227 (1.7), 226 (2.4), 201 (63), 185 (50), 184 (32), and 157 (24); nmr ($CDCl_3$) δ 2.07 [s, 3, $CH_3(C{=}O)O$], 2.58 [s, 3, $CH_3(C{=}O)N$], 3.21 (q, 1, $J_{gem} \cong 15$ Hz, $J_{a,a} \cong 10$ Hz, C-2 axial), 4.95 (q, 1, $J_{gem} \cong -15$ Hz, $J_{e,e} \cong 7$ Hz, C-2 equatorial), and 7.25 (m, 4, C-6–9).

Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.34; N, 9.78. Found: C, 67.29; H, 6.79; N, 9.57.

The second compound was eluted from the column with 50% pyridine–50% EtOAc and was crystallized from CH_2Cl_2–EtOAc to give 0.308 g (25%) of **21**, mp 172–173° dec. An analytical sample was obtained: mp 176° dec; uv (CH_2Cl_2) λ_{max} 282 mμ (ε 10,200), 292 (9190), and 320 (3990); ir (Nujol) 1750 [$CH_3(C{=}O)O$], and 1650 cm^{-1} (C=N); mass spectrum *m/e* (rel intensity) 244 (78), 201 (100), 185 (95), 184 (54), and 157 (88); nmr [$CDCl_3$ + $(CD_3)CDO$] δ 2.10 [s, 3, $CH_3(C{=}O)O$].

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.16; H, 6.67; N, 11.43.

2,2-Dideuterio-2,3,4,5-tetrahydroazepino[2,3-*b*]indol-5a(1H)-ol (19) Hydrochloride.—Compound **14** (1.18 g, 5.90 mmol) was added under N_2 to an ice-cold, stirred suspension of $LiAlD_4$ (1.0 g) in tetrahydrofuran (100 ml) and the resulting mixture was refluxed for 10 hr, allowed to stand at ambient temperature for 18 hr, cooled in an ice bath, and treated successively with water (1.0 ml), 15% aqueous NaOH (1.0 ml), and water (3 ml). This mixture was stirred for a few minutes and filtered. The filtrate was concentrated *in vacuo*. The residue was dissolved in MeOH and allowed to crystallize during 18 hr to give 0.867 g (72%) of **19**, mp 246–250° dec. A sample of this material was suspended in MeOH and acidified with methanolic hydrogen chloride. The salt was crystallized from MeOH–EtOAc to give **19** hydrochloride: mp 231–232.5°; uv (EtOH) λ_{max} 221 mμ (ε 20,900), 224 (20,950), 278 (7150), and 290 (5850) and inflections at 272 (6350) and 305 (3800); ir (Nujol) 3180, 3060, 3020 (OH and N^+H) and 1690 cm^{-1} ($C{=}N^+$); mass spectrum *m/e* (rel intensity) 204 (85), 187 (7), 175 (19), 174 (14), 173 (16), 147 (12), 146 (18), 145 (23), 103 (61), 90 (42), 85 (48), 57 (50), 43 (83), 42 (74), 41 (100), and 29 (100); nmr (D_2O) δ 1.2–2.45 (m, 6, C-3–5), and 7.22 (m, 4, C-6–9).

Anal. Calcd for $C_{18}H_{13}D_2ClN_2O$: C, 59.88; H, 5.44; D, 1.66. Found: C, 59.77; H, 5.26; D, 1.61.

1-Acetyl-2,2-dideuterio-2,3,4,5-tetrahydroazepino[2,3-*b*]indol-5a-(1H)-ol Acetate Ester (18).—Compound **19** (0.759 g, 3.72 mmol) was added to a stirred solution of acetic anhydride (3 ml) in pyridine (50 ml) and the resulting mixture was kept in the dark under N_2 for 17 hr and concentrated *in vacuo*. A solution of the residue in xylene was concentrated to dryness to remove last traces of pyridine. A solution of this residue in benzene was washed successively with ice-cold, dilute $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel (50 g) with 40% EtOAc–60% cyclohexane. The first compound eluted from the column was crystallized from EtOAc–Skellysolve B to give 0.157 g, mp 126–127.5°, and 0.031 g, mp 121–127°, of **18**. An analytical sample was obtained: mp 120.5–121.5°; uv (CH_2Cl_2) λ_{max} 288 mμ (ε 8100), 297 (9550), and 308 (9150); ir (Nujol) 1745 [$CH_3(C{=}O)O$], and 1675 cm^{-1} [$CH_3(C{=}O)N$]; mass spectrum *m/e* (rel intensity) 288 (42), 246 (100), 203 (57), 187 (42), 185 (30), and 159 (18); nmr ($CDCl_3$) δ1.14–2.5 (m, 6, C-3–5), 2.08 [s, 3, $CH_3(C{=}O)O$], 2.59 [s, 3, $CH_3(C{=}O)N$], and 7.22 (m, 4, C-6–9).

Anal. Calcd for $C_{16}H_{16}D_2N_2O_3$: C, 66.65; H, 6.98. Found: C, 66.94; H, 6.72.

1-Ethyl-2,3,4,5-tetrahydroazepino[2,3-*b*]indol-5a(1H)-ol (23). A.—Compound **25** (0.500 g, 2.19 mmol) was added under N_2 to an ice-cold, stirred suspension of $LiAlH_4$ (0.500 g) in tetrahydrofuran (50 ml). The resulting mixture was refluxed for 17 hr, cooled in an ice bath, and treated successively with water (0.5 ml) 15% aqueous NaOH (0.5 ml), and water 1.5 ml. The mixture was stirred for a few minutes and filtered. The filtrate was concentrated under reduced pressure. The residue was dissolved in MeOH, filtered to remove a small amount of flocculent solid, and crystallized from MeOH–EtOAc to give 0.279 g, mp 250–252° dec, and 0.100 g, mp 248.5–251.5° dec (75.2%), of **23**. The analytical sample was crystallized from methanol: mp 251.5–252.5° dec; uv (EtOH) end absorption, λ_{max} 224 mμ (ε 21,400), 282 (11,400), 291 (11,150), and 320 (5370); ir (Nujol) 3120 (OH) and 1615 cm^{-1} (C=N); mass spectrum *m/e* (rel intensity) 230 (100), 213 (51), 202 (23), 174 (41), and 146 (20); nmr (C_5D_5N) δ 1.10 (t, 3, J = 7 Hz, CH_3CH_2N), 2.96 (q, 1, $J_{gem} \cong 14$ Hz, $J_{e,e} \cong 5$ Hz, C-2 equatorial), 3.65 (q, 2, J = 7 Hz, CH_3CH_2N), 4.64 (q, 1, $J_{gem} \cong -14$ Hz, $J_{a,a} \cong 10$ Hz, C-2 axial), and 8.72 (s, 1, OH).

Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 73.08; H, 7.67; N, 12.20.

B.—A solution of **34** (100 mg, 0.365 mmol) and *p*-toluenesulfonic acid (10 mg) in benzene (10 ml) was refluxed under nitrogen for 1.5 hr. The cooled solution was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give a noncrystalline oil. A solution of this oil in absolute ethanol (1 ml) was added under N_2 to a stirred solution of sodium (17 mg) in ethanol (2 ml), and the resulting solution was kept at ambient temperature for 35 min and poured into water. This mixture was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated. Crystallization of the residue from MeOH–EtOAc gave 43 mg (51%) of **23**, mp 245–251° dec. This material was identical with the authentic sample by ir and uv comparison.

C.—Compound **22** was added, under N_2, to an ice-cold, stirred suspension of $LiAlH_4$ (300 mg) in tetrahydrofuran (30 ml) and the mixture was refluxed for 18 hr, cooled in an ice bath, and treated successively with water (0.3 ml), 15% aqueous NaOH (0.3 ml), and water (0.9 ml). This mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (15 g) with 2% Et_2NH–3% MeOH–95% EtOAc. The first compound eluted from the column was crystallized from MeOH–EtOAc to give **23**, mp 252.5–253.5° dec, which was identical with the authentic sample by comparison of the ir (Nujol) and uv spectra. The second compound eluted from the column was crystallized from MeOH to give **17**, mp 248.5–251.5° dec, which was identical with the authentic sample by comparison of the ir and uv spectra.

1-Acetyl-10-ethyl-1,2,3,4,5,10-hexahydroazepino[2,3-*b*]indole (26), 10-Acetyl-1-ethyl-2,3,4,5,10,10a-hexahydroazepino[2,3-*b*]-indol-5a(1H)-ol (34), 1-Acetyl-10-ethyl-2,3,4,5,10,10a-hexahydroazepino[2,3-*b*]indol-5a(1H)-ol (31), and 1,10-Diacetyl-2,3,4,-5,10,10a-hexahydroazepino[2,3-*b*]indol-5a(1H)-ol (32).—A mixture of **17** (7.00 g, 0.0346 mol), 10% palladium on carbon (3.5 g), and acetic anhydride (700 ml) was hydrogenated at an initial pressure of 30 psi for 8 hr and allowed to stand under hydrogen for an additional 16 hr. It was then filtered through Celite and the filtrate was concentrated *in vacuo*. A solution of the residue in xylene was concentrated *in vacuo* to remove last traces of acetic anhydride; the residual oil was chromatographed on silica gel (400 g). Compounds **26** and **34** were eluted with 30% EtOAc–70% Skellysolve B and compounds **31** and **32** were eluted with EtOAc. The first compound eluted from the column was crystallized from EtOAc–Skellysolve B to give 0.658 g, mp 141–142.5°, 0.183 g, mp 140–142°, and 0.053 g, mp 138.5–140.5° (10.8%), of **26**. An analytical sample was obtained: mp 140.5–141.5°; uv (EtOH) λ_{max} 226 mμ (ε 39,750), 284 (9230), 293 (7870), and 278 (inflection, 8520); ir (Nujol) 1675 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 256 (100), 241 (3.2), 288 (4.1), 227 (2.6), 214 (35), and 213 (60); nmr ($CDCl_3$) δ 1.29 (t, 3, J = 7 Hz, CH_3CH_2N), 1.91 [s, 3, $CH_3(C{=}O)N$], 4.06 (octet, 2, J = 7 and 2.5 Hz, CH_3CH_2N), 4.73 (sextet, 1, $J_{gem} \cong -13$ Hz, $J_{e,e} \cong 3$ Hz, C-2 equatorial), and 7.34 (m, 4, C-6–9).

Anal. Calcd for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86. Found: C, 74.89; H, 7.83.

The second compound eluted from the column was crystallized from EtOAc–Skellysolve B to give 2.30 g, mp 162.5–164°, and 0.185 g, mp 161.5–162.5° (26.2%), of **34**. The analytical sample was crystallized from EtOAc: mp 164–165°; uv (EtOH) end absorption, λ_{max} 248 mμ (ε 13,900) and inflections at 278 (2460) and 286 (1685); ir (Nujol) 3330 (OH) and 1650 cm^{-1} [$CH_3(C{=}O)N$]; mass spectrum *m/e* (rel intensity) 274 (74), 259 (13), 257 (8), 256 (11), 245 (100), 231 (10), 203 (44), 186 (11), 185 (18), 146 (25), 120 (26), and 112 (24); nmr ($CDCl_3$) δ 0.91 (t, 3, J = 7 Hz, CH_3CH_2N), 2.08 [s, 3, $CH_3(C{=}O)N$], 2.54 (q, 2, J = 7 Hz, CH_3CH_2N), 3.3 (br s, 1, OH), 4.87 (s, 1, C-10a), 7.22 (m, 3, C-6–8), and 8.2 (m, 1, C-9).

Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.98; H, 8.21; N, 10.19.

The third compound eluted from the column was crystallized from EtOAc–Skellysolve B to give 0.261 g, mp 124–125°, and 0.094 g, mp 117.5–119° (3.74%), of **31**. An analytical sample was obtained: mp 111.5–112.5°; uv (EtOH) λ_{max} 208 mμ (ε 34,200), 251 (13,840), and 309 (2670); ir (Nujol) 3310 (OH) and 1620 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 274 (9.1), 256 (100), 215 (54), 214 (60), 213 (85), 185 (13.6), 174 (11.9), 160 (7.2), 158 (7.8), 146 (8.7), 144 (9.1), and 130 (9.1); nmr ($CDCl_3$)[25] δ 1.13, 1.10 (t, 3, J = 7 Hz, CH_3CH_2N), 2.19, 2.26 [s, 3, $CH_3(C=O)N$], 2.92–3.54 (m, 2, CH_3CH_2N), 3.48, 3.83 (s, 1, OH), 6.09, and 5.34 (s, 1, C-10a).

Anal. Calcd for $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.12; H, 8.22; N, 10.31.

The fourth compound eluted from the column was crystallized from MeOH–EtOAc to give 2.58 g (25.8%) of **32**, mp 199–201°. An analytical sample was obtained: mp 200–201°; uv (EtOH) end absorption, λ_{max} 246 mμ (ε 14,150), 278 (2040), and 287 (1600); ir (Nujol) 3370 (OH) and 1645 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 288 (4.6), 270 (28), 228 (100), and 186 (53); nmr [$(CD_3)_2SO$][26] δ 2.03 [s, 3, $CH_3(C=O)N$], 2.18 [s, 3, $CH_3(C=O)N$], 3.57 (br d, 1, $J \cong -16$ Hz, C-2 equatorial), 5.75 [5.89] (s, 1, OH), 6.69 [5.98] (s, 1, C-10a), 7.28 (m, 3, C-6–8), and 8.17 (m, 1, C-9).

Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.99; N, 9.72. Found: C, 66.31; H, 6.96; N, 9.55.

1-Acetyl-10-ethyl-1,2,3,4,5,10-hexahydroazepino[2,3-*b*]indole (26).—A stirred mixture of **31** (81 mg, 0.295 mmol), *p*-toluenesulfonic acid (5 mg), and benzene (10 ml) was warmed under N_2 to 80° during 20 min, cooled, and poured into ice water. This mixture was extracted with ether. The extract was dried ($MgSO_4$) and concentrated *in vacuo*. Crystallization of the residue from EtOAc–Skellysolve B gave 59 mg (78%) of **26**, mp 140–141°. The mixture melting point with authentic **26** was undepressed. It was identical with the authentic sample by comparison of the ir and nmr spectra.

1-Ethyl-1,2,3,4,5,5a-hexahydroazepino[2,3-*b*]indole Hydrochloride (24).—A mixture of **34** (250 mg), *p*-toluenesulfonic acid (20 mg), and benzene (25 ml) was refluxed under N_2 for 1.5 hr. The resulting solution was cooled, washed with cold water, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was dissolved in petroleum ether, filtered through a little silica gel, and concentrated; no crystalline material was obtained. The oil was acidified with ethereal hydrogen chloride and the resulting salt was crystallized from MeOH–EtOAc to give 94 mg of **24**, mp 226–228° dec. An analytical sample was obtained: mp 226.5–228° dec; uv (EtOH) λ_{max} 216 mμ (ε 18,640) and 274 (12,720) and inflections at 265 (10,640), 269 (11,760), and 283 (10,550); ir (Nujol) 2620 (N^+H) and 1675 cm^{-1} ($C=N^+$); nmr (D_2O) δ 1.30 (t, 3, J = 7 Hz, CH_3CH_2N), 3.59 (q, 2, J = 7 Hz, CH_3CH_2N), *ca.* 3.71 (m, 2, C-2), 4.17 (q, 1, $J \cong 12$ and 3 Hz, C-5a), and 7.24 (m, 4, C-6–9).

Anal. Calcd for $C_{14}H_{19}ClN_2$: C, 67.05; H, 7.64; Cl, 14.14; N, 11.17. Found: C, 66.59; H, 7.70; Cl, 13.86; N, 10.96.

1,10-Diacetyl-1,2,3,4,5,10-hexahydroazepino[2,3-*b*]indole (27).—A mixture of **32** (200 mg, 0.694 mmol), *p*-toluenesulfonic acid (20 mg), and benzene (30 ml) was refluxed under N_2 for 30 min. The cooled solution was washed with water and brine, dried ($MgSO_4$), and concentrated *in vacuo*. Crystallization of the residue from ether gave 172 mg (91.7%) of **27**, mp 112–115.5°. An analytical sample was obtained: mp 113.5–115.5°; uv (EtOH) end absorption, λ_{max} 243 mμ (ε 15,950), 273 (10,150), 293 (7000), and 302 (6450); ir (Nujol) 1705, 1695, and 1675 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 270 (37), 228 (100), 186 (53), ad 185 (33); nmr ($CDCl_3$) δ 1.90 [s, 3, $CH_3(C=O)$-N-1], 2.50 [s, 3, $CH_3(C=O)$-N-10], 4.69 (sextet, 1, $J_{gem} \cong -13$ Hz, $J_{e,e} \cong$ 3 Hz, C-2 equatorial), 7.39 (m, 3, C-6–8), and 8.42 (m, 1, C-9).

Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.98; H, 6.58; N, 10.54.

3,4-Dihydro-9-methylcarbazol-1(2H)-one Oxime (9).—A mixture of 2[18] (112.2 g, 0.563 mol), hydroxylamine hydrochloride (59.4 g), anhydrous sodium acetate (76.6 g), water (510 ml), and ethanol (2100 ml) was refluxed under N_2 for 18 hr and cooled in an ice bath. The crystalline product was collected by filtration, washed with water, and dried to give 106.3 g (87.9%) of **9**, mp 183–185° (lit.[18] mp 185–186°).

3,4-Dihydro-9-methylcarbazol-1(2H)-one Oxime *p*-Toluenesulfonate (10).—A solution of **9** (112.2 g, 0.524 mol) and *p*-toluenesulfonyl chloride (198 g, 1.05 mol) in pyridine (6 l.) was prepared at 0°, stored under N_2 at ambient temperature in the dark for 98 hr, and poured into ice–water (12 l.). This mixture was stirred for *ca.* 1 hr and the crystalline product was collected by filtration, washed with water, dried, and recrystallized from EtOAc–Skellysolve B to give 161.8 g (84.1%) of **10**, mp 119.5–121.5°. An analytical sample was obtained: mp 120–121.5°; uv (EtOH) end absorption, λ_{max} 207 mμ (ε 29,600), 226 (26,350), and 310 (26,050), and inflections at 243 (16,700), 274 (3450), and 345 (6500).

Anal. Calcd for $C_{20}H_{20}N_2O_3S$: C, 65.19; H, 5.47; N, 7.60; S, 8.70. Found: C, 65.15; H, 5.39; N, 7.64; S, 8.53.

3,4,5,10-Tetrahydro-10-methylazepino[2,3-*b*]indol-2(1H)-one (16).—A solution of 10 (153.7 g, 0.417 mol) in benzene (1.5 l.) was adsorbed on a column of neutral alumina (15 kg) which had been deactivated with 0.4% water. The column was developed with 32 l. of benzene and eluted with 10 l. of $CHCl_3$ followed by 25 l. of 20% MeOH–80% $CHCl_3$. The combined product was chromatographed on silica gel (4.5 kg) with 60% EtOAc–40% cyclohexane. The product obtained from this column was dissolved in MeOH–EtOAc, decolorized with Darco G-60, and crystallized from EtOAc to give 20.6 g (23.1%) of **16**, mp 189–191°. An analytical sample was obtained: mp 193–194.5°; uv (EtOH) λ_{max} 232 mμ (ε 30,500) and 297 (13,800) and inflections at 211 (29,250) and 292 (12,700); ir (Nujol) 3200, 3110 (NH), and 1670 cm^{-1} (C=O); nmr [$(CD_3)_2SO$] δ 3.6 (s, 3, CH_3N), 7.21 (m, 4, C-6–9), and 9.7 (s, 1, NH).

Anal. Calcd for $C_{15}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.89; H, 6.58; N, 13.22.

3,4,5,10-Tetrahydro-10-methylazepino[2,3-*b*]indol-5a(2H)-ol (35).—Compound **16** (17.7 g, 0.0824 mol) was added under N_2 to an ice-cold, stirred suspension of $LiAlH_4$ (18 g) in tetrahydrofuran. The resulting mixture was refluxed for 18 hr, cooled in an ice bath, and treated successively with water (18 ml), 15% aqueous NaOH (18 ml), and water (54 ml). This mixture was stirred for 1.5 hr and filtered. The filtrate was concentrated under reduced pressure. An EtOAc solution of the residue was allowed to stand at ambient temperature for 3 hr and was then cooled in an ice bath and acidified with methanolic hydrogen chloride. The precipitate was collected by filtration and dried to give 14.7 g (70.6%) of **35** hydrochloride, mp 268–269°. An analytical sample was obtained: mp 264.5–265°; uv (EtOH) λ_{max} 219 mμ (ε 20,550), 271 (5930), 278 (5810), 296 (4120) and 222 (inflection, 20,000); ir (Nujol) 3120, 3000 (OH and N^+H), and 1675 cm^{-1} ($C=N^+$); mass spectrum *m/e* (rel intensity) 216 (100), 199 (7.1), 188 (69), and 160 (34); nmr (D_2O) δ 3.64 (s, 3, CH_3N), 3.82 (q, 1, $J \cong -13$ and 4 Hz, C-2 equatorial), 4.40 (q, 1, $J \cong -13$ and 10 Hz, C-2 axial), and 7.60 (m, 4, C-6–9).

Anal. Calcd for $C_{13}H_{17}ClN_2O$: C, 61.77; H, 6.78; Cl, 14.03; N, 11.09. Found: C, 61.69; H, 6.91; Cl, 14.05; N, 11.12; H_2O, <0.1.

A solution of **35** hydrochloride in water was cooled in an ice bath, made alkaline with NaOH, and extracted with ether. The extract was washed with brine, dried (K_2CO_3), and concentrated *in vacuo*. The residue was crystallized from EtOAc to give **35**: mp 129–133°; uv (EtOH) λ_{max} 217 mμ (ε 24,050), 277 (13,650), and 302 (inflection, 2700); ir (Nujol) 3180 (OH) and 1665 cm^{-1} (C=N); nmr [$(CD_3)_2SO$] δ 3.00 (s, 3, CH_3N), 3.39 (q, 1, $J \cong -12.5$ and 4 Hz, C-2 equatorial), 4.14 (q, 1, $J \cong -12.5$ and 10.5, C-2 axial), 5.82 (s, 1, OH), and *ca.* 6.91 (m, 4, C-6–9).

Anal. Calcd for $C_{15}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 71.83; H, 7.78; N, 12.75.

1-Ethyl-1,2,3,4,5,10-hexahydro-10-methylazepino[2,3-*b*]indole (29) Hydrochloride, 1-Acetyl-1,2,3,4,5,10-hexahydro-10-methylazepino[2,3-*b*]indole (30), 3,4,5,10-Tetrahydro-10-methylazepino[2,3-*b*]indol-5a(2H)-ol Acetate Ester (36), and 1-Acetyl-2,3,4,5,10,10a-hexahydro-10-methylazepino[2,3-*b*]indol-5a(1H)-ol (33).—A mixture of **35** (5.00 g, 0.0231 mol), 10% palladium-on-carbon catalyst (2.5 g), and acetic anhydride (500 ml) was hydrogenated at an initial pressure of 30 psi for 8 hr and allowed to stand under hydrogen without shaking for an additional 16 hr. The catalyst was removed by filtration through Celite, the solid was washed with EtOAc, and the combined filtrate was concentrated *in vacuo*. The residue was dissolved in xylene and concentrated to remove last traces of acetic anhydride. This residue was chromatographed on silica gel (250 g). The first two compounds were eluted from the column with 30% EtOAc–70% cyclohexane. A solution of the first compound in EtOAc was

(25) This material was a mixture of two isomers; the two sets of peaks are indicated.

(26) This material was a mixture of isomers; peaks assigned to the minor isomer are in brackets.

acidified with methanolic hydrogen chloride and the salt was crystallized from EtOH–EtOAc to give 1.12 g, mp 211–212° dec, and 0.344 g, mp 207.5–5–208.5° dec (23.9%), of **29** hydrochloride. An analytical sample was obtained: mp 209–210° dec; uv (EtOH) λ_{max} 219 mμ (ε 17,700), 276 (8550), 283 (8700), and 293 (inflection, 7650); ir (Nujol) 1640 cm^{-1} (C=N⁺); mass spectrum *m/e* (rel intensity) 228 (100), 213 (6.5), 200 (34), 199 (34), and 171 (16); nmr [$(CD_3)_2SO$–D_2O] δ 1.42 (t, 3, J = 7 Hz, CH_3CH_2N), 3.69 (s, 3, CH_3N), 3.87 (q, 2, J = 7 Hz, CH_3CH_2N), and 7.39 (m, 4, C-6–9).

Anal. Calcd for $C_{15}H_{21}ClN_2$: C, 68.03; H, 7.99; Cl, 13.39; N, 10.58. Found: C, 67.73; H, 7.89; Cl, 13.46; N, 10.10.

The second compound eluted from the column was crystallized from EtOAc–Skellysolve B to give 1.42 g (25.4%) of **30**, mp 130–132.5°. The analytical sample was crystallized from EtOH–Skellysolve B: mp 125–125.5°; uv (EtOH) λ_{max} 226 mμ (ε 40,000), 285 (9290), 293 (8100), and 279 (inflection, 8560); ir (Nujol) 1670 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 242 (100), and 199 (77); nmr [$(CD_3)_2SO$] δ 1.81 [s, 3, CH_3(C=O)N], 3.59 (s, 3, CH_3N), 4.56 (sextet, 1, $J \cong -13$ and 3 Hz, C-2 equatorial), and 7.31 (m, 4, C-6–9).

Further elution of the column with EtOAc gave a mixture of two additional compounds which was rechromatographed on silica gel (150 g) with 2% Et_3N–23% cyclohexane–75% EtOAc.

The first compound eluted from this column was crystallized from EtOAc–Skellysolve B to give 0.408 g (6.87%) of **36**, mp 108.5–110°. An analytical sample was obtained: mp 105–108°; uv (EtOH) λ_{max} 217 mμ (ε 23,430), 277 (15,070), and 311 (2450); ir (Nujol) 1740 [CH_3(C=O)O] and 1675 cm^{-1} (C=N); mass spectrum (high resolution) *m/e* 258.1369; nmr ($CDCl_3$) δ 2.04 [s, 3, CH_3(C=O)O], 3.13 (s, 3, CH_3N), 3.72 (m, 2, C-2), and 6.91 (m, 4, C-6–9).

Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.61; H, 7.04; N, 10.36.

The second compound eluted from the column was crystallized from EtOAc–Skellysolve B (Darco) to give 0.169 g (2.81%) of **33**, mp 139–141°. An analytical sample was obtained: mp 141.5–142.5°; uv (EtOH) end absorption, λ_{max} 250 mμ (ε 12,950) and 306 (2625); ir (Nujol) 3280 (OH), and 1615 cm^{-1} (C=O); mass spectrum (high resolution) *m/e* 260.1514 (M^+) and 242.1429 ($M^+ - 18$); nmr ($CDCl_3$)[27] δ 2.18, 2.23 [s, 3, CH_3(C=O)N], 2.68, 2.72 (s, 3, CH_3N), 5.85, 5.20 (s, 1, C-10a), and 6.89 (m, 4, C-6–9).

Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 68.96; H, 7.86; N, 10.71.

1-Acetyl-1,2,3,4,5,10-hexahydro-10-methylazepino[2,3-*b*]indole (30).—A solution of **33** in benzene was treated with a few crystals of *p*-toluenesulfonic acid, stirred at ambient temperature under N_2 for 30 min, and poured into water. This mixture was extracted with ether; the extract was washed with water, dried (K_2CO_3), and concentrated. Crystallization of the residue from Et_2O–Skellysolve B gave **30**, mp 126.5–127.5°. This material was identical to the authentic sample by mixture melting point and ir and uv comparison.

(27) This material was a mixture of two isomers; the more intense peaks are listed first.

Registry No.—**3,** 23240-49-5; **5,** 14384-39-5; **6,** 23240-51-9; **7,** 23240-52-0; **10,** 23240-53-1; **11,** 23240-54-2; **12,** 23240-55-3; **13** hydrochloride, 23240-56-4; **14,** 23240-57-5; **15,** 23240-58-6; **16,** 23240-59-7; **17,** 23240-60-0; **17** hydrochloride, 23240-61-1; **17** hydrobromide, 23240-62-2; **18,** 23240-63-3; **19** hydrochloride, 23240-64-4; **20** hydrochloride, 23240-65-5; **21,** 23240-66-6; **22,** 23240-67-7; **23,** 23231-29-0; **24** hydrochloride, 23231-00-7; **25,** 23231-01-8; **26,** 23231-02-9; **27,** 23231-03-0; **29** hydrochloride, 23231-04-1; **30,** 23231-05-2; **31,** 23263-76-5; **32,** 23231-06-3; **33,** 23231-07-4; **34,** 23240-68-8; **35,** 23231-08-5; **35** hydrochloride, 23231-09-6; **36,** 23231-10-9.

Acknowledgment.—The author is indebted to Dr. A. A. Forist and his associates for physical and analytical data. In particular the author is grateful to Dr. M. Grostic for helpful discussions with regard to the mass spectra, to Mr. F. A. MacKellar for special nmr studies, and to Dr. D. J. Duchamp for carrying out the X-ray crystallographic study. The author is also indebted to Mr. D. B. Hooker and Mr. J. R. Greene for laboratory assistance.

The Mannich Reaction of Imidazoles

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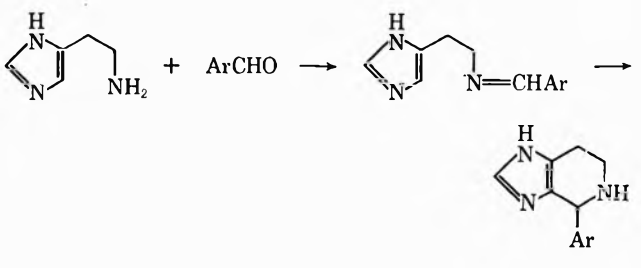
Received August 4, 1969

In the Mannich reaction of imidazoles, the ring is shown to be reactive at the four possible sites, the 1, 2, 4, and 5 positions. Only N-substituted imidazole Mannich bases are formed in acidic media. Both N-substituted and C-substituted products are formed in basic media. The process of N substitution is reversible in base, while C substitution is irreversible, resulting in the accumulation of C-substituted products over time in basic media. The 1 position is most reactive, with the 4 and 5 positions more reactive than the 2 position. Imidazoles having substituents at the 1 position do not react in the Mannich reaction. A mechanism is proposed which explains the behavior of the imidazole ring in the Mannich reaction.

The chemistry of imidazoles has considerable significance owing to the occurrence of this ring system in various biologically important compounds. Some 4-disubstituted aminomethyl imidazoles prepared by Turner, Huebner, and Scholz[2] in a multistep process were shown to have antihistaminic action, while others imitated histamine. It was of interest to study the Mannich reaction as a one-step method of introducing aminomethyl groups on to the imidazole ring.

Part of the rationale for studying the Mannich reaction of imidazoles grew out of our findings on the related facile base-catalyzed cyclization of histamine

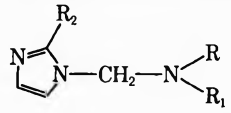


(1) (a) To whom all inquiries should be addressed. (b) This work was supported in part by the Public Health Service, National Institute of General Medical Sciences, Grant GM 10612-06.

(2) R. A. Turner, C. F. Huebner, and C. R. Scholz, *J. Amer. Chem. Soc.*, **71**, 2801 (1949).

TABLE I

N-SUBSTITUTED MANNICH BASES[a]

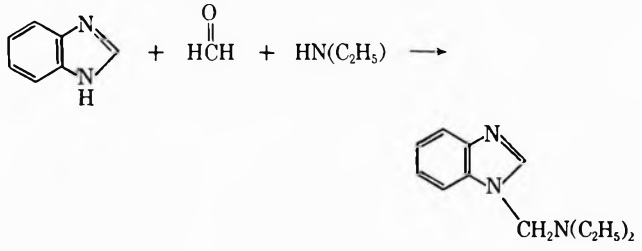


Registry no.	R	R_1	R_2	Nmr chemical shifts[b] 2 proton	4 proton	5 proton	CH_2 protons	Yield,[c] %	Bp (mm) or mp, °C
23230-39-9	CH_3	CH_3	H	7.60	7.15	7.04	4.68	82	95 (1.5)[d]
23230-40-2	CH_3	$C_6H_5CH_2$	H	7.45	7.04	6.94	4.71	94	73.5–75[e]
23230-41-3	$C_6H_5CH_2$	$C_6H_5CH_2$	H	7.40	7.12	6.94	4.78	90	67–68[e]
23230-42-4	N-RR_1 = piperidino		H	7.54	7.08	6.98	4.70	70	*f–h*
23230-43-5	N-RR_1 = morpholino		H	7.45	7.04	6.96	4.64	84	69–71[e,i]
23230-44-6	*j*		H	7.45	7.02	6.92	4.64	62	159–60[k]
23230-45-7	N-RR_1 = piperidino		CH_3	...	6.80	6.80	4.43	84	*f, l, m*
23230-46-8	*j*		CH_3	...	6.84	6.84	4.47	74	135.5–137[e]

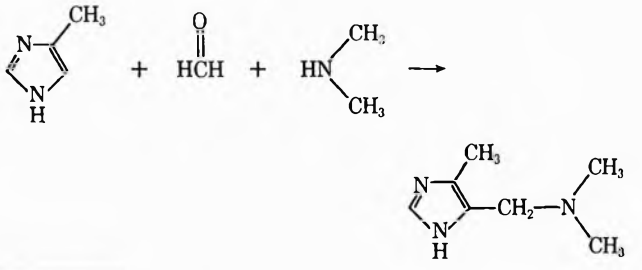
[a] Satisfactory analytical data (±0.3%) were obtained for these compounds (Ed.). [b] Shift values (δ 0) were determined in $CDCl_3$ with tetramethylsilane as an internal reference. [c] Crude yield. [d] $n^{23}D$ 1.4950. [e] Recrystallized from ligroin. [f] Separated by falling-film molecular distillation at 1.5 mm. [g] Pot temperature 97.2° (1-propanol). [h] $n^{23}D$ 1.5206. [i] Hygroscopic. [j] Piperazino-1,4-bis compound. [k] Recrystallized from benzene. [l] Pot temperature 80.1° (benzene). [m] $n^{23}D$ 1.5155.

Schiff bases.[3] The cyclization step is catalyzed by base.

Imidazole, 2-ethylimidazole, and 2-methyl-4,5-diphenylimidazole were initially reported as unreactive under normal Mannich reaction conditions by Bachman and Heisey[4] in 1946. Benzimidazole was reported to give Mannich bases substituted on the 1 position as shown.



Imidazole itself has four possible sites of reaction, the 1, 2, 4, and 5 positions. Heath, Lawson, and Rimington,[5] in 1951, reported substitution on the 5(4) position of the imidazole ring in the Mannich reaction on 2-mercapto-4(5)-methylimidazole. No proof of the site of the substitution was offered for the product. In 1952, Kato, Morkawa, and Suzuki[6] reported the reaction of imidazole and 4(5)-methylimidazole in the Mannich reaction with dimethylamine, giving a 4(5)-substituted product.



We now report that the Mannich reaction is successful at all four possible positions of the imidazole ring, and we describe factors affecting the orientation of substitution on the ring.

Results

Imidazoles unsubstituted at the 1 position readily undergo the Mannich reaction under conventional conditions. The classical, acidic conditions favor the formation of N-substituted imidazole Mannich bases (see Table I). These compounds were identified as N-substituted Mannich based primarily by nmr studies. The structural assignments were made on the basis of the singlet peak, owing to the methylene hydrogens of the substituted aminomethyl group, which appeared at *ca.* δ 4.7 in each nmr spectrum. The observed chemical shift is in good agreement with a theoretical value of δ 4.77 for the methylene hydrogens in a 1-substituted product, calculated by using shielding constants[7] and a spectrum of 1-benzylimidazole, and the observed shift is considerably different from the predicted value of δ 3.5[8] for C-substituted Mannich bases. The assignments are further supported by the absence of an imino hydrogen peak and by the 1:1 ratio of the methylene peak area to the peak area of the 4- and 5-position imidazole hydrogens.

Examination of nmr spectra of some crude 2-methylimidazole Mannich reaction mixtures produced in basic media indicated resonances expected of C substitution and peak area ratios consistent with a mixture composed of mono-, di-, and trisubstitution products.

By conducting reactions in basic conditions, using various alkyl-substituted imidazoles, the imidazole ring is shown to be reactive in the Mannich reaction at all four available positions. Some representative C-substituted Mannich bases have been isolated which illustrate substitution at each position. (See Table II.) The assignments of structures of the C-substituted prod-

(3) F. Stocker, M. Fordice, J. Larson, and J. Thorstenson, *J. Org. Chem.*, **31**, 2380 (1966).

(4) G. B. Bachman and L. V. Heisey, *J. Amer. Chem. Soc.*, **68**, 2496 (1946).

(5) H. Heath, A. Lawson, and C. Rimington, *J. Chem. Soc.*, 2217 (1951).

(6) T. Kato, T. Morkawa, and Y. Suzuki, *J. Pharm. Soc. Jap.*, **72**, 1177 (1952).

(7) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1963, p 141.

(8) This value was indicated by shielding-constant calculations and was experimentally verified after synthesis of 4-(diethylaminomethyl)imidazole from 4(5)-hydroxymethylimidazole by the method of Turner, Huebner, and Scholz.[2]

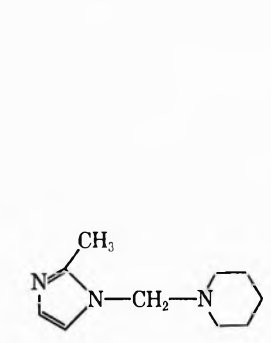
TABLE II
C-SUBSTITUTED IMIDAZOLE MANNICH BASES[a]

Imidazole	Registry no.	Substituent groups	Mp, °C	Methylene hydrogens[b]
2-Methyl-	23230-47-9	1,4,5-Tris(N-piperidinomethyl)	92–93	4.59, 3.53, 3.41
2-Methyl-	23230-48-0	4,5-Bis(N-piperidinomethyl)	149–150	3.43, 3.43
2-Methyl-	23230-49-1	4(5)-(N-Piperidinomethyl)	204–207[c]	3.52
4,5-Dimethyl-	23230-50-4	2-(N-Diethylaminomethyl)	112–113.5	3.54
2,4(5)-Dimethyl-	23230-51-5	5(4)-(N-Diethylaminomethyl)	75–77	3.48

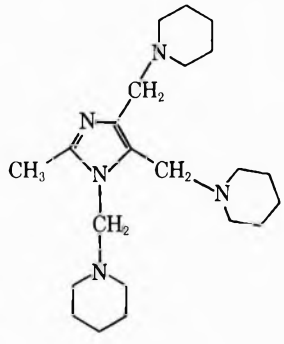
[a] Satisfactory analyses (±0.3%) were obtained for all compounds (Ed.). [b] Nmr shift values (δ 0) of aminomethylene hydrogens of substituent groups were determined in $CDCl_3$ using tetramethylsilane as an internal reference. [c] Melting point of dipicrate.

ucts were made by analysis of their nmr spectra and particularly the presence of methylene proton resonance in the δ 3.4–3.7 region. Table II shows the key aminomethylene shift values from the nmr spectra.

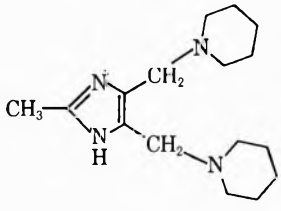
There are six possible products of a Mannich reaction between 2-methylimidazole, piperidine, and formaldehyde. Three of these products have been isolated and purified: 2-methyl-1-(N-piperidinomethyl)imidazole (I), 2-methyl-1,4,5-tris(N-piperidinomethyl)imidazole (II), and 2-methyl-4,5-bis(N-piperidinomethyl)-imidazole (III). A fourth compound, 2-methyl-4(5)-(N-piperidinomethyl)imidazole (IV), was isolated, but it failed to crystallize as the free base, thus making it necessary to form a derivative, the dipicrate, and crystallize it in the salt form.



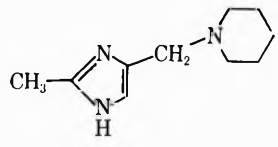
I



II



III



IV

The purification of C-substituted Mannich bases is difficult, chiefly because of the formation of multiple reaction products having similar physical and chemical properties. The simple N-substituted products are less associated and therefore more volatile than the other products and therefore they could sometimes be isolated by ordinary vacuum distillation or falling-film molecular distillation. Elution chromatography using an alumina column and a benzene–chloroform eluent effected the separation of some of the C-substituted products. Because of the difficulty of product separation, the Mannich reaction of imidazoles is most useful in the preparation of N-substituted Mannich bases, which can be isolated by distillation procedures, and for imidazoles that have a limited number of available sites, which restricts the number of reaction products.

A systematic study was made of the effect of pH on the position or substitution on the imidazole ring in the Mannich reaction. Diethylamine was used as the amine reagent and three imidazole compounds were used: imidazole, 2-methylimidazole, and 2,4-dimethylimidazole. Six reactions over a range of pH were run with each imidazole compound. No significant change in pH was observed during the reaction. Table III summarizes the results of this study in terms of per cent substitution on the carbon positions out of the total amount of substitution. The data were obtained from nmr spectra by comparing the areas of methylene hydrogen peaks owing to C substitution and N substitution.

TABLE III[a]
PER CENT C SUBSTITUTION *vs.* pH

pH (±0.07)	1.00	5.00	7.00	9.00	11.00	12.00
Imidazole	0	0	8	16	23	29
2-Methylimidazole	0	0	0	44	94	94
2,4-Dimethylimidazole	0	0	18	91	94	91

[a] 24 hr allowed for reaction.

It is evident from the pH study that only nitrogen-site substitution of the imidazole ring occurs in the acidic pH range. In basic reaction media, C substitution reaches significant proportions within the 24 hr allowed for reaction; nmr spectra of the products show the carbon positions to be the most substituted, except in the case of imidazole itself, in which 1 substitution still predominates. The statistical factor of the number of available sites apparently is not a significant factor; imidazole showed the least amount of C substitution, although it has a 3:1 ratio of available carbon to nitrogen sites. The 4 and 5 positions are more reactive than the 2 position, but experiments with 4,5-dimethylimidazole indicate that, when the 4 and 5 positions are blocked, the 2 position is reactive and follows the same general pattern of increased reactivity in basic media.

The formation, in basic conditions, of N-substituted imidazole Mannich products is a readily reversible process. A sample of 2-methyl-1-(N-piperidinomethyl)-imidazole in aqueous solution at pH 11.9 underwent reversal to reactants and reacted again until *ca.* 50% of the aminomethyl groups were substituted on the 4 and 5 positions within a 24-hr period. It could not be determined with certainty whether N-substituted products reverse in acid, although change in site of substitution or loss of substitution owing to such reversal was discovered to be less than 5% in 24 hr at pH 0.7. The formation of C-substituted imidazole Mannich bases is an irreversible process in basic conditions. A sample of 4-diethylaminomethylimidazole in aqueous solution at pH 11.8 for 24 hr showed no change of sub-

stitution site and no loss of substitution. This combination of irreversible C substitution and reversible N substitution in basic conditions results in an accumulation of C-substituted products and a decrease in N substitution over a period of time. A time study following the progress of the Mannich reaction of diethylamine with formaldehyde and 2-methylimidazole, at pH 12.3 using nmr analysis, indicated that the nitrogen position is the most reactive position in basic as well as acidic media, but C substitution reaches substantial proportions owing to the steady accumulation at the carbon positions as the reversal of N substitution provides reactants. The formation of C-substituted products is not due to an internal-shift mechanism, because complete loss of aminomethyl groups is seen during N-substitution reversal when a volatile amine is used.

The percentages of carbon- *vs.* nitrogen-site substitution can easily be determined from the nmr spectra of reaction mixtures, but the information obtainable from the spectra is neither sufficient nor accurate enough in most cases to determine the percentages of the actual compounds contained in the mixtures. Several combinations of variously substituted Mannich bases and unreacted imidazole could account for the observed peaks and integration ratios. The exact percentages reported in the pH study using diethylamine cannot be extended to reactions involving other amines, although the trend of high pH favoring C-substituted products is generally applicable.

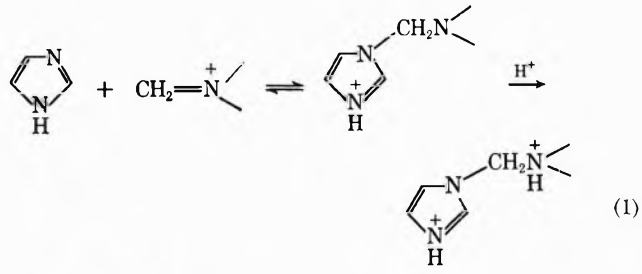
Experiments carried out on 1-alkyl-substituted imidazoles indicate that the 1 position of the imidazole ring must be unsubstituted for the Mannich reaction to be successful. Mannich reactions were attempted in both acidic and basic media on 1-methylimidazole, 1-benzylimidazole, 1-benzyl-2-methylimidazole, and 1,2-dimethylimidazole. In all cases, the imidazole compound was recovered unreacted.

Kato's[6] procedure in the Mannich reaction of imidazole with dimethylamine in acidic media was repeated and a 1-substituted product was obtained instead of the 4(5)-substituted product he reported. The nmr spectrum of the crude reaction mixture indicated N substitution, with no peaks that could be attributed to the resonance of methylene protons of a C-substituted product. Moreover, we were unable to prepare the picrate he reported, thereby casting some doubt on the formation of a 4(5)-substituted Mannich base in his procedure. However, we suggest that a C-substituted product may have been obtained if the reaction products were to remain long enough in conditions favoring reversal of N-substituted products and formation of C-substituted products.

Discussion

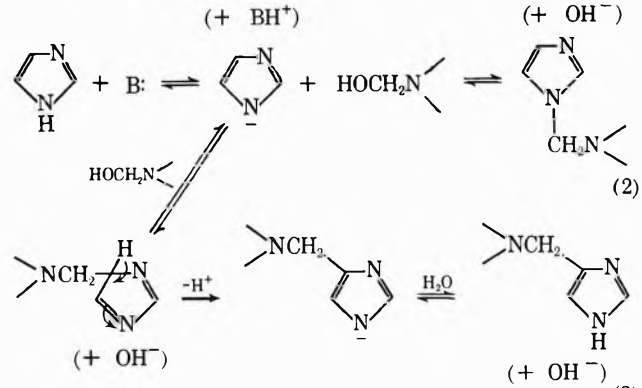
Cummings and Shelton[9] postulated from their kinetic study of cyclohexanone in the Mannich reaction that the reaction in basic media involves the condensation of a carbanion, derived from the active hydrogen compound, with an aminomethylol, R_2NCH_2OH, formed from the amine and formaldehyde. In acidic media, they suggested that the reaction involves the reaction of a carbonium ion, $R_2NCH_2^+ \leftrightarrow R_2\overset{+}{N}CH_2$, derived from the aminomethylol or methylene bisamine formed in reaction between the amine and formaldehyde, with the active hydrogen compound. Assuming the mechanistic steps of Cummings and Shelton in forming the aminomethyl intermediates, we propose the following processes for the final step in the mechanisms of the Mannich reaction of imidazoles, in explanation of the behavior of the imidazole ring in the reaction.[10]

In acid, eq 1 is proposed.



(1)

In base, eq 2 and 3 are proposed.



(2)

(3)

In acidic media, the experimental evidence indicates that substitution occurs only at the 1 position. In the proposed mechanism (eq 1), the cationic imine reacts at the electron-rich basic nitrogen site of the neutral imidazole molecule, which is in equilibrium with the protonated imidazole in acid. As shown experimentally, the final step of nitrogen-site substitution in acid may be slightly reversible, with reversal requiring a free amino group and a protonated imidazole ring.

Experimental observations showing that the 1 position of the imidazole ring must be unsubstituted for the Mannich reaction to be successful imply that the imidazole anion, resulting from the loss of the imino proton, is the reactive species in the Mannich reaction mechanism which results in carbon-site substitution. No reaction occurs when formation of the anion is prohibited by substitution on the 1 position. If the imidazole anion is required for the mechanism of C substitution, C substitution would be expected to occur only in basic media, as is reported in this paper. In base, the reaction (eq 2) between the aminomethylol intermediate and the imidazole anion, which results in N substitution, is a reversible step, whereas C substitution (eq 3) is irreversible. As observed experimentally, in base the nitrogen position is substituted first, then C substitution occurs slowly as the N-substitution reversal supplies the imidazole anion. In the mechanistic scheme we propose, the equilibrium of eq 2 would be forced to the

(9) T. F. Cummings and J. R. Shelton, *J. Org. Chem.*, **25**, 419 (1960).

(10) A referee has suggested that, instead of the methylolamine itself, the imonium cation available from the reversible dissociation of the methylolamine might be the intermediate functioning in basic media.

left with increasing base strength, thereby increasing the proportion of C substitution. Thus, in base, N substitution is favored kinetically while C substitution is favored thermodynamically.

Experimental Section

General.—All nmr spectra were determined on a Jeolco C-60HL or a Varian A-60A spectrometer using $CDCl_3$ as a solvent with tetramethylsilane as an internal reference. Melting points are corrected. Microanalyses were by Galbraith Laboratories, Inc., Knoxville, Tenn. The crude products of imidazole Mannich reactions are typically pale yellow syrups. The 1-substituted Mannich bases were purified by vacuum distillation, falling-film distillation, or recrystallization (see Table I), depending on the specific properties of the product. Thermal decomposition is a serious factor during distillation of the liquid products if the temperature and pressure are allowed to exceed 100° and 1.5 mm. After separation from other products, C-substituted Mannich bases were purified by recrystallization from ligroin or benzene–ligroin. (The ligroin used in this work has a boiling range of 66–75°.) Given below are descriptions of representative reactions of the formation of a 1-substituted and a C-substituted Mannich base. The separate procedures for isolation of the C-substituted products from the crude mixtures are given.

2-(N-Diethylaminomethyl)-4,5-dimethylimidazole.—To a solution of 0.99 g (0.0135 mol) of $(C_2H_5)_2NH$ and 1.64 g (0.020 mol) of 37% formalin in 10 ml of H_2O, 1.30 g (0.0135 mol) of 4,5-dimethylimidazole in 10 ml of H_2O was added dropwise with stirring over 0.5 hr. Reaction was allowed to continue for 48 hr at room temperature without further stirring. The mixture was made distinctly alkaline with a 20% KOH solution, and the organic material was salted out with K_2CO_3 and extracted with three 10-ml portions of $CHCl_3$. The $CHCl_3$ extracts were combined, dried (K_2CO_3), and concentrated to give 1.20 g of a yellow, semicrystalline syrup. The syrup was taken up in 10 ml of absolute EtOH and combined with 1.10 g of HCl in dry EtOH, and the dihydrochloride was crystallized by addition of ether. The dihydrochloride (mp 214–217°, uncorrected) was recrystallized twice from EtOH–ether, and then the base was freed by addition of NaOH solution and extracted with $CHCl_3$. The free Mannich base was recrystallized from ligroin, then sublimed under vacuum at 100° to give white needles, mp 112–113.5°, yield 0.98 g (40%).

2-Methyl-1-(N-piperidinomethyl)imidazole.—To a solution of 4.10 g (0.05 mol) of 2-methylimidazole and 4.25 g (0.05 mol) of piperidine in 15 ml of H_2O was added, with cooling, 8.4 ml (0.10 mol) of 12 *N* HCl. The 37% formalin (4.86 g, 0.06 mol) was poured into the solution and the mixture was stirred for 1 hr. Reaction was allowed to continue for 24 hr at room temperature without further stirring. The mixture was made distinctly alkaline with a 20% KOH solution, and the organic material was salted out with K_2CO_3 and extracted with three 25-ml portions of $CHCl_3$. The $CHCl_3$ extracts were combined, dried (K_2CO_3), and concentrated to give 8.22 g (92%) of a pale yellow liquid which was purified by repeated treatment on a falling-film molecular still at 80.1° (benzene) and 1.5 mm.

2-Methyl-1,4,5-tris(N-piperidinomethyl)imidazole.—This compound was isolated from the crude product obtained by the nonacidic reaction process followed by extraction procedures by elution chromatography with an alumina column. A 60% $CHCl_3$–benzene solvent was used for elution, which on concentration yielded a yellow semisolid. Recrystallization from ligroin gave a white solid, mp 92–93°.

2-Methyl-4,5-bis(N-piperidinomethyl)imidazole.—This compound was eluted from the same column as the above trisubstituted product in later fractions of the 60% $CHCl_3$–benzene solvent. Thin layer chromatography was used to follow the progress of the elution chromatography. The product was isolated as a yellow semisolid which was recrystallized from benzene–ligroin to give light yellow crystals, mp 149–150°.

2-Methyl-4(5)-(N-piperidinomethyl)imidazole.—For this compound the general procedure was altered to use 2 equiv of 2-methylimidazole. After $CHCl_3$ extraction, the $CHCl_3$ solution was washed with H_2O to remove excess 2-methylimidazole. The yellow syrup was concentrated, taken up in benzene, and absorbed on an alumina column, and the products were eluted by a 60% $CHCl_3$–benzene solvent. This compound was eluted after the above tri- and disubstituted products. When it failed to crystallize as the free base, it was converted into the dipicrate, which was recrystallized from 95% EtOH, mp 204–207°.

5(4)-(N-Diethylaminomethyl)-2,4(5)-dimethylimidazole.—Following the general reaction and extraction procedures, the dipicrate was formed and recrystallized from 95% EtOH several times, mp 195–197°. The product was freed from the picrate and sublimed under vacuum at 100° to give white crystals, mp 75–77°.

General Reaction Procedure of pH Experiment.—Precooled 6 *N* HCl was added to a solution of 0.010 mol of the imidazole compound and 0.73 g (0.010 mol) of diethylamine in 3 ml of H_2O until the desired pH was reached. The 37% formalin (1.22 g, 0.015 mol) was poured into the solution with stirring, and reaction was allowed to continue for 24 hr at room temperature without further stirring. The mixture was made distinctly alkaline with 20% KOH solution and was extracted with four 4-ml portions of $CHCl_3$. The $CHCl_3$ extracts were combined and dried (K_2CO_3), and a nmr spectrum was run immediately on the $CHCl_3$ solution.

Registry No.—2-(N-Diethylaminomethyl)-4,5-dimethylimidazole dihydrochloride, 23263-75-4.

Acknowledgment.—We are indebted to Dr. James D. White, Harvard University, for helpful discussions in connection with this work, and to Research Corporation, New York, N. Y., for a grant in support of this research.

1,3-Dipolar Cycloaddition Reactions of the Geometrical Isomers of Some Methyl 1-Alkyl-2-(*p*-biphenyl)-3-aziridinecarboxylates[1]

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Received August 14, 1969

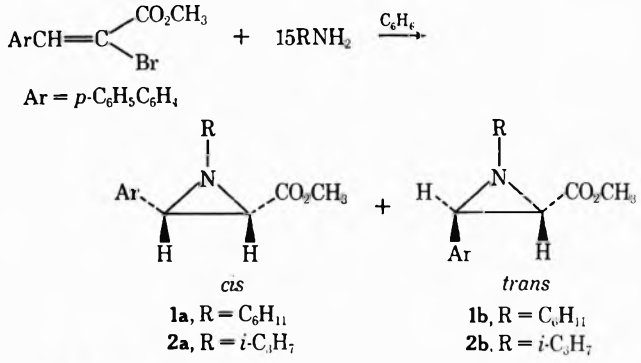
The *cis* and *trans* forms of methyl 1-cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate and methyl 1-isopropyl-2-(*p*-biphenyl)-3-aziridinecarboxylate react stereospecifically with activated alkenes and dimethyl acetylenedicarboxylate in refluxing benzene to produce pyrrolidines and Δ^3-pyrrolines, respectively. The base-catalyzed tautomerization of the Δ^3-pyrrolines to Δ^2-pyrrolines and the extremely facile epimerization of the kinetically favored H_2,H_5-*trans*-Δ^3-pyrrolines to the thermodynamically more stable H_2,H_5-*cis* isomers in methanol, chloroform, or refluxing benzene are described and a possible explanation of these results is presented. In benzene at 80° the aziridine esters equilibrate to a mixture containing 68–70% *cis*-aziridine and 30–32% corresponding *trans* isomer.

In a previous publication[4] we reported the thermolysis of methyl *cis*- and methyl *trans*-1-cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (**1a,b**) in refluxing benzene and methanol. The products of these cleavage reactions were believed to arise *via* a 1,3-dipolar intermediate (azomethine ylide) resulting from heterolytic scission of the C–C bond of the aziridine ring.[5] When aziridines **1a** and **1b** were heated to 80° in a benzene solution containing dimethyl fumarate, trimethyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrolidine-2,3,-4-tricarboxylate (**3a**) was produced in good yield. Reports of similar 1,3-dipolar cycloaddition reactions of aziridines with activated alkenes and alkynes have appeared in the literature.[6–10]

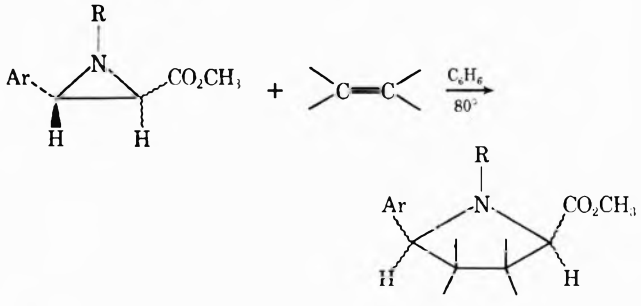
We now wish to report in detail the reaction of two pairs of *cis*-*trans*-aziridine esters (**1a,b** and **2a,b**) with several activated olefins and with one activated alkyne, the thermal equilibration of these aziridines, and the salient features of the ^1H nmr spectra of the cycloaddition products. Stereochemical assignment of the cycloadducts was made on the basis of pmr spectroscopy; the observed coupling constants are consistent with the Karplus correlation.[11]

Results

The aziridine esters **1a,b** and **2a,b** employed in this study were synthesized by reaction of a 15-fold excess of the primary amine with methyl α-bromo-*p*-phenylcinnamate in benzene. Stereochemical assignment of the *cis* and *trans* isomers are consonant with pmr, ir, and uv spectral data[12] (Table I).



In general, benzene solutions of equimolar quantities of the aziridine and the olefin were heated at reflux for 24–48 hr. After evaporation of the solvent the crude material was chromatographed to yield substituted pyrrolidines (Chart I).



In this manner both **1a** and **1b** afforded the pyrrolidines **3a,b** and **4a,b** when treated with dimethyl fumarate and dimethyl maleate, respectively. The stereochemical relationship of the protons at C_4 and C_5 in these adducts is readily ascertained by an examination of the pmr spectra. In both **3a** and **4a** one of the methoxycarbonyl proton resonance signals appears at 0.6 ppm higher field than those of the remaining two (δ 3.6–4.0). An inspection of models reveals that only the methyl group of the C_4 substituent can be oriented in the shielding cone of the phenyl nucleus, and this can occur only when the C_4 and C_5 substituents are *cis*. The observed couplings of 8.3–9.5 Hz are in good agreement with reported

(1) (a) Presented in part by N. H. Cromwell at the Second International Congress of Heterocyclic Chemistry, Montpellier, France, July 1969. (b) This work was supported in part by an ACS–PRF Graduate Fellowship held by P. B. W. and in part by a U. S. Public Health Service Grant CA-02931.

(2) Petroleum Research Foundation Fellow, 1968–1969.

(3) To whom inquiries should be addressed.

(4) P. B. Woller and N. H. Cromwell, *J. Heterocycl. Chem.*, **5**, 579 (1968).

(5) For other examples of aziridine rearrangements involving C–C bond scission of the aziridine ring, see (a) G. H. Coleman and G. P. Waugh, *Proc. Iowa State Acad. Sci.*, **40**, 115 (1933); **49**, 286 (1942); *Chem. Abstr.*, **29**, 2527 (1935); **37**, 5707 (1943); (b) A. Padwa and W. Eisenhardt, *Chem. Commun.*, **7**, 380 (1968); (c) S. V. Zovota, G. V. Loza, and M. Y. Lukina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 432 (1967); *Chem. Abstr.*, **67**, 21278 (1967); (d) B. K. Campbell and K. N. Campbell, *J. Org. Chem.*, **9**, 178 (1944).

(6) (a) H. W. Heine and R. E. Peavy, *Tetrahedron Lett.*, 3123 (1965); (b) H. W. Heine, R. E. Peavy, and A. J. Durbetaki, *J. Org. Chem.*, **31**, 3924 (1966); (c) H. W. Heine, A. B. Smith, III, and J. D. Bower, *ibid.*, **33**, 1097 (1968); (d) H. W. Heine and R. Henzel, *ibid.*, **34**, 171 (1969).

(7) (a) A. Padwa and L. Hamilton, *Tetrahedron Lett.*, 4363 (1965); (b) A. Padwa and L. Hamilton, *J. Heterocycl. Chem.*, **4**, 118 (1967).

(8) (a) R. Huisgen, W. Scheer, G. Szemies, and H. Huber, *Tetrahedron Lett.*, 397 (1966); (b) R. Huisgen, W. Scheer, and H. Huber, *J. Amer. Chem. Soc.*, **89**, 1753 (1967).

(9) The authors kindly thank Dr. J. A. Deyrup, University of Florida, for sending us a preprint of a paper submitted for publication.

(10) (a) F. Texier and R. Carrier, *Tetrahedron Lett.*, 823 (1969); (b) S. Oida and E. Ohki, *Chem. Pharm. Bull.* (Tokyo), **16**, 764 (1968); (c) J. W. Lown, R. K. Smalley, and G. Dallas, *Chem. Commun.*, 1543 (1968).

(11) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

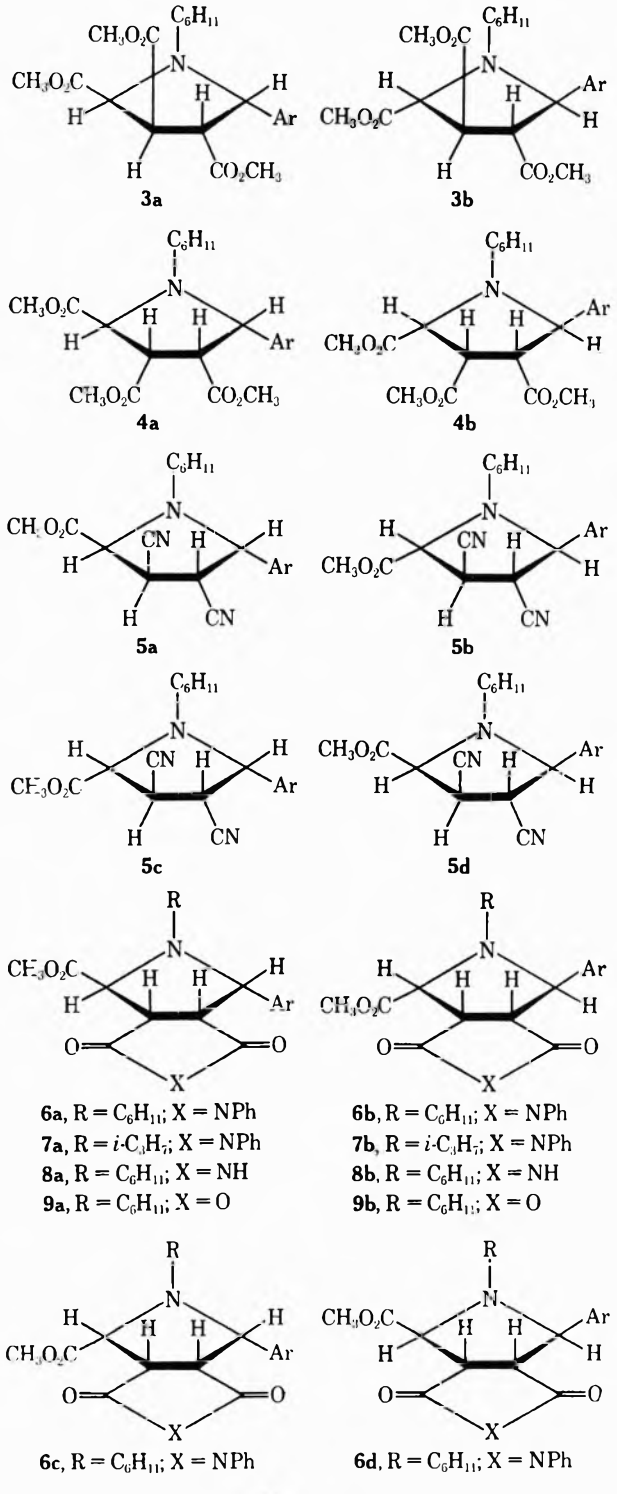
(12) A. E. Pohland, R. D. Badger, and N. H. Cromwell, *ibid.*, 4369 (1969).

TABLE I

SPECTRAL DATA OF METHYL 1-CYCLOHEXYL-2-(p-BIPHENYL)-3-AZIRIDINECARBOXYLATE, *cis* (**1a**) AND *trans* (**1b**)

Compd	Nmr (CDCl3) H_2, δ	Nmr (CDCl3) H_3, δ	Nmr (CDCl3) J, Hz	Ir $\nu_{C=O}$ cm^{-1} CCl4	Ir $\nu_{C=O}$ cm^{-1} Nujol	Uv (CH3OH) λ, mμ	Uv (CH3OH) ε
1a	2.88	2.49	7.0	1757, 1730	1747	257	23,900
1b	3.26	2.73	2.5	1734	1727	257	26,600

CHART I



values for *cis* vicinal couplings in pyrrolidines.[5b] On the other hand, adducts **3b** and **4b** exhibit three distinct signals for the methoxycarbonyl protons in the range δ 3.6–4.0; coupling constants ($J_{4,5}$) of 5.7 and 3.9 Hz for **3b** and **4b**, respectively, indicate C_4 H and C_5 H to be *trans* in these isomers. The pertinent chemical shifts and coupling constants (Table II) are consonant with the assigned stereochemistry.

The *cis*-aziridine **1a** and fumaronitrile afforded two isomeric adducts which were assigned the gross structure methyl 1-cyclohexyl-5-(*p*-biphenyl)-3,4-dicyanopyrrolidine-2-carboxylate (**5a**,**b**). Adducts **3a** and **5a** both exhibited unexpectedly large *trans* vicinal coupling constants for C_3H and C_4H ($J_{3,4}$ = 11.0–11.5 Hz). These values were confirmed by deuterium labeling, spin-decoupling experiments, and computer simulation.[13] Presumably in **3a** and **5a** steric repulsion between the substituents at C_2 and C_3 and at C_4 and C_5 distorts the skeleton in such a manner as to cause the C_3H–C_4H angle to increase to well above 120°. Attainment of this particular conformation is aided by relief of eclipsing of the protons and substituents at C_2 and C_5 with those at C_3 and C_4, respectively.[14] In the all-*trans* **3b** and **5b**, the steric interactions are minimized and *trans* vicinal couplings in these compounds are restored to their normal magnitude.[11]

N-Phenylmaleimide was found to react with the *cis*-aziridines **1a** and **2a** in refluxing benzene to produce the isomeric adducts **6a**,**b** and **7a**,**b**, respectively. Cycloadducts of the same stereochemistry were obtained from **1a** when it was allowed to react with maleimide and maleic anhydride.

In contrast to the reaction of the *trans*-aziridine **1b** with the maleate and fumarate esters, this same aziridine, on reacting with N-phenylmaleimide afforded, in addition to **6a** and **6b**, two additional products which were found to be isomeric with **6a**,**b**. Only one of the two new isomers could be obtained as a pure compound and was assigned the all-*cis* stereochemistry (**6c**). The fourth isomer was believed to have the H_2,H_3-*trans*-H_3,H_4-*cis*-H_4,H_5-*trans* configuration (**6d**). The pmr spectrum of cycloadduct **6c** did not exhibit the expected doublets for C_2 H and C_5 H, but rather a series of three evenly spaced resonance signals was observed for each proton with the outer two signals of greater intensity than the center signal. This type of splitting pattern is attributed to virtual coupling[15] arising from the fact that the chemical shifts of C_3 H and C_4 H are nearly identical.

The reaction of **1b** with fumaronitrile was followed by pmr spectroscopy and found to give a mixture of four isomeric adducts. The pmr spectrum of the crude material exhibited four distinct methyl ester resonance signals, two of which had chemical shifts identical with those resonances in **5a** and **5b**, respectively. The products from this reaction could not be separated by the conventional means but, by analogy

(13) A. A. Bothner-By and A. Castellano, LAOCN 3, Program III, Quantum Chemistry Program Exchange, Indiana University, Bloomington, Ind., 1968.

(14) A similar result has been observed in 2,3-disubstituted indoles: see C. Lagercrantz and M. Yhland, *Acta Chem. Scand.*, **16**, 1799 (1963); A. A. Bothner-By, *Advan. Magn. Resonance*, **1**, 205 (1965).

(15) J. I. Musher and E. J. Corey, *Tetrahedron*, **18**, 791 (1968).

TABLE II

CHEMICAL SHIFTS AND COUPLING CONSTANTS OF METHINE PROTONS[a]

Adduct	δ, ppm from $(CH_3)_4Si$				J, Hz		
	H_2	H_3	H_4	H_5	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
3a	4.50	3.95	4.13	4.89	6.9	11.5	9.5
3b	4.57	3.55[b]	3.70[b]	4.91	1.0	...[b]	5.7
4a	4.63	3.39	3.88	5.00	3.5	9.0	8.3
4b	4.28	3.53	3.16	5.07	6.3	10.0	3.9
5a	4.43	3.50	4.25	4.89	6.5	11.0	9.4
5b	4.44	3.46	3.24	4.81	0.8	3.0	6.6
6a	4.63	3.29	3.80	5.11	0.0	8.0	9.5
6b	4.53	3.77	3.32	4.92	8.7	10.0	5.4
6c	4.11	3.50[b]	3.65[b]	4.56	7.6	...[b]	8.8
7a	4.63	3.33	3.83	5.03	0.0	8.4	9.8
7b	4.53	3.75	3.36	4.85	8.7	10.3	5.4
8a	4.45	3.10	3.58	4.98	0.0	8.0	9.6
8b	4.49	3.70	3.26	4.86	8.8	10.0	5.4
9a	4.59	3.48	3.88	5.13	0.0	8.7	9.6
9b	4.44	...[c]	...[c]	4.80	8.3	...[c]	5.0
10a	5.17	...	...	5.60	...	$J_{2,5}$ = 7.0	...
10b	4.81	...	...	5.31	...	$J_{2,5}$ = 4.6	...
11a	5.15	...	...	5.58	...	$J_{2,5}$ = 7.0	...
11b	4.81	...	...	5.31	...	$J_{2,5}$ = 4.5	...
13a	...	...	3.73	5.00	...	...	5.4
13b	...	...	3.70	4.93	...	...	6.0
14a	...	...	4.43	5.26	...	...	13.0
14b	...	...	4.39	5.19	...	...	13.4

[a] Pmr spectra were determined at *ca.* 35° on a Varian Associates Model A-60 spectrometer as deuteriochloroform solutions with tetramethylsilane as internal standard (δ 0.0); decoupling experiments were performed on a Varian Associates Model A-60D spectrometer equipped with a Model V-6058A field sweep spin decoupler. [b] Chemical shifts of H_3 and H_4 were nearly identical, giving rise to complex multiplets; coupling constants were not determined. [c] Resonance signals for H_3 and H_4 were masked by those of **9a**.

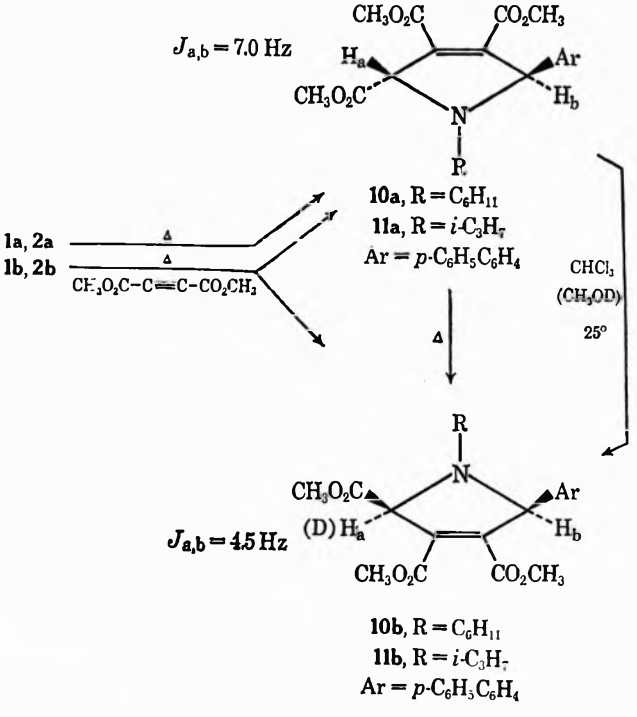
to **1b** and N-phenylmaleimide, were assigned the structures **5a**–**5d**.

The adducts obtained from reaction of 2 molar equiv of dimethyl acetylenedicarboxylate and 1 mol equiv of aziridines **1a,b** and **2a,b** in refluxing benzene were assigned the gross structure trimethyl 1-alkyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (**10a,b**, R = C_6H_{11}; **11a,b**, R = *i*-C_3H_7) (Scheme I). The pmr spectra of these compounds are unusual in that C_2 H and C_5 H exhibit long-range coupling constants in the range 4.5–7.0 Hz.[16]

Evidence for the Δ^3-pyrroline structure was obtained from the variety of reactions and rearrangements these compounds undergo (Scheme II). Thus oxidation of **10b** and **11b** with chloranil in boiling xylene produced the corresponding trimethyl 1-alkyl-5-(*p*-biphenyl)-pyrrole-2,3,4-tricarboxylates **12a** and **12b**. In methanol containing a catalytic amount of sodium methoxide, **10b** and **11b** were tautomerized to a mixture of the H_4,H_5-*trans* trimethyl 1-alkyl-5-(*p*-biphenyl)-Δ^2-pyrroline-2,3,4-tricarboxylate (**13a**, R = C_6H_{11}; **13b**, R = *i*-C_3H_7) and the corresponding H_4,H_5-*cis* isomer (**14a**, R = C_6H_{11}; **14b**, R = *i*-C_3H_7). The structure and stereochemistry of compounds **13a,b** and **14a,b** were assigned on the basis of pmr spectroscopy. Just as in the case of adducts **3a** and **4a**, the methoxycarbonyl protons at C_3 in **14a** and **14b** are shielded by *ca.* 0.8 ppm relative to the remaining methyl ester resonance signals (δ 3.81 and 4.00). Furthermore, the chemical shifts of C_4H and C_5H in **14a,b** and **13a,b** are as expected for the anisotropic effects exerted by the aryl and methoxycarbonyl groups on these protons in the two configurations. The observed coupling constants ($J_{4,5}$) of 5.4–6.0 and 13.0 Hz, in **13a,b** and **14a,b**, respectively, are also in support of the assigned stereochemistry. Deuterium was incorporated at C_4 in **13a,b** and **14a,b** when the tautomerization was conducted in methanol-d_1. Aluminum oxide (Woelm, neutral, activity grade I) induced isomerization of **10b** and **11b** to **14a** and **14b**, respectively.

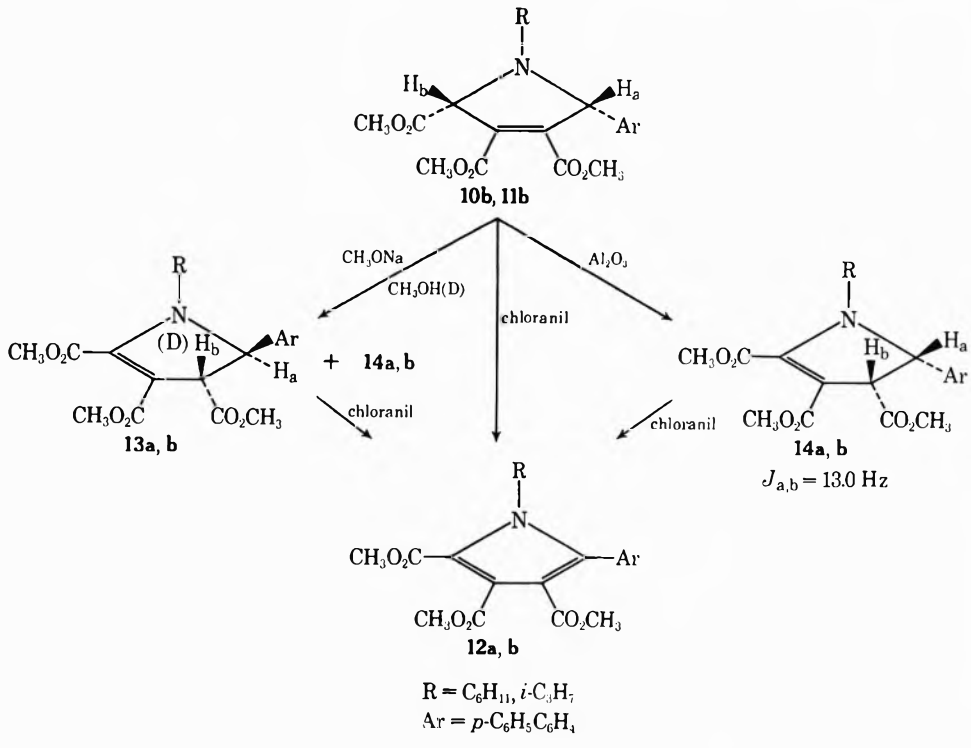
The reaction conditions had a pronounced effect on the proportions of **10a** (or **11a**) and **10b** (or **11b**) produced in the reaction of aziridines **1a,b** (or **2a,b**) with 2 molar equiv of dimethyl acetylenedicarboxylate

SCHEME I



(16) Long-range couplings of similar magnitude have been observed in Δ^3-pyrrolines by Huisgen and Deyrup (ref 9).

SCHEME II



in refluxing benzene. Thus, after a 24-hr period of reflux, aziridine **2b** and dimethyl acetylenedicarboxylate afforded a mixture of **11a** (50–60%) and **11b** (40–50%) at which time *ca.* 75% of the aziridine had been consumed. The corresponding *cis*-aziridine **2a** under identical reaction conditions also produced a mixture of the H_2,H_3-*trans* Δ^3-pyrroline **11a** (30–35%) and the H_2,H_3-*cis* Δ^3-pyrroline **11b** (65–70%) with greater than 90% of the aziridine having reacted.

Shorter periods of reflux (10–12 hr) resulted in an increase in the amount of **11a**, while only **11b** could be detected by pmr spectroscopy when the period of reflux was increased to 48 hr. Column chromatography (silica gel or Florisil) of a mixture of **11a** (80%) and **11b** (20%) resulted in isolation of only **11b** (80%). It was noted that, if chloroform or methanol solutions of the crude reaction mixtures containing both **11a** and **11b** were allowed to stand for 10–24 hr at room temperature, the sole detectable isomer was **11b**. In methanol-d_1, the same mixture of **11a** and **11b** afforded the H_2,H_5-*cis* Δ^3-pyrroline **11b** as a mixture of the deuterium-labeled and -unlabeled products. A pure sample of **11b** was recovered unchanged and without deuterium exchange after standing for 24 hr at room temperature in methanol-d_1. These results seem to suggest that the H_2,H_5-*trans*-Δ^3-pyrrolines **10a** and **11a** are readily epimerized to the corresponding H_2,H_5-*cis* isomers **10b** and **11b**, respectively, and that the epimerization occurs more rapidly in polar solvents. As a result, we have been unable to obtain pure samples of **10a** or **11a** and thus to establish whether or not the presence of unreacted aziridine or dimethyl acetylenedicarboxylate catalyzes the isomerization.

The thermal equilibration of aziridines **1a** and **1b** at 80° in benzene-d_6 was followed by pmr spectroscopy, and at equilibrium the mixture consisted of 38% *trans* and 62% *cis* isomer. These same aziridines were not epimerized by strong base. Solutions of **1a** and **1b** in an ether–methanol-d_1 mixture containing a catalytic amount of sodium methoxide were refluxed for 3 days. The respective isomers were recovered unchanged and without deuterium exchange at C_3.

Discussion

All of the aforementioned reactions of aziridines **1a,b** and **2a,b** with activated alkenes and dimethyl acetylenedicarboxylate conform to the concept of 1,3-dipolar cycloaddition reactions as proposed by Huisgen.[17] The thermal process of ring cleavage of aziridines involves stereospecific, conrotatory ring opening.[8b] Thus aziridines **1a** and **1b** would be expected to yield the azomethine ylides **15a** and **15b**, respectively (Scheme III). The ylides can either equilibrate and ring close back to the aziridines (path A)[8b,9] or, in the presence of an unsaturated substrate, undergo stereospecific reaction to form five-membered-ring heterocycles (path B).[17a] Most such reactions are known to be stereospecific and hence concerted.[17b] The results obtained from reaction of aziridines **1a** and **1b** with the fumarate and maleate esters alone confirm that these reactions also proceed stereospecifically.

The cycloaddition to dipolarophiles competes with the equilibration process. In the present investigation not even dimethyl acetylenedicarboxylate was reactive enough to supress the equilibration of the *cis* and *trans* aziridines. The fumarate and maleate esters were found to be of lowest reactivity, while fumaronitrile, maleimide, and N-phenylmaleimide were of about the same reactivity as the acetylene ester.

Orientation phenomena in 1,3-dipolar cycloaddition reactions have been discussed as an interplay of steric and electronic factors.[17b,c] In most instances, the 1,3 dipole reacted with unsymmetrically bonded dipolaro-

(17) (a) R. Huisgen, *Angew. Chem., Intern. Ed. Engl.*, **2**, 565 (1963); (b) *ibid.*, **2**, 633 (1963); (c) R. Huisgen, *J. Org. Chem.*, **33**, 2291 (1968).

TABLE III

ISOMER DISTRIBUTION IN CYCLOADDITION REACTIONS

Aziridine		Dipolarophile	Adduct[a] (%)
R	Configuration		
C_6H_{11}	*cis*	Dimethyl fumarate[b]	**3a** (70), **3b** (30)
C_6H_{11}	*trans*	Dimethyl fumarate[b]	**3a** (50), **3b** (50)
C_6H_{11}	*cis*	Dimethyl maleate[b]	**4a** (75), **4b** (25)
C_6H_{11}	*trans*	Dimethyl maleate[c]	**4a** (77), **4b** (23)
C_6H_{11}	*cis*	N-Phenyl maleimide[b]	**6a** (33), **6b** (67)
C_6H_{11}	*trans*	N-Phenyl maleimide[c]	**6a** (35), **6b** (10), **6c** (40), **6d** (15)
i-C_3H_7	*cis*	N-Phenyl maleimide[b]	**7a** (35), **7b** (65)
C_6H_{11}	*cis*	Fumaronitrile[c]	**5a** (50), **5b** (50)
C_6H_{11}	*trans*	Fumaronitrile[c]	**5a** (20), **5b** (20), **5c** (30), **5d** (30)
C_6H_{11}	*cis*	Maleimide[c]	**8a** (50), **8b** (50)
C_6H_{11}	*cis*	Maleic anhydride[c]	**9a** (70), **9b** (30)

[a] Per cent of isomer formed in reaction. [b] Based on total product isolated. [c] By electronic integration of appropriate resonance signals in the pmr spectrum of the crude reaction mixture.

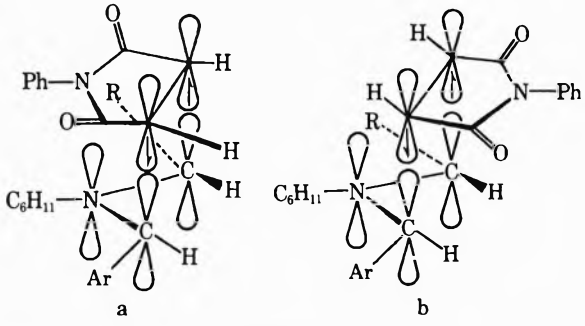
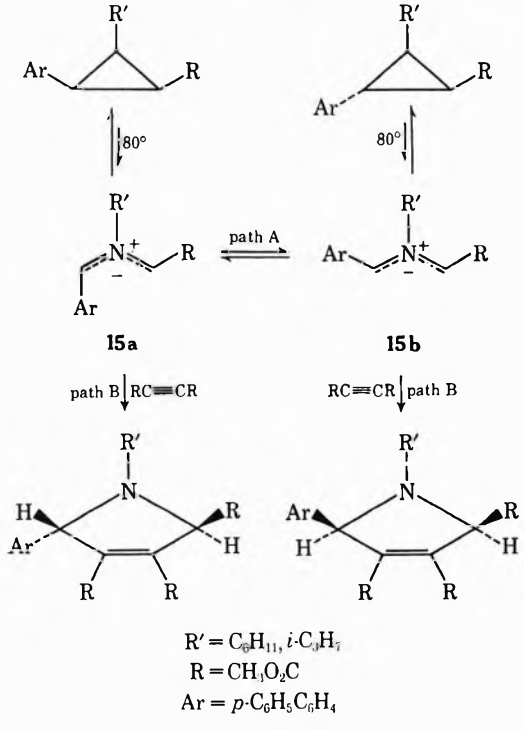


Figure 1.

philes which contained heteroatoms or which were of the alkene or alkyne series. Moreover, kinetic studies[17b] have amply demonstrated the influence of steric factors on the rates of these cycloaddition reactions. In the present investigation, each of the azomethine ylides would be expected to produce two adducts corresponding to two orientations of the 1,3 dipole and the dipolarophile in the activated complex

SCHEME III



leading to the transition state. It is interesting to note that, with the exception of N-phenylmaleimide, aziridine **1a** and the remaining dipolarophiles employed produced mainly that isomer in which the C_4 and C_5 substituents are *cis*. The reverse was observed with **1a** and N-phenylmaleimide (Table III). On the other hand, the corresponding *trans*-aziridine **1b** reacted with N-phenylmaleimide to afford the all-*cis* cycloadduct **6c** in major amount. Conrotatory ring opening of the *trans*-aziridines would be expected to proceed in such a manner as to minimize any steric compression of the ring substituents during the rotation process. Thus one might expect exclusive formation of ylide **15b** from either 1a or 2a. Figure 1 indicates the orientation of the 1,3 dipole and the dipolarophile (N-phenylmaleimide) required for formation of **6c** and **6d**, respectively. Approach of the two components as shown in Figure 1a would be expected to be severely hindered as a result of eclipsing of the aryl and the methoxycarbonyl groups of the 1,3 dipole with the carbonyl groups of the dipolarophile. Further nonbonded interactions exist between the N-aryl and N-alkyl groups in the two components, implying that formation of **6d** would be favored. However, the orientation depicted in Figure 1a is more like that proposed for the Diels–Alder reaction, in which there is maximum overlap of the π orbitals in the two components.[18]

The situation with the *cis*-aziridine is further complicated by the fact that ring opening may proceed by either clockwise or counterclockwise rotation of the substituents. Morevoer, until it can be demonstrated that the product distribution in these reactions is kinetically controlled, any attempt to explain these results in accordance with established concepts[17b,c] is premature.

The isolation of Δ^3-pyrrolines from reaction of aziridines **1a**,**b** and 2a,**b** with dimethyl acetylenedicarboxylate is in accordance with the results of other workers[6,8b,9,10a] but is in contrast to the results reported by Padwa and Hamilton,[7b] in which *cis*- and *trans*-1-cyclohexyl-2-phenyl-3-benzoylaziridine reacted with dimethyl acetylenedicarboxylate in refluxing benzene and were reported to produce dimethyl 1-cyclohexyl-2-phenyl-5-benzoyl-Δ^2-pyrroline-3,4-dicarboxylate and dimethyl 1-cyclohexyl-2-phenyl-5-benzoyl-pyrrole-3,4-dicarboxylate. The same dipolarophile, when heated

(18) R. Woodward and T. Katz, *Tetrahedron*, **5**, 70 (1959).

to 78–100° with the respective *cis* and *trans* forms of some 1-aryl-2-carbonyl-substituted aziridines[8b,9] afforded H_2,H_5-*trans* and H_2,H_5-*cis* Δ^3-pyrrolines, respectively. The N-aryl-Δ^3-pyrrolines were found to be stable under the reaction conditions.

These results lend support to our proposal that the N-alkyl-Δ^3-pyrrolines **10a** and **11a** are considerably less stable than the N-phenyl-Δ^3-pyrrolines in that the former compounds readily undergo epimerization to the corresponding H_2,H_5-*cis* isomers **10b** and **11b**, respectively. The epimerization of the H_2,H_5-*trans* isomer **10a** in refluxing benzene does not appear to proceed by reversal of **10a** to the aziridine and the dipolarophile with subsequent recombination, for, when a benzene solution of **10a**, **10b**, and methyl *cis*-1-cyclohexyl-2-d_1-2-(*p*-biphenyl)-3-aziridinecarboxylate (**1c**) was refluxed for 24 hr, pmr spectroscopy revealed that the sole adduct **10b** contained no deuterium at C_5. Presumably an important factor in the epimerization is the basicity of the Δ^3-pyrroline nitrogen atom. However, until suitable evidence is available, speculation concerning the mechanistic question of whether the epimerization proceeds by an intermolecular or by an intramolecular process must be postponed.

While the H_2,H_5-*trans* Δ^3-pyrrolines **10a** and **11a** are the kinetically favored products, molecular models indicate that the corresponding H_2,H_3-*cis* isomers **10b** and **11b** could possibly derive their apparent thermodynamic stability from relief of nonbonded interactions between the N-alkyl group and the substituents at C_2 and C_5. A similar explanation can be invoked to explain, at least in part, the greater stability of the *cis* forms of some 1-alkyl-2,3-dibenzoylaziridines,[19] 1-alkyl-2-aryl-3-aroylaziridines,[12,19] and methyl 1-alkyl-2-aryl-3-aziridinecarboxylates[20] relative to the corresponding *trans* isomers and is the subject of a forthcoming publication.

Experimental Section

Melting points were determined by the capillary method and are uncorrected. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill. The infrared spectra were determined on Perkin-Elmer Model 237 and Perkin-Elmer Model 21 instruments as solutions (carbon tetrachloride, chloroform), potassium bromide disks, or neat. Ultraviolet spectra were obtained with a Cary Model 11 or a Cary Model 14 instrument employing methanol solutions. The 60-MHz nmr spectra were determined on a Varian A-60 spectrometer and the chemical shifts are reported in parts per million (δ) relative to internal tetramethylsilane (δ 0.0). Mass spectral analyses were determined on a Hitachi Perkin-Elmer RMU-6D spectrometer operating at 80 eV.

Synthesis of *cis*- and *trans*-Methyl 1-Alkyl-2-(*p*-biphenyl)-3-aziridinecarboxylates. A. Preparation of Methyl α-Bromo-*p*-phenylcinnamate. *trans*-*p*-Phenylcinnamic Acid.—Condensation of *p*-phenylbenzaldehyde (mp 57–58°, Kent Chemicals Ltd., Vancouver, Canada) with malonic acid according to the method of Koo, *et al.*,[21] afforded *p*-phenylcinnamic acid, mp 223–224° (lit.[22] mp 224–225°), in 97% yield.

***trans*-Methyl *p*-Phenylcinnamate.**—Esterification of *p*-phenylcinnamic acid in a refluxing benzene–methanol mixture containing a catalytic amount of concentrated H_2SO_4 gave the crystalline product (90%): mp 150–151°; pmr ($CDCl_3$) δ 3.81 (s, 3 H, methoxy), 6.48 (d, 1 H, J = 16.6 Hz, α-vinyl), 7.2–7.7 (m, 9 H, aromatic), and 7.77 (d, 1 H, J = 16.6 Hz, β-vinyl); ir (CCl_4) $\nu_{C=O}$ 1725 cm^{-1}; uv (CH_3OH) λ_{max} 308 mμ (ϵ 29,000).

Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.64; H, 5.92. Found: C, 80.54; H, 5.80.

Methyl 2,3-dibromo-3-(*p*-biphenyl)propionate, mp 148–149°, was obtained in 94% yield by bromination of methyl-*p* phenylcinnamate in carbon tetrachloride: pmr ($CDCl_3$) δ 3.90 (s, 3 H, methoxy), 4.90 and 5.46 (two d, 1 H each, J = 12.4 Hz, C_2H and C_3H, respectively), and 7.1–7.8 (m, 9 H, aromatic); ir (CCl_4) $\nu_{C=O}$ 1757 cm^{-1}; uv (CH_3OH) λ_{max} 269 mμ (ϵ 21,000).

Anal. Calcd for $C_{16}H_{14}Br_2O_2$: C, 48.27; H, 3.45; Br, 40.14. Found: C, 48.53; H, 3.52; Br, 40.30.

Methyl α-Bromo-*p*-phenylcinnamate (*cis* **and** *trans*).—Dehydrohalogenation of the dibromo ester with N-methylpiperidine in refluxing benzene for 24 hr gave the desired α-bromo-α,β-unsaturated ester as a mixture of the *cis* and *trans* isomers.

The *trans* isomer gave the following data: mp 128–129°; pmr ($CDCl_3$) δ 3.83 (s, 3 H, methoxy), 7.1–8.0 (m, 9 H, aromatic), and 8.25 (s, 1 H, vinyl); ir (CCl_4) $\nu_{C=O}$, 1721 and 1734 cm^{-1}; ir (Nujol) $\nu_{C=O}$, 1725 cm^{-1}; uv (CH_3OH) λ_{max} 312 mμ (ϵ 29,000).

Anal. Calcd for $C_{16}H_{13}BrO_2$: C, 60.59; H, 4.13; Br, 25.19. Found: C, 60.76; H, 4.18; Br, 25.16.

The *cis* isomer gave the following data: mp 65–66°; pmr ($CDCl_3$) δ 3.75 (s, 3 H, methoxy) and 7.2–7.6 (m, 10 H, aromatic and β-vinyl proton); ir (KBr) $\nu_{C=O}$ 1723 cm^{-1}; ir (CCl_4) 1733 cm^{-1}; uv (CH_3OH) λ_{max} 300 mμ (ϵ 24,600).

Anal. Found: C, 60.63; H, 4.23; Br, 25.20.

B. Aziridine Esters. Methyl 1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (*cis* **and** *trans*) **(1a,b).**—A solution of *trans*-methyl α-bromo-*p*-phenylcinnamate (10 g, 3.15 mmol) in dry benzene (10 ml) containing cyclohexylamine (4.67 g, 47.2 mmol) was stirred for 48 hr at room temperature. The reaction mixture was diluted with ether, the precipitated amine salt was collected, and the solvent was evaporated under reduced pressure. The excess amine was removed under high vacuum with gentle heating (*ca.* 40°) and the residue was diluted with low-boiling petroleum ether (bp 30–60°). The solid material was extracted twice with hot petroleum ether and the remaining solid was recrystallized from this same solvent to afford 0.5 g of pure methyl *cis*-1-cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (**1a**): mp 122–124°; pmr ($CDCl_3$) δ 1.0–2.0 (m, 11 H, cyclohexyl), 2.49 and 2.88 (two d, 1 H each, J = 7.0 Hz, C_3 H and C_2 H, respectively), 3.45 (s, 3 H, methoxy), and 7.2–7.7 (m, 9 H, aromatic); ir (CCl_4) $\nu_{C=O}$ 1752 and 1730 cm^{-1}; ir (Nujol) 1747 cm^{-1}; uv (CH_3OH) λ_{max} 257 mμ (ϵ 23,900).

Anal. Calcd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.51; N, 4.18; mol wt, 335.43. Found: C, 78.84; H, 7.63; N, 4.16; mol wt, 335 (mass spectrum).

The combined petroleum ether extracts were evaporated and the remaining oil was diluted with methanol. Cooling produced a crystalline solid which was recrystallized twice from methanol to give 0.31 g of pure methyl *trans*-1-cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (**1b**): mp 94–95°; pmr ($CDCl_3$) δ 1.0–2.0 and 2.2–2.5 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 2.73 (d, 1 H, J = 2.5 Hz, C_3 H), 3.26 (br s, 1 H, C_2 H), 3.71 (s, 3 H, methoxy), and 7.2–7.7 (m, 9 H, aromatic); ir (CCl_4) $\nu_{C=O}$ 1734 cm^{-1}; ir (Nujol) 1727 cm^{-1}; uv (CH_3OH) λ_{max} 257 mμ (ϵ 26,600).

Anal. Found: C, 78.60; H, 7.60; N, 4.21; mol wt, 335 (mass spectrum).

Methyl 1-Isopropyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (*cis* **and** *trans*) **(2a,b).**—A solution of the *trans*-α-bromo-α,β-unsaturated ester (2.0 g, 6.3 mmol) dissolved in benzene (20 ml) was treated with a 15-fold excess (5.57 g, 94.5 mmol) of isopropylamine. After being stirred for 48 hr at room temperature, the reaction mixture was diluted with ether, the amine salt was removed, and the solution was evaporated to dryness. The residue was recrystallized from methanol and two successive crops of pure methyl *trans*-1-isopropyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (**2b**), mp 122–124°, were obtained totaling 0.80 g: pmr ($CDCl_3$) δ 1.03 and 1.12 (two d, 6 H, J = 9.4 Hz, isopropyl methyls), 2.73 (d, J = 2.5 Hz), 3.25 (br s), and 2.7–3.4 (m) (3 H, C_3 H, C_2 H, and isopropyl methine, respectively), 3.71 (s, 3 H, methoxy), and 7.2–7.7 (m, 9 H, aromatic); ir (CCl_4) $\nu_{C=O}$ 1732 cm^{-1}; ir (KBr) 1725 cm^{-1}.

Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.49; H, 7.26; N, 4.76.

(19) (a) R. E. Lutz and A. B. Turner, *J. Org. Chem.*, **33**, 516 (1968); (b) A. B. Turner, J. Irving, and J. B. Bush, Jr., *J. Amer. Chem. Soc.*, **87**, 1050 (1965); (c) F. A. L. Anet and J. M. Osyany, *ibid.*, **89**, 352 (1967), footnote 6.

(20) P. B. Woller and N. H. Cromwell, unpublished results.

(21) J. Koo, *et al.*, in "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., John Wiley & Sons, Inc., New York, N. Y., 1963, p 327.

(22) V. Skvarchenko, D. Tsybikova, and R. Levina, *Zh. Obshch. Khim.*, **31**, 1819 (1961).

Evaporation of the methanol filtrate yielded an oil which was diluted with petroleum ether. Cooling produced 0.48 g of pure methyl *cis*-1-isopropyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (**2a**): mp 88–90°; pmr ($CDCl_3$) δ 1.20 (d, J = 5.4 Hz) and 1.66 (m, 7 H, isopropyl methyls and methine, respectively), 2.44 and 2.86 (two d, 1 H each, J = 7.0 Hz, C_2 H and C_3 H, respectively), 3.40 (s, 3 H, methoxy), and 7.1–7.6 (m, 9 H, aromatic); ir (CCl_4) $\nu_{C=O}$ 1727 and 1753 cm^{-1}; ir (KBr) 1750 cm^{-1}.

Anal. Found: C, 77.22; H, 7.19; N, 4.78.

C. Deuterium-Labeled Aziridine Esters. Preparation of Methyl α-Bromo-β-d_1-*p*-phenylcinnamate.—*p*-Phenylbenzaldehyde-d_1, mp 57–58°, was prepared in a manner analogous to that described for benzaldehyde-d_1.[23] Subsequent condensation with malonic acid, esterification, bromination, and dehydrohalogenation as previously described afforded *trans*-methyl α-bromo-β-d_1-*p*-phenylcinnamate, mp 129–130°.

Methyl 1-Cyclohexyl-2-(*p*-biphenyl)-2-d_1-3-aziridinecarboxylate (*cis* and *trans*) (1c,d).—These compounds were prepared by reaction of *trans*-methyl α-bromo-β-d_1-*p*-phenylcinnamate with a 15-fold excess of cyclohexylamine in benzene. The products were isolated as described for the synthesis of **1a** and **1b**. The ring-proton spectra of the deuterium-labeled aziridines **1c** and **1d** consisted of singlets at δ 2.88 and 2.73 for the *cis* (**1c**) and *trans* (**1d**) forms, respectively, and confirmed the previous chemical-shift assignments of the ring protons in **1a** and **1b**.

Methyl 1-Cyclohexyl-2,3-d_2-2-(*p*-biphenyl)-3-aziridinecarboxylate (*cis* and *trans*) (1e,f).—Reaction of cyclohexylamine-N-d_2[24] with the deuterium-labeled α-bromo-α,β-unsaturated ester as described for the synthesis of **1a** and **1b** produced the deuterium-labeled aziridine esters **1e** and **1f**. The ring-proton spectra of these compounds indicated >90% deuterium labeling at C_2 and C_3.

1,3-Dipolar Cycloaddition Reactions with Activated Olefins. General Procedure.—Equimolar quantities of the aziridine and the dipolarophile were refluxed in dry benzene for 24–48 hr, after which time the solution was filtered. In all cases, evaporation of the solvent under reduced pressure afforded a pale yellow to yellow oil which was chromatographed on silica gel, alumina, or Florisil.

Methyl *cis*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1a) and Dimethyl Fumarate.—A sample (335 mg, 1.0 mmol) of the aziridine ester **1a** and diethyl fumarate (144 mg, 1.0 mmol) in benzene (10 ml) was refluxed for 24 hr, cooled to room temperature, and filtered. The pale yellow oil obtained after removal of the solvent was diluted with methanol and cooled to afford 310 mg (63%) of H_2,H_3-*cis*-H_3,H_4-*trans*-H_4,H_5-*cis* trimethyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrolidine-2,3,4-tricarboxylate (**3a**) as a crystalline solid: mp 146–148°; pmr ($CDCl_3$) δ 1.3–2.1 and 2.3–2.8 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.11 (s, 3 H, methoxy of C_4 substituent), 3.66 and 3.67 (two s, 3 H each, two methoxy groups), 3.99–4.35 (m, 2 H, C_3 H and C_4 H), 4.50 (d of d, 1 H, J = 6.9, −0.6 Hz, C_3 H), 4.89 (br d, 1 H, J = 9.5 Hz, C_5 H), and 7.1–7.9 (m, 9 H, aromatic); ir (KBr) $\nu_{C=O}$ 1730 and 1744 cm^{-1}.

Anal. Calcd for $C_{28}H_{33}NO_6$: C, 70.12; H, 6.94; N, 2.92; mol wt, 479.55. Found: C, 70.06; H, 6.93; N, 3.04; mol wt, 479 (mass spectrum).

The methanol filtrate was evaporated to dryness and the residual oil was chromatographed on a column of Florisil (13 g). Elution with benzene (500 ml) and then with 3% ether–benzene (300 ml) gave small amounts of unreacted aziridine ester **1a** and dimethyl fumarate in the benzene fractions. The ether–benzene eluents contained 125 mg (26%) of a colorless oil which resisted all attempts to induce crystallization. This material was recognized as being isomeric with the crystalline pyrrolidine **3a** and assigned the structure H_2,H_3-*trans*-H_3,H_4-*trans*-H_4,H_5-*trans* trimethyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrolidine-2,3,4-tricarboxylate (**3b**) on the basis of spectral data: pmr ($CDCl_3$) δ 0.6–2.3 and 2.4–3.0 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.55–3.70 (m, 2 H, C_3 H and C_4 H), 3.77 and 4.00 (two s, 9 H, three methoxy groups), 4.57 (d, 1 H, J = 1.0 Hz, C_2 H), 4.91 (br d, 1 H, J = 5.7 Hz, C_5 H), and 7.3–7.8 (m, 9 H, aromatic); ir (CCl_4) $\nu_{C=O}$ 1743 cm^{-1}; mol wt, 479 (mass spectrum).

Methyl *cis*-1-Cyclohexyl-2,3-d_2-2-(*p*-biphenyl)-3-aziridinecarboxylate (1c) and Dimethyl Fumarate.—Trimethyl 1-cyclohexyl-2,5-d_2-5-(*p*-biphenyl)-pyrrolidine-2,3,4-tricarboxylate (**3a′**), mp 147–148°, was produced by reaction of the deuterium-labeled aziridine ester **1c** and dimethyl fumarate in refluxing benzene: pmr ($CDCl_3$) δ 1.3–2.1 and 2.3–2.8 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.11, 3.66, and 3.67 (three s, 3 H each, three methoxy groups), 3.95 and 4.13 (two d, 1 H each, J = 11.5 Hz, C_3 H and C_4 H), and 7.1–7.9 (m, 9 H, aromatic).

Methyl *cis*-1-Cyclohexyl-2-d_1-2-(*p*-biphenyl)-3-aziridinecarboxylate (1e) and Dimethyl Fumarate.—Reaction of equimolar quantities of **1e** and dimethyl fumarate in refluxing benzene afforded trimethyl 1-cyclohexyl-5-d_1-5-(*p*-biphenyl)pyrrolidine-2,3,4-tricarboxylate: mp 147–148°; pmr ($CDCl_3$) δ 1.3–2.1 and 2.3–2.8 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.11, 3.66, and 3.67 (three s, 3 H each, three methoxy groups), 3.99–4.35 (m, 2 H, C_3 H and C_4 H), 4.50 (d, 1 H, J = 6.9 Hz, C_2 H), and 7.1–7.9 (m, 9 H, aromatic).

Computer simulation of the pmr spectrum of this adduct and spin-decoupling experiments permitted assignment of chemical shifts of δ 3.95 and 4.13 for C_3 H and C_4 H, respectively.

Methyl *trans*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1b) and Dimethyl Fumarate.—The *trans*-aziridine ester **1b** and dimethyl fumarate in refluxing benzene (48 hr) reacted to give 44% crystalline pyrrolidine **3a** and 45% isomeric adduct **3b**.

Methyl *cis*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1a) and Dimethyl Maleate.—Refluxing a benzene (10 ml) solution of the *cis* aziridine ester **1a** (335 mg, 1.0 mmol) and dimethyl maleate (144 mg, 1.0 mmol) for 24 hr gave, after removal of the solvent, a pale yellow oil. Column chromatography (Florisil, 50 g) of the crude material afforded 320 mg (67%) of a colorless oil from early 3% ether–benzene fractions after initial elution of small amounts of unreacted aziridine and dimethyl maleate with benzene (1 l.). The oil was diluted with a small amount of methanol and cooled to yield white granules of H_2,H_3-*trans*-H_3,H_4-*cis*-H_4,H_5-*cis* trimethyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrolidine-2,3,4-tricarboxylate (**4a**): mp 92–93°; pmr ($CDCl_3$) δ 0.7–2.2 and 2.3–2.8 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.15 (s, 3 H, methoxy of C_4 substituent), 3.39 (d of d, 1 H, J = 9.0, 3.5 Hz, C_3 H), 3.67 and 3.76 (two s, 3 H each, two methoxy groups), 3.88 (d of d, 1 H, J = 9.0, 8.3 Hz, C_4 H), 4.63 (d, 1 H, J = 3.5 Hz, C_2 H), 5.00 (d, 1 H, J = 8.3 Hz, C_5 H), and 7.3–7.8 (m, 9 H, aromatic); ir (KBr) $\nu_{C=O}$ 1725, 1730, and 1735 cm^{-1}.

Anal. Calcd for $C_{23}H_{33}NO_6$: C, 70.12; H, 6.94; N, 2.92; mol wt, 479.55. Found: C, 70.10; H, 6.90; N, 2.90; mol wt, 479 (mass spectrum).

Further elution with ether gave 105 mg (22%) of a crystalline solid which was recrystallized from methanol and identified as H_2,H_3-*cis*-H_3,H_4-*cis*-H_4,H_5-*trans* trimethyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrolidine-2,3,4-tricarboxylate (**4b**): mp 122–124°; pmr ($CDCl_3$) δ 0.8–2.0 and 2.2–2.7 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.16 (d of d, 1 H, J = 3.9, 10.0 Hz, C_4 H), 3.53 (d of d, 1 H, J = 10.0, 6.3 Hz, C_3 H), 3.67, 3.73, and 3.75 (three s, 3 H each, three methoxy groups), 4.28 (d, 1 H, J = 6.3 Hz, C_2 H), 5.07 (d, 1 H, J = 3.9 Hz, C_5 H), and 7.3–7.8 (m, 9 H, aromatic); ir (KBr) $\nu_{C=O}$ 1742 cm^{-1}.

Anal. Found: C, 70.18; H, 6.93; N, 3.02; mol wt, 479 (mass spectrum).

The reaction was repeated in refluxing toluene and the percentages of **4a** and **4b** were determined to be 83:17, respectively, by pmr spectroscopy.

Methyl *trans*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1b) and Dimethyl Maleate.—Reaction of the *trans*-aziridine ester **1b** and dimethyl maleate in refluxing benzene (48 hr) produced 70 and 21% **4a** and **4b**, respectively.

Methyl *cis*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1a) and Fumaronitrile.—A sample (335 mg, 1.0 mmol) of the *cis*-aziridine was dissolved in benzene (10 ml) containing fumaronitrile (78 mg, 1.0 mmol) and the resulting solution was refluxed for 24 hr. The oil remaining after evaporation of the solvent was chromatographed on a column of Florisil (50 g) and initially eluted with benzene (500 ml) to afford small amounts of the two reactants. Subsequent elution with 2% ether–benzene afforded 360 mg of a colorless oil. Crystalline material was obtained by diluting the oil with ether and addition of pentane until turbid. The crystalline solid analyzed correctly for the gross structure methyl 1-cyclohexyl-3,4-dicyano-5-(*p*-biphenyl)pyrrolidine-2-carboxylate. The pmr spectrum of this material indicated a mixture of two isomers in a ratio of *ca.* 1:1.

(23) D. Seebach, R. W. Erickson, and G. Singh, *J. Org. Chem.*, **31**, 4303 (1966).

(24) D. B. Denney and M. A. Greenbaum, *J. Amer. Chem. Soc.*, **79**, 3701 (1957).

Anal. Calcd for $C_{26}H_{27}N_3O_2$: C, 75.52; H, 6.58; N, 10.16. Found: C, 75.33; H, 6.56; N, 10.29.

A pure sample of H_2,H_3-*cis*-H_3,H_4-*trans*-H_4,H_5-*cis* methyl 1-cyclohexyl-3,4-dicyano-5-(*p*-biphenyl)pyrrolidine-2-carboxylate (**5a**), mp 138–141°, was obtained by column chromatography of the mixture on alumina and elution with benzene: pmr ($CDCl_3$) δ 0.7–2.0 and 2.1–2.8 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.50 (d of d, 1 H, J = 6.5, 11.0 Hz, C_3 H), 3.85 (s, 3 H, methoxy), 4.25 (d of d, 1 H, J = 9.4, 11.0 Hz, 4.43 (d, 1 H, J = 6.5 Hz, C_2 H), 4.89 (d, 1 H, J = 9.4 Hz, C_5 H), and 7.3–7.7 (m, 9 H, aromatic); ir (KBr) $\nu_{C\equiv N}$ 2252 cm^{-1}; $\nu_{C=O}$ 1735 cm^{-1}.

The second product was assigned the structure H_2,H_3-*trans*-H_3,H_4-*trans*-H_4,H_5-*trans* methyl 1-cyclohexyl-3,4-dicyano-5-(*p*-biphenyl)pyrrolidine-2-carboxylate (**5b**) on the basis of pmr spectral data. This product could not be isolated without contamination of **5a** and apparently decomposed during chromatography of the crude material on alumina: pmr ($CDCl_3$) δ 0.7–2.0 and 2.1–2.8 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.24 (d of d, 1 H, J = 6.6, 3.0 Hz, C_3 H), 3.46 (d of d, 1 H, J = 3.0, 0.8 Hz, C_3 H), 3.78 (s, 3 H, methoxy), 4.44 (d, 1 H, J = 0.8 Hz, C_2 H), 4.81 (d, 1 H, J = 6.6 Hz, C_5 H), and 7.3–7.7 (m, 9 H, aromatic).

The reaction was repeated and monitored by pmr spectroscopy. A solution of the *cis*-aziridine ester **1a** (167 mg, 0.5 mmol) and the dipolarophile (39 mg, 0.5 mmol) in benzene-d_6 (0.3 ml) was transferred to an nmr tube, and the tube was sealed and placed in an oil bath maintained at 80 ± 1°. At 8-hr intervals the reaction mixture was examined by pmr spectroscopy. After 32 hr, all aziridine had been consumed and **5a** and **5b** were present in equal amounts. The methyl ester resonance signals for **5a** and **5b** were located at δ 3.53 and 3.56, respectively.

Methyl *trans*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1b) and Fumaronitrile.—The reaction of the *trans*-aziridine ester **1b** with fumaronitrile in benzene at 81° was monitored as described for reaction of **1a** with fumaronitrile. After 48 hr, the reaction mixture was examined by pmr spectroscopy. Four distinct methyl ester resonance signals were observed at δ 3.53 (**5a**, 20%), 3.56 (**5b**, 20%), 3.58 (**5c**, 30%), and 3.61 (**5d**, 30%).

Methyl *cis*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1a) and N-Phenylmaleimide.—A sample (335 mg, 1.0 mmol) of the *cis*-aziridine ester **1a** and N-phenylmaleimide (173 mg, 1.0 mmol) in benzene (10 ml) was refluxed for 24 hr and the crude reaction mixture was chromatographed on a column of Florisil (50 g). Initial elution with benzene (500 ml) gave small amounts of unreacted aziridine and dipolarophile while a colorless solid was obtained upon further elution with benzene (500 ml) and 3% ether–benzene (250 ml). This material was recrystallized from methanol to give 300 mg (59%) of pure H_2,H_3-*cis*-H_3,H_4-*cis*-H_4,H_5-*trans* methyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrolidine-2-carboxylate N-phenyl-3,4-dicarboximide (**6b**): mp 191–192°; pmr ($CDCl_3$) δ 0.8–2.0 and 2.2–2.9 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.32 (d of d, 1 H, J = 10.0, 5.4 Hz, C_4 H), 3.66 (s, 3 H, methoxy), 3.70 (d of d, 1 H, J = 8.7, 10.0 Hz, C_3 H), 4.53 (d, 1 H, J = 8.7 Hz, C_2 H), 4.92 (d, 1 H, J = 5.4 Hz, C_5 H), and 7.1–7.7 (m, 14 H, aromatic); ir (KBr) $\nu_{C=O}$ 1790 and 1725 cm^{-1}.

Anal. Calcd for $C_{32}H_{32}N_2O_4$: C, 75.57; H, 6.34; N, 5.51. Found: C, 75.55; H, 6.35; N, 5.65.

Further elution with 3% ether–benzene afforded a colorless oil which was crystallized by the addition of pentane. Recrystallization from an ether–pentane mixture gave 150 mg (30%) of a solid material, mp 150–151°, which was assigned the structure of H_2,H_3-*trans*-H_3,H_4-*cis*-H_4,H_5-*cis* methyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrolidine-2-carboxylate N-phenyl-3,4-dicarboximide (**6a**): pmr ($CDCl_3$) δ 0.8–2.0 and 2.2–2.8 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.29 (d, 1 H, J = 8.0 Hz, C_3 H), 3.73 (s, 3 H, methoxy), 3.80 (d of d, 1 H, J = 9.5, 8.0 Hz, C_4 H), 4.63 (s, 1 H, C_2 H), 5.11 (d, 1 H, J = 9.5 Hz, C_5 H), and 7.0–7.7 (m, 14 H, aromatic); ir (KBr) $\nu_{C=O}$ 1770 and 1750 cm^{-1}.

Anal. Found: C, 75.76; H, 6.46; N, 5.23.

Methyl *trans*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1b) and N-Phenylmaleimide.—A benzene (10 ml) solution of the *trans*-aziridine ester **1b** (670 mg, 2.0 mmol) and N-phenylmaleimide (346 mg, 2.0 mmol) was refluxed for 48 hr. Evaporation of the solvent afforded a pale yellow oil which was chromatographed on Florisil (70 g). Elution with benzene (1.5 l.) gave small amounts (<10%) of unreacted starting materials in early fractions and 300 mg (29%) of **6a** in later fractions. Further elution with a 3% ether–benzene mixture (1.5 l.) gave a mixture of two isomeric adducts. Recrystallization from a minimal amount of ether gave 300 mg (29%) of crystalline material, mp 205–207°, which was assigned the structure of H_2,H_3-*cis*-H_3,H_4-*cis*-H_4,H_5-*cis* methyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrolidine-2-carboxylate N-phenyl-3,4-dicarboximide (**6c**): pmr ($CDCl_3$) δ 0.7–2.1 and 2.2–3.0 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.5–3.7 (m, 2 H, C_3 H and C_4 H), 3.83 (s, 3 H, methoxy), 4.11 and 4.56 (two m, 1 H each, C_2 H and C_3 H, respectively) (these assignments and couplings of 7.6 and 8.8 Hz, respectively, were verified by spin-decoupling experiments) and 6.8–7.8 (m, 14 H, aromatic); ir (KBr) $\nu_{C=O}$ 1715 and 1760 cm^{-1}.

Anal. Found: C, 75.43; H, 6.28; N, 5.60.

The ether filtrate was reduced in volume and diluted with pentane. Cooling afforded 90 mg (9%) of **6b**. The column was washed with ethyl acetate (250 ml) to give only trace amounts of material.

When the experiment was repeated and monitored by pmr spectroscopy as described for the reaction of **1a** with fumaronitrile, a fourth methyl ester resonance signal was observed which did not correspond to the signals for **6a–6c** and was ascribed to the presence of **6d**. The percentages of the four isomeric adducts **6a–6d** were estimated to be 25:10:40:15, respectively.

Methyl *cis*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1a) and Maleimide.—A solution of aziridine **1a** (167 mg, 0.5 mmol) and maleimide (49 mg, 0.5 mmol) in benzene (5 ml) was refluxed for 24 hr and the solvent was evaporated. The residue was recrystallized from methanol–chloroform (1:1, v/v) to afford 86 mg (40%) of H_2,H_3-*trans*-H_3,H_4-*cis*-H_4,H_5-*cis* methyl 1-cyclohexyl-2-(*p*-biphenyl)pyrrolidine-2-carboxylate 3,4-dicarboximide (**8a**), mp 211–212°. The analytical sample, recrystallized from methanol, was found to contain water of crystallization: pmr ($CDCl_3$) δ 0.7–2.0 and 2.3–2.8 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.10 (d, 1 H, J = 8.0 Hz, C_3 H), 3.58 (d of d, 1 H, J = 9.8, 8.0 Hz, C_4 H), 3.73 (s, 3 H, methoxy), 4.45 (s, 1 H, C_2 H), 4.98 (d, 1 H, J = 9.8 Hz, C_5 H), and 7.1–7.7 (m, 10 H, aromatic and NH); ir (KBr) ν_{NH} 3400 cm^{-1}; $\nu_{C=O}$ 1720 and 1780 cm^{-1}.

Anal. Calcd for $C_{20}H_{28}N_2O_4 \cdot H_2O$: C, 69.31; H, 6.71; N, 6.22. Found: C, 69.41; H, 6.63; N, 6.11.

Evaporation of the filtrate afforded a colorless oil which was chromatographed on a column of silica gel (5 g). Initial elution with benzene (200 ml) gave small amounts of unreacted starting materials. H_2,H_3-*cis*-H_3,H_4-*cis*-H_4,H_5-*trans* methyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrolidine-2-carboxylate 3,4-dicarboximide (**8b**) was obtained as a crystalline solid (75 mg, 35%), mp 220–221°, from 1% ethyl acetate–benzene fractions: pmr ($CDCl_3$) δ 0.7–2.0 and 2.1–2.7 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.26 (d of d, 1 H, J = 10.0, 5.4 Hz, C_4 H), 3.70 (d of d, J = 8.8, 10.0 Hz) and 3.71 (s, 4 H, C_3 H and methoxy), 4.49 (d, 1 H, J = 8.8 Hz, C_2 H), 4.86 (d, 1 H, J = 5.4 Hz, C_5 H), and 7.2–7.8 (m, 10 H, aromatic and NH); ir (KBr) ν_{NH} 3450 cm^{-1}; $\nu_{C=O}$ 1701, 1742, and 1779 cm^{-1}.

Anal. Calcd for $C_{26}H_{28}N_2O_4$: C, 72.20; H, 6.53; N, 6.48. Found: C, 72.61; H, 6.63; N, 6.37.

The adducts **8a** and **8b** were found to be present in equal amounts as determined from the pmr spectrum of the crude reaction mixture.

Methyl *cis*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1a) and Maleic Anhydride.—Refluxing a benzene (5 ml) solution of the *cis* aziridine **1a** (167 mg, 0.5 mmol) and maleic anhydride (48 mg, 0.5 mmol) for 24 hr and evaporation of the solvent afforded a pale yellow oil. Crystalline material, mp 159–180°, was obtained by dilution with ether and addition of pentane until turbid. Repeated recrystallization did not improve the melting point. The infrared spectrum (KBr) exhibited prominent carbonyl absorptions at 1722, 1785, and 1865 cm^{-1}. Elemental analysis of the solid was consonant with the molecular formula $C_{26}H_{27}NO_5$. Pmr spectral data indicated the presence of two isomeric compounds, the structures of which were assigned as H_2,H_3-*trans*-H_3,H_4-*cis*-H_4,H_5-*cis* and H_2,H_3-*cis*-H_3,H_4-*cis*-H_4,H_5-*trans* methyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrolidine-2-carboxylate 3,4-dicarboxylic anhydride (**9a** and **9b**, respectively).

Anal. Calcd for $C_{26}H_{27}NO_5$: C, 72.02; H, 6.28; N, 3.23. Found: C, 72.01; H, 6.31; N, 3.23.

Compound **9a** gave the following data: pmr ($CDCl_3$) δ 0.7–2.1 and 2.2–2.8 (two m, cyclohexyl methylenes and methine, respectively), 3.48 (d, J = 8.7 Hz, C_3 H), 3.76 (s, methoxy),

3.88 (d of d, J = 9.8, 8.7 Hz, C_4 H), 4.59 (s, C_2 H), 5.13 (d, J = 9.6 Hz, C_5 H), and 7.2–7.8 (m, aromatic).

Compound **9b** gave the following data: pmr ($CDCl_3$) δ 3.73 (s, methoxy), 4.44 (d, J = 8.3 Hz, C_2H), and 4.80 (d, J = 5.0 Hz, C_5H).

Electronic integration of the appropriate resonance signals in the pmr spectrum of the crude material indicated 70% **9a** and 30% **9b**.

Methyl *cis*-1-Isopropyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (2a) and N-Phenylmaleimide.—A solution of the *cis* aziridine **2a** (295 mg, 1.0 mmol) and N-phenylmaleimide (173 mg, 1.0 mmol) was refluxed in 10 ml of benzene for 24 hr. Evaporation of the solvent gave a pale yellow oil which was chromatographed on Florisil (40 g) and eluted as previously described for reaction of **1a** with N-phenylmaleimide. The first eluted product (260 mg, 55%) was recrystallized from methanol and assigned the structure H_2,H_3-*cis*-H_3,H_4-*cis*-H_4,H_5-*trans* methyl 1-isopropyl-5-(*p*-biphenyl)pyrrolidine-2-carboxylate N-phenyl-3,4-dicarboximide (**7b**): mp 185–187°; pmr ($CDCl_3$) δ 0.81 and 1.11 (two d, 6 H, J = 7.0 Hz, two methyls), 2.95 (m, 1 H, isopropyl methine), 3.36 (d of d, 1 H, J = 5.4, 10.3 Hz, C_3 H), 3.65 (s, 3 H, methoxy), 3.75 (d of d, 1 H, J = 8.7, 10.3 Hz, C_4 H), 4.53 (d, 1 H, J = 8.7 Hz, C_2 H), 4.85 (d, 1 H, J = 5.4 Hz, C_5 H), and 7.2–7.8 (m, 14 H, aromatic); ir (KBr) $\nu_{C=O}$ 1705, 1725, and 1775 cm^{-1}.

Anal. Calcd for $C_{29}H_{28}N_2O_4$: C, 74.34; H, 6.02; N, 5.98. Found: C, 74.18; H, 6.13; N, 5.92.

H_2,H_3-*trans*-$H_3$$H_4$-*cis*-$H_4$,$H_5$-*cis* methyl 1-isopropyl-5-(*p*-biphenyl)pyrrolidine-2-carboxylate N-phenyl-3,4-dicarboximide (**7a**) was obtained from 3% ether–benzene fractions. Recrystallization from methanol afforded 140 mg (30%) of pure **7a**: mp 171–172°; pmr ($CDCl_3$) δ 0.81 and 1.16 (two d, 3 H, J = 7.0 Hz, isopropyl methyls), 3.02 (m, 1 H, isopropyl methine), 3.33 (d, 1 H, J = 8.4 Hz, C_3 H), 3.75 (s, 3 H, methoxy), 3.83 (two d, 1 H, J = 9.8, 8.4 Hz, C_4 H), 4.63 (s, 1 H, C_2 H), 5.03 (d, 1 H, J = 9.8 Hz, C_5 H), and 7.1–7.8 (m, 14 H, aromatic); ir (KBr) $\nu_{C=O}$ 1710, 1725, 1770 cm^{-1}.

Anal. Found: C, 74.14; H, 6.22; N, 5.94.

Electronic integration of the pmr spectrum of the crude material indicated the percentages of **7a** and **7b** to be 35:65, respectively.

Dipolar Cycloaddition Reactions with Dimethyl Acetylenedicarboxylate. General Procedure.—Benzene solutions of 1 molar equiv of the aziridine ester and 2 molar equiv of dimethyl acetylenedicarboxylate were refluxed for varying periods of time, the solvents were removed under reduced pressure, and the residue was examined by pmr spectroscopy. The products were isolated by column chromatography on silica gel or Florisil.

Methyl *cis*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1a) with Dimethyl Acetylenedicarboxylate.—A solution of this aziridine (335 mg, 1.0 mmol) and the dipolarophile 284 mg, 2.0 mmol) was refluxed in benzene (10 ml) for 24 hr. The solvent was removed and the residue was chromatographed on silica gel (40 g). The column was eluted successively with 50% petroleum ether–benzene (250 ml), benzene (500 ml), and 1% ethyl acetate–benzene (500 ml). The benzene and ethyl acetate–benzene fractions contained the excess dimethyl acetylenedicarboxylate. Further elution with ethyl acetate–benzene mixtures (1:49, 500 ml; 3:97, 500 ml; 2:48, 500 ml) afforded 380 mg (80%) of a pale yellow oil. This material could not be obtained in a crystalline form and was assigned the structure H_2,H_5-*cis* trimethyl 1-cyclohexyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (**10b**) on the basis of spectral and chemical evidence cited below: pmr ($CDCl_3$) δ 0.8–2.8 and 2.3–2.8 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.55, 3.68, and 3.80 (three s, 3 H each, three methoxy groups), 4.81 and 5.31 (two d, 1 H each, J = 4.6 Hz, C_2 H and C_5 H, respectively), and 7.2–7.7 (m, 9 H, aromatic); ir (neat) $\nu_{C=O}$ 1726 and 1742 cm^{-1}, $\nu_{C=C}$, 1670 cm^{-1}.

When this material was chromatographed on alumina (Woelm, neutral, activity grade I) and eluted with ethyl acetate, a bright yellow oil was obtained. This material resisted all attempts to induce crystallization. The pmr spectrum indicated the structure of H_4,H_5-*cis* trimethyl 1-cyclohexyl-5-(*p*-biphenyl)-Δ^2-pyrroline-2,3,4-tricarboxylate (**14a**): pmr ($CDCl_3$) δ 0.8–2.0 and 2.8–3.2 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.09 (s, 3 H, methoxy of C_4 substituent), 3.81 and 4.00 (two s, 3 H each, two methoxy groups), 4.43 and 5.26 (two d, 1 H each, J = 13.0 Hz, C_4 H and C_5 H, respectively), and 7.3–7.9 (m, 9 H, aromatic); ir (neat) $\nu_{C=O}$ 1745 cm^{-1}, $\nu_{C=C}$ 1680 and 1580 cm^{-1}.

Oxidation of H_2,H_5-*cis* Trimethyl 1-Cyclohexyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (10b).—A solution of **10b** (238 mg, 0.5 mmol) and chloranil (246 mg, 1.0 mmol) in xylene (15 ml) was refluxed for 6 hr. The cooled solution was diluted with ether (50 ml), and washed successively with three 20-ml portions of 4% aqueous sodium hydroxide solution containing 1% sodium bisulfite and then with water. The organic layer was dried (anhydrous $MgSO_4$) and the solvent was evaporated. The residue was recrystallized from methanol to afford 75 mg (31%) of trimethyl 1-cyclohexyl-5-(*p*-biphenyl)pyrrole-2,3,4-tricarboxylate (**12a**): mp 176–178°; pmr ($CDCl_3$) δ 0.8–2.5 (m, 10 H, cyclohexyl methylene), 3.66, 3.83, and 3.91 (three s, 3 H, each, three methoxy groups), 3.8–4.6 (m, 1 H, cyclohexyl methine), and 7.3–7.8 (9 H, aromatic); ir (KBr) $\nu_{C=O}$ 1705, 1730, and 1745 cm^{-1}.

Anal. Calcd for $C_{28}H_{29}NO_6$: C, 70.72; H, 6.15; N, 2.95. Found: C, 70.75; H, 5.99; N, 2.92.

Oxidation of H_4,H_5-*cis* Trimethyl 1-Cyclohexyl-5-(*p*-biphenyl)-Δ^2-pyrroline-2,3,4-tricarboxylate (14a).—A sample (119 mg, 0.25 mmol) of **14a** was oxidized with chloranil as described for the oxidation of **10b** to afford 24 mg (20%) of **12a**.

Base-Catalyzed Isomerization of H_2,H_5-*cis* Trimethyl 1-Cyclohexyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (10b).—A sample (238 mg, 0.5 mmol) of **10b** in methanol (10 ml) was treated with sodium methoxide (5 mg). A deep yellow color developed immediately and the solution was allowed to stand for 24 hr at room temperature, after which time the solvent was evaporated under reduced pressure. The residue was diluted with ether, washed with water, and dried (anhydrous $MgSO_4$). The bright yellow oil which remained after evaporation of the solvent was chromatographed on a column of silica gel (15 g). A small amount (10 mg) of a bright yellow material was eluted with 1% ethyl acetate–benzene (500 ml), and a colorless oil was obtained upon elution with 2% ethyl acetate–benzene. Crystallization was induced by dilution with ether and then addition of pentane until turbid. Cooling produced colorless crystals (175 mg, 74%) of H_4,H_5-*trans* trimethyl 1-cyclohexyl-5-(*p*-biphenyl)-Δ^2-pyrroline-2,3,4-tricarboxylate (**13a**): mp 130–131°; pmr ($CDCl_3$) δ 0.8–2.2 and 2.8–3.3 (two m, 11 H, cyclohexyl methylenes and methine, respectively), 3.63 (s, 3 H, methoxy), 3.73 (d, 1 H, J = 5.4 Hz, C_4 H), 3.76 and 3.96 (two s, 3 H each, two methoxy groups), 5.00 (d, 1 H, J = 5.4 Hz, C_5 H), and 7.2–7.8 (m, 9 H, aromatic); ir (KBr) $\nu_{C=O}$ 1750 and 1745 cm^{-1}, $\nu_{C=C}$ 1685 and 1600 cm^{-1}.

Anal. Calcd for $C_{28}H_{31}NO_6$: C, 70.42; H, 6.54; N, 2.93. Found: C, 70.63; H, 6.62; N, 2.88.

The experiment was repeated in methanol-d_1 as solvent and the ether extracts were washed with D_2O during work-up. The pmr spectrum of the crystalline solid, mp 130–131°, obtained upon column chromatography of the crude material was identical with that of **13a**, with the exception that the high-field doublet ascribed to C_4 H was absent and the resonance signal for C_5 H appeared as a slightly broadened singlet at δ 5.00.

Oxidation of H_4,H_5-*trans* Trimethyl 1-Cyclohexyl-5-(*p*-biphenyl)-Δ^2-pyrroline-2,3,4-tricarboxylate (13a).—A solution of **13a** (238 mg, 0.5 mmol) was oxidized with chloranil (246 mg, 1.0 mmol) in refluxing xylene. After 10 hr, the product was isolated as described for oxidation of **10b** to **12a** to afford 50 mg (21%) of **12a**.

Methyl *trans*-1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (1b) and Dimethyl Acetylenedicarboxylate.—A sample (335 mg, 1.0 mmol) of the *trans*-aziridine ester **1b** and the dipolarophile (284 mg, 2.0 mmol) in benzene (10 ml) was heated to reflux, during which time the solution developed a deep red color. The reaction mixture was refluxed for 30 hr and worked up according to the procedure described for the reaction of the *cis* aziridine **1a** and dimethyl acetylenedicarboxylate to afford 360 mg (75%) of a pale yellow oil. The pmr spectrum of this material was identical with that of H_2,H_5-*cis* trimethyl 1-cyclohexyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (**10b**).

The experiment was repeated with the period of reflux decreased to 20 hr. Examination of the crude material by pmr spectroscopy indicated the presence of **10b** and a second adduct which was recognized as being isomeric with **10b**. The second product was assigned the structure H_2,H_5-*trans* trimethyl 1-cyclohexyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (**10a**). The pyrroline ring proton spectrum of **10a** consisted of two doublets located at δ 5.17 (C_2 H) and 5.60 (C_5 H) with $J_{2,5}$ = 7.0 Hz. Electronic integration indicated the ratio of **10a** to **10b** to be 3:1 (40%); *ca.* 60% of the aziridine had been con-

sumed. After an additional 28-hr period of reflux, the ratio of **10a** to **10b** was 1:3 and 80% of the aziridine had reacted. None of the isomeric *cis*-aziridine **1a** could be detected at either time. Repetition of this experiment with equimolar quantities of the two reactants produced nearly identical results.

Attempted Isolation of H_2,H_5-*trans* Trimethyl 1-Cyclohexyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (10a).—A solution of aziridine **1b** (335 mg, 1.0 mmol) and dimethyl acetylenedicarboxylate (142 mg, 1.0 mmol) in benzene (10 ml) was refluxed for 24 hr. The residue which remained after evaporation of the solvent was examined by pmr spectroscopy and found to consist of nearly equal amounts of **10a** and **10b**. Column chromatography of this material on silica gel and elution as described for the reaction of **1a** and dimethyl acetylenedicarboxylate afforded 150 mg (45%) of aziridine **1b** and 200 mg (42%) of **10b**. None of the isomeric Δ^3-pyrroline **10a** could be detected in any of the ethyl acetate–benzene fractions or in the ethyl acetate washings.

Methyl *cis*-1-Isopropyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (2a) and Dimethyl Acetylenedicarboxylate.—A solution of this aziridine (590 mg, 2.0 mmol) and the dipolarophile (568 mg, 4.0 mmol) was refluxed for 24 hr in benzene. Evaporation of the solvent afforded a yellow oil which was chromatographed on silica gel (80 g) as described for the reaction of aziridine **1a** with dimethyl acetylenedicarboxylate to afford 700 mg (80%) of a pale yellow oil. This material could not be obtained in a crystalline form and was assigned the structure H_2,H_5-*cis* trimethyl-1-isopropyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (**11b**) on the basis of spectral data: pmr ($CDCl_3$) δ 0.99 and 1.02 (two d, 6 H, J = 6.5 Hz, isopropyl methyls), 3.10 (m, 1 H, isopropyl methine), 3.59, 3.74, and 3.83 (three s, 3 H each, three methoxy groups), 4.81 and 5.31 (two d, 1 H each, J = 4.5 Hz, C_2 H and C_5 H, respectively), and 7.4–7.8 (m, 9 H, aromatic); ir (neat) $\nu_{C=O}$ 1724 and 1739 cm^{-1}, $\nu_{C=C}$ 1667 cm^{-1}.

Repetition of the experiment and examination of the crude material by pmr spectroscopy indicated a mixture of **11b** and a second isomeric product which was assigned the structure H_2,H_5-*trans* trimethyl 1-isopropyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (**11a**). The ring-proton spectrum of **11a** consisted of two doublets (J = 4.6 Hz) located at δ 5.15 (C_2 H) and 5.58 (C_5 H). The isomeric adducts were formed in a ratio of **11a** to **11b** of 2:3 and in a combined yield of *ca.* 90%. This ratio was not appreciably altered when the experiment was conducted with the rigorous exclusion of light during the period of reflux and evaporation of the solvent. In contrast, shorter periods of reflux (10–12 hr) produced a ratio of **11a** to **11b** of 4:1 while prolonged refluxing (48 hr) afforded only **11b**.

Methyl *trans*-1-Isopropyl-2-(*p*-biphenyl)-3-aziridinecarboxylate (2b) and Dimethyl Acetylenedicarboxylate.—A solution of this aziridine (295 mg, 1.0 mmol) and the dipolarophile (284 mg, 2.0 mmol) in benzene (10 ml) was refluxed for 24 hr and the solvent was removed under reduced pressure. Examination of the residue by pmr spectroscopy indicated a ratio of **11a** to **11b** of 3:2 and *ca.* 25% of aziridine **2b** as yet unreacted.

Epimerization of H_2,H_5-*trans* Trimethyl 1-Isopropyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-Tricarboxylate (11a) to 11b.—A mixture of **11a** and **11b** was produced by the reaction of the *cis*-aziridine **2a** (590 mg, 2.0 mmol) with dimethyl acetylenedicarboxylate (568 mg, 4.0 mmol) in refluxing benzene (20 ml) for 20 hr. The reaction mixture was divided into three equal portions and treated as described below.

Method A. In Chloroform.—After evaporation of the solvent from two of the samples the residues were each diluted with deuteriochloroform (0.5 ml) and examined by pmr spectroscopy. The isomeric Δ^3-pyrrolines **11a** and **11b** were in a ratio of **11a** to **11b** of 1:1. The pmr spectrum was again determined after an 18-hr time lapse, during which time one sample was placed in the dark and the other was exposed to normal laboratory lighting and diffuse sunlight. Conversion of **11a** into **11b** was nearly quantitative in both instances at room temperature.

Method B. In Methanol-d_1.—The residue remaining after evaporation of the solvent from the third sample was diluted with methanol-d_1 (2.0 ml). After 10 hr at room temperature the solvent was removed under reduced pressure and the residue was examined by pmr spectroscopy ($CDCl_3$). None of the H_2,H_5-*trans* Δ^3-pyrroline **11a** could be detected and the epimeric H_2,H_5-*cis* product **11b** was present as a mixture of deuterium-labeled and -unlabeled compounds. No loss of deuterium from the labeled product was observed after 24 hr in methanol. A pure sample of **11b** in methanol-d_1 did not exchange deuterium during a 24-hr period at room temperature.

Oxidation of H_2,H_5-*cis* Trimethyl 1-Isopropyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (11b).—A sample (546 mg, 1.25 mmol) of **11b** was oxidized with chloranil in boiling xylene as previously described for the oxidation of **10b**. After work-up, the crude material was recrystallized from methanol to afford 200 mg (37%) of trimethyl 1-isopropyl-5-(*p*-biphenyl)pyrrole-2,3,4-tricarboxylate (**14b**): mp 171–173°; pmr ($CDCl_3$) δ 1.45, (d, 6 H, J = 7.3 Hz, isopropyl methyls), 3.59, 3.86, and 3.95 (three s, 3 H each, methoxy groups), 4.70 (m, 1 H, isopropyl methine), and 7.3–7.8 (m, 9 H, aromatic); ir (KBr) $\nu_{C=O}$ 1720 cm^{-1} (broad).

Anal. Calcd for $C_{25}H_{25}NO_6$: C, 68.95; H, 5.79; N, 3.22. Found: C, 69.11; H, 5.91; N, 3.19.

Base-Catalyzed Isomerization of H_2,H_5-*cis* Trimethyl 1-Isopropyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (11b).—Treatment of a sample of **11b** (300 mg, 0.68 mmol) in methanol (10 ml) with sodium methoxide (5 mg) resulted in the development of a deep yellow color upon addition of the base. After 6 hr at room temperature, the reaction was worked up as previously described for the isomerization of **10b** to **13a**. The crude material was examined by pmr spectroscopy and found to be a mixture of two isomeric products. The isomer present in major amount (90%) was assigned the structure H_4,H_5-*trans* trimethyl 1-isopropyl-5-(*p*-biphenyl)-Δ^2-pyrroline-2,3,4-tricarboxylate (**13b**). The epimeric compound, H_4,H_5-*cis* trimethyl 1-isopropyl-5-(*p*-biphenyl)-Δ^2-pyrroline-2,3,4-tricarboxylate (**14b**), was present to the extent of 10%.

Compound **13b** gave the following data: pmr ($CDCl_3$) δ 0.93 and 1.24 (two d, 6 H, J = 6.5 Hz, isopropyl methyls), 3.33–3.80 and 3.63 (m and s, 4 H, isopropyl methine and methoxy group), 3.73 (d, 1 H, J = 6.0 Hz, C_4 H), 3.76 and 3.96 (two s, 3 H each, two methoxy), 4.93 (d, 1 H, J = 6.0 Hz, C_5 H), and 7.3–7.8 (m, 9 H, aromatic).

Compound **14b** gave the following data: pmr ($CDCl_3$) δ 1.00 and 1.20 (two d, 6 H, J = 6.5 Hz, two methyls), 3.13 (s, 1 H, methyl of C_4 substituent), 3.33–3.80 (m, 1 H, isopropyl methine), 3.76 and 3.96 (two s, 3 H each, two methoxy groups), 4.39 and 5.19 (two d, 1 H, J = 13.4 Hz, C_4 H and C_5 H, respectively), and 7.3–7.8 (m, 9 H, aromatic).

These products were not characterized further.

Thermal Epimerization of H_2,H_5-*trans* Trimethyl 1-Cyclohexyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (10a) to 10b in the Presence of Methyl *cis*-1-Cyclohexyl-2-d_1-2-(*p*-biphenyl)-3-aziridinecarboxylate (1c).—A benzene (10 ml) solution of aziridine ester **1a** (252 mg, 0.75 mmol) and dimethyl acetylenedicarboxylate (105 mg, 0.75 mmol) was refluxed for 24 hr. The reaction mixture was cooled to room temperature and the deuterium-labeled aziridine **1c** (167 mg, 0.5 mmol) was added. The resulting solution was refluxed for an additional 24 hr, the solvent was evaporated, and the residue was examined by pmr spectroscopy. The crude material was found to be a mixture of **1c** and **10b**. No detectable amount of deuterium was incorporated in **10b**.

Thermal Stability of H_2,H_5-*cis* Trimethyl 1-Isopropyl-5-(*p*-biphenyl)-Δ^3-pyrroline-2,3,4-tricarboxylate (11b).—A sample (437 mg, 1.0 mmol) of **11b** in toluene (20 ml) was refluxed for 12 hr and the solvent was evaporated. Examination of the residue by pmr spectroscopy indicated the presence of **11b** (95%) and **13b** (5%). None of the isomeric H_2,H_5-*cis* Δ^3-pyrroline **11a** could be detected.

Attempted Epimerization of Methyl 1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylates 1a and 1b. Method A (Refluxing Methanol).—A solution of the *cis*-aziridine ester **1a** (110 mg, 0.33 mmol) in methanol-d_1 (10 ml) containing sodium methoxide (5 mg) was refluxed for 24 hr. The solvent was removed under reduced pressure, diluted with D_2O, and extracted with ether. The ether extracts were dried (anhydrous $MgSO_4$) and concentrated to give an oil which smelled of cyclohexylamine. The pmr spectrum of this oil indicated the absence of either of the aziridine esters **1a** and **1b**. Concentration of the sample, addition of methanol, and cooling produced 25 mg of a crystalline material, mp 57–58°. A mixture melting point experiment with an authentic sample of *p*-phenylbenzaldehyde showed no depression.

Identical results were obtained upon treatment of the *trans*-aziridine ester **1b** as described for **1a**.

Method B (Refluxing Ether).—A sample (110 mg, 0.33 mmol) of the *cis*-aziridine ester **1a** and sodium methoxide (5 mg) in 25 ml of an ether–methanol-d_1 mixture (4:1, v/v) was refluxed for

24 hr. The solvent was then evaporated, and the residue was diluted with D_2O and extracted with ether. The dried (anhydrous $MgSO_4$) ether extracts were evaporated and the residue (95 mg) was examined by pmr spectroscopy. The sole product was the starting aziridine **1a** with no detectable incorporation of deuterium.

The corresponding *trans*-aziridine ester was recovered unchanged and without deuterium exchange when subjected to identical reaction conditions.

Thermal Equilibration of Methyl 1-Cyclohexyl-2-(*p*-biphenyl)-3-aziridinecarboxylates (1a and 1b).—A solution of the *cis*-aziridine ester (167 mg, 0.5 mmol) in benzene-d_6 (0.3 ml) was transferred to an nmr tube, and the tube was sealed and placed in a constant-temperature bath maintained at 80 ± 0.2°. At 8-hr intervals the pmr spectrum was determined. After 40 hr, the percentages of **1a** and **1b** were determined as 68:32, respectively, by electronic integration. These percentages were not altered after an additional 16 hr at 80°.

Similarly, the corresponding *trans*-aziridine ester **1b** afforded the same equilibrium mixture after being heated to 80° for 72 hr in benzene-d_6.

Registry No.—**1a**, 19474-27-2; **1b**, 23214-20-2; **2a**, 23214-21-3; **2b**, 23214-22-4; **3a**, 23214-23-5; **3a′**, 23214-24-6; **3b**, 23214-25-7; **4a**, 23263-68-5; **4b**, 23214-26-8; **5a**, 23263-69-6; **5b**, 23214-27-9; **6a**, 23263-70-9; **6b**, 23214-28-0; **6c**, 23263-71-0; **7a**, 23214-29-1; **7b**, 23263-72-1; **8a**, 23214-30-4; **8b**, 23263-73-2; **9a**, 23214-31-5; **9b**, 23214-32-6; **10a**, 23214-33-7; **10b**, 23214-34-8; **11a**, 23214-35-9; **11b**, 23214-36-0; **12a**, 23230-36-6; **13a**, 23214-37-1; **13b**, 23214-38-2; **14a**, 23263-74-3; **14b**, 23214-39-3; *trans*-methyl *p*-phenylcinnamate, 22837-75-8; methyl 2,3-dibromo-3-(*p*-biphenyl)propionate, 23230-37-7; *cis*-methyl α-bromo-*p*-phenylcinnamate, 23214-40-6; *trans*-methyl α-bromo-*p*-phenylcinnamate, 23214-41-7; methyl α-bromo-β-d_1-*p*-phenylcinnamate (*trans*), 23214-42-8; trimethyl 1-cyclohexyl-5-d_1-5-(*p*-biphenyl)pyrrolidine-2,3,4-tricarboxylate, 23230-38-8.

Hydroboration of Dihydropyrans and Dihydrofurans

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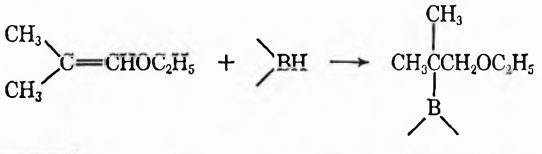
Received June 23, 1969

The hydroborations of Δ²-dihydropyran, Δ³-dihydropyran, 2-ethoxy-3,4-dihydropyran, 2,3-dihydrofuran, 2,5-dihydrofuran, and 2-methyl-4,5-dihydrofuran with diborane and with disiamylborane[bis(3-methyl-2-butyl)-borane] have been investigated. Except in the case of Δ³-dihydropyran, the hetero oxygens direct the addition of boron nearly exclusively to the β positions. Oxidation of the intermediate β-organoboranes with alkaline hydrogen peroxide affords the corresponding β-hydroxy derivatives in better than 70% yields. Addition of boron trifluoride to the β-organoboranes derived from the heterocyclic olefins results in β elimination to give, after hydrolysis, the corresponding acyclic unsaturated alcohols in 70–90% yields. Hydroboration of dihydropyrans and dihydrofurans with excess diborane followed by oxidation produces mixtures of acyclic diols.

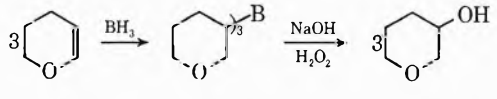
In connection with our pursuit of certain synthetic objectives, we were confronted with the problem of developing simple, high-yield syntheses of 3-hydroxytetrahydropyrans and 3-hydroxytetrahydrofurans. We had previously synthesized 3-hydroxytetrahydropyran; however, it was obtained in only a modest yield and required a four-step synthesis starting with dihydropyran.[1] Thus we were prompted to examine the hydrations of dihydropyrans and dihydrofurans *via* the hydroboration–oxidation reaction.

Various research groups have observed marked directive effects by alkoxy groups in the hydroboration of vinyl ethers. Thus Mikhailov and Shchegoleva reported that the hydroboration of ethyl vinyl ether produces *tris*(2-ethoxyethyl)borane in 67% yield.[2] Likewise, Pasto and Cumbo found that enol ethers undergo hydroboration predominantly at their β positions.[3] β-Ethoxystyrene gives, after hydroboration followed by oxidation of the intermediate organoborane, a 75% yield of 2-ethoxy-1-phenylethanol. Ethoxycyclohexene is converted by the same reaction sequence into *trans*-2-ethoxycyclohexanol. Finally, Brown and Sharp have recently shown that the hydroboration of isobutenyl ethyl ether results in the sterically unfavorable addition of at least 88% of the boron to the hindered tertiary carbon.[4]



Results and Discussion

Hydroboration of Dihydropyrans and Dihydrofurans.—The reaction of Δ²-dihydropyran with borane (BH_3) in a 3:1 ratio in tetrahydrofuran solution at 0° proceeded rapidly to the trialkylborane stage. To assess the direction of addition of BH to the double bond, the trialkylborane was oxidized with alkaline hydrogen peroxide. Gas–liquid partition chromatography (glpc) revealed the formation of a single alcohol, 3-hydroxytetrahydropyran, in 86% yield. No evidence was ob-



tained for the formation of any 2-hydroxytetrahydropyran. It is possible, however, that a small amount of the boron may have added to the 2 position of the pyran ring, but that the α-boron intermediate is unstable under the reaction conditions.

The hydroboration of 2-ethoxy-3,4-dihydropyran in tetrahydrofuran solvent was quite slow at 0°. However, if the hydroboration was carried out at 25° for 3 hr, analysis for residual hydride indicated that the

(1) S. A. Barker, J. S. Brimacombe, A. B. Foster, D. H. Whiffen, and G. Zweifel, *Tetrahedron*, **7**, 10 (1959).

(2) B. M. Mikhailov and T. A. Shchegoleva, *Izv. Akad. Nauk SSSR*, 546 (1959).

(3) D. J. Pasto and C. C. Cumbo, *J. Amer. Chem. Soc.*, **86**, 4343 (1964).

(4) H. C. Brown and R. L. Sharp, *ibid.*, **90**, 2915 (1968).

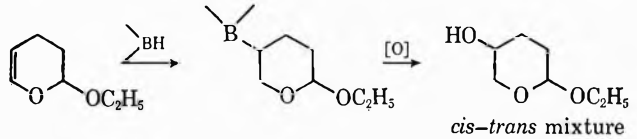
TABLE I

ALCOHOLS DERIVED FROM HYDROBORATION–OXIDATION OF DIHYDROPYRANS AND DIHYDROFURANS

Olefin	Reacn temp, °C	Reacn time, hr	Alcohol	Yield, %[a]
Δ^2-Dihydropyran	0	4	3-Hydroxytetrahydropyran	86
Δ^3-Dihydropyran	25	2	3-Hydroxytetrahydropyran	55
			4-Hydroxytetrahydropyran	30
2-Ethoxy-3,4-dihydropyran	25	3	2-Ethoxy-5-hydroxytetrahydropyran	70[b]
2,3-Dihydrofuran	0	2	3-Hydroxytetrahydrofuran	78
2,5-Dihydrofuran	0	2	3-Hydroxytetrahydrofuran	84
2-Methyl-4,5-dihydrofuran	0	2	*trans*-2-Methyl-3-hydroxytetrahydrofuran	80

[a] Yield by glpc examination. [b] Yield by isolation.

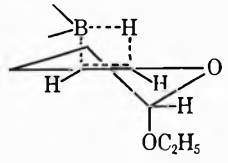
olefin was completely converted into the trialkylborane. Oxidation of the organoborane produced a 72:28 mixture of isomeric 2-ethoxy-5-hydroxytetrahydropyrans, which was isolated in 70% yield. Increasing the steric



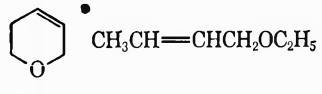
cis–trans mixture

requirements of the hydroborating agent altered the *cis/trans* ratio only slightly. Thus hydroboration of the olefin with disiamylborane [bis(3-methyl-2-butyl)-borane] and subsequent oxidation gave a 92% yield (glpc) of an 80:20 mixture of 2-ethoxy-5-hydroxytetrahydropyrans.

The methoxy group in 2-methoxytetrahydropyran has been reported to occupy the axial rather than the equatorial position (anomeric effect).[5] Assuming that the ethoxy group in 2-ethoxy-3,4-dihydropyran exhibits a similar conformational preference, and that the activated complex for the hydroboration reaction resembles the reactants in structure and energy,[6] the *trans*-2-ethoxy-5-hydroxytetrahydropyran should be the isomer which is formed preferentially.[7]

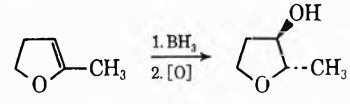


The effect of the ring oxygen on the direction of BH addition is markedly attenuated with Δ^3-dihydropyran. Thus hydroboration of this olefin with diborane followed by oxidation gave a 55% yield of 3-hydroxytetrahydropyran and a 30% yield of 4-hydroxytetrahydropyran. It is noteworthy that the analogous acyclic allyl ether, crotyl ethyl ether, yields on treatment with diborane 84% β-ethoxyalkylborane derivative.[8] Both of these observations must result as a consequence of the electron-withdrawing inductive effect of the alkoxy substituent, since the oxygens in these systems are not able to affect the electron distribution by mesomeric interaction with the double bonds.



Hydroboration of the 2,3- and 2,5-dihydrofurans with diborane at 0° proceeded readily to the trialkylborane stage. Oxidation of the trialkylborane derived from 2,3-dihydrofuran gave an 78% yield of 3-hydroxytetrahydrofuran, pointing again to the strong directive influence of a vinyl ether oxygen. Hydroboration of the symmetrically substituted double bond of 2,5-dihydrofuran followed by oxidation afforded an 84% yield of 3-hydroxytetrahydrofuran.

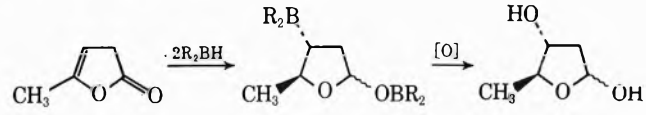
Finally, addition of diborane to 2-methyl-4,5-dihydrofuran, which resulted in the formation of the trialkylborane, gave after oxidation an 80% yield of *trans*-3-hydroxy-2-methyltetrahydrofuran. The assignment of



the *trans* configuration to the alcohol is based on the well established facts that the BH addition proceeds in a *cis* manner and that oxidation of the B–C bond occurs with retention of configuration.

A summary of the experimental results obtained from the hydroborations of the oxygen-containing heterocyclic olefins is shown in Table I.

It should be pointed out here that the hydroboration–oxidation of α,β-unsaturated dihydropyrans and dihydrofurans containing alkoxy groups adjacent to the ring oxygens provides a novel approach to the synthesis of deoxy sugars. Unsaturated lactones, such as crotonolactone and the α- and β-angelicalactones, may also serve as precursors for deoxy derivatives, since the lactone function is reduced by dialkylboranes to the corresponding hydroxyaldehyde.[9]



Relative Reactivity Studies.—In determining the reaction stoichiometries in the hydroborations of the dihydropyrans and dihydrofurans, we noticed major differences in their reactivities toward diborane. To gather more information about the effects of olefin structure on the rates of hydroboration, a number of dihydropyrans and dihydrofurans, as well as their corresponding carbocyclic analogs, were subjected to competition experiments using disiamylborane. In a typical example, 25 mmol of Δ^2-dihydropyran and 25 mmol of cyclohexene were treated at 25° with 26 mmol of disiamylborane. After completion of the hydroboration, the reaction mixture was analyzed by glpc for

(5) C. B. Anderson and D. T. Sepp, *Chem. Ind.* (London), 2054 (1964); *J. Org. Chem.*, **32**, 607 (1967).

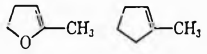
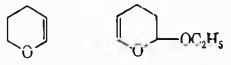
(6) J. Klein, E. Dunkelblum, and D. Avrahami, *ibid.*, **32**, 935 (1967).

(7) A slight preference for the addition of boron *trans* to a methoxy group was also observed in the hydroborations of 3- and 4-methoxycyclohexene: D. J. Pasto and J. Hickman, *J. Amer. Chem. Soc.*, **90**, 4445 (1968).

(8) H. C. Brown and R. M. Gallivan, *ibid.*, **90**, 2906 (1968).

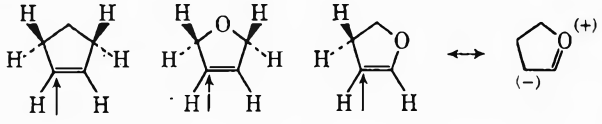
(9) H. C. Brown and D. B. Bigley, *ibid.*, **83**, 486 (1961).

TABLE II
COMPETITIONS OF VARIOUS HETEROCYCLIC AND CARBOCYCLIC OLEFINS FOR DISIAMYLBORANE

Olefin pair	Reacn temp, °C	Reacn time, hr	Ratio of olefins reacted (normalized)
	0	2	54:46
	0	1	90:10
	0	1	98:2
	0	2	94:6
	25	2	53:47
	25	2	58:42

unreacted olefins using cyclohexane as an internal standard. The results of these experiments are summarized in Table II.

Inspection of the data reveals several interesting features. 2,5-Dihydrofuran reacts with disiamylborane at a rate comparable with that of cyclopentene. However, the vinyl ether, 2,3-dihydrofuran, exhibits a marked rate enhancement as compared with the 2,5-dihydro derivative or with its carbocyclic analog, although the steric environments for attack by disiamylborane should be quite similar for all three olefins.



It has been suggested that the four-center[10] or π-complexlike[11] activated complexes for the hydroboration of olefins have structures resembling the starting materials.[6] Electron donation by resonance from oxygen into the double bond[12] would explain both the favored electrophilic attack by disiamylborane at the C-3 of 2,3-dihydrofuran and its enhanced reactivity.

It must be pointed out that, although Δ^2-dihydropyran reacts with disiamylborane to give the β-organoborane in 90% yield, it does not show rate enhancement when compared with cyclohexene. Besides the increased steric hindrance factors, reduced mesomeric interaction of the nonbonded pair of electrons on oxygen with the double bond in the less planar dihydropyran may be responsible for the decreased reactivity of this olefin.

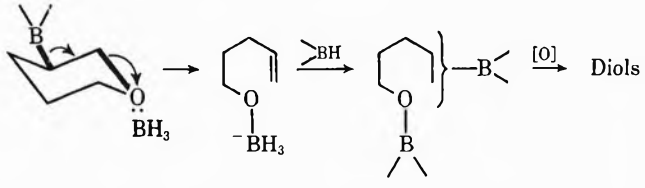
Formation of Acyclic Diols from Hydroboration of Δ^2-Dihydropyran.—It was observed that the 3-hydroxytetrahydropyrans and 3-hydroxytetrahydrofurans, produced from hydroborations of the appropriate olefins with diborane in a 3:1 ratio followed by oxidation, were obtained along with 5–10% yields of acyclic diols. Moreover, it was noticed that the amount of diols produced increased significantly when an excess of diborane was utilized in the hydroboration step. To investigate the nature of the reactions leading to the formation of diols, Δ^2-dihydropyran was hydroborated under various conditions. The experimental results are shown in Table III.

TABLE III
EFFECT OF ADDING ADDITIONAL BORANE[a] AT 25° TO THE TRIALKYLBORANE DERIVED FROM HYDROBORATION OF Δ^2-DIHYDROPYRAN

Hydroborating agent	Additional added borane	Reacn time, hr	Oxidation products, %[b] 3-Hydroxytetrahydropyran	Pentanediol 1,4-	Pentanediol 1,5-
BH_3	None	2	83	4	5
		24	82	2	4
	BH_3	1	45	27	24
		24	31	27	36
		24[c]	36	20	33
R_2BH[d]	None	24	89	Trace	Trace
	R_2BH[d]	24	83	<2	<3
	BH_3	1	72	10	14
		24	49	14	23

[a] The additional borane (25 mmol) in tetrahydrofuran solution was added to 8.3 mmol of the trialkylborane in tetrahydrofuran. [b] Yield by glpc analysis. [c] Diborane (33 mmol of BH_3) was added in one portion to 25 mmol of the olefin. [d] R_2BH = disiamylborane.

A possible mechanism for formation of the diols can be envisaged as proceeding *via* a BH_3-catalyzed elimination. This produces the unsaturated derivative,[13] which is subsequently rehydroborated to afford, after oxidation, the observed diols.



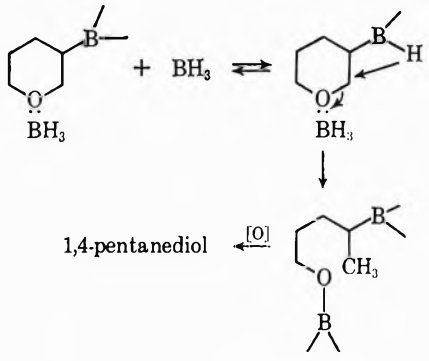
Evidence in support of the proposed function of BH_3 in the elimination step comes from the observation that the β-organoborane does not undergo elimination in the presence of added disiamylborane (Table II). Disiamylborane exists as a dimer in tetrahydrofuran solution,[14] and hence cannot coordinate with the ring oxygen of the pyran ring. That a *trans* elimination should be the preferred reaction path is suggested by the arrangement of the departing groups, the boron moiety and oxygen, with the boron being in an equatorial position.

In exploring this reaction in more detail, it became apparent that the postulated unsaturated boron derivative, $H_2C{=}CH(CH_2)_2CH_2OB<$, could not be the sole precursor for the observed diols. To simulate the rehydroboration step, 25 mmol of 4-penten-1-ol in tetrahydrofuran was added to 25 mmol of BH_3 at 25°. Oxidation of the reaction mixture and glpc analysis revealed the formation in 86% yield of a 12:88 mixture of 1,4- and 1,5-pentanediol.[15] This ratio is markedly different from the 43:57 ratio observed in the hydroboration of Δ^2-dihydropyran with excess diborane (Table

(10) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **83**, 2544 (1961).
(11) A. Streitwieser, L. Verbit, and R. Bittman, *J. Org. Chem.*, **32**, 1530 (1967).
(12) Hückel molecular orbital calculations on enol ethers predict the greatest electron density at the β carbon: A. Hassner, R. E. Barnett, P. Catsoulacos, and S. H. Wilen, *J. Amer. Chem. Soc.*, **91**, 2632 (1969).
(13) The reaction may involve the intermediacy of a cationic boron species which is stabilized by solvation with the electron-donating solvent tetrahydrofuran (>B$^+$THF).[3]
(14) H. C. Brown and G. J. Klender, *Inorg. Chem.*, **1**, 204 (1962).
(15) Hydroboration of 3-buten-1-ol with diborane followed by oxidation yielded a 15:85 mixture of 1,3- and 1,4-butanediol: H. C. Brown and M. K. Unni, *J. Amer. Chem. Soc.*, **90**, 2902 (1968).

III). Consequently, at least part of the 1,4 diol must have arisen *via* an alternate route.

Possible mechanisms which could account for formation of the extra 1,4 diol are cleavage of the tetrahydropyran ring by diborane[16] and/or intramolecular transfer of hydride from boron to C-2.[17] In the latter case a redistribution reaction would have to precede the transfer reaction.



The results in Table III also indicate that the elimination–rehydroboration reaction proceeds at a much slower pace when diborane is added to the organoborane derived from Δ^2-dihydropyran and disiamylborane. It is conceivable that the bulky siamyl groups hinder coordination of tetrahydrofuran with boron, which should facilitate the *trans* elimination.[13,18]

Routes to Unsaturated Alcohols *via* Hydroboration of Dihydropyrans and Dihydrofurans.—The use of a Lewis acid which does not react with double bonds should permit the synthesis of unsaturated alcohols from dihydropyrans and dihydrofurans *via* the hydroboration–elimination sequence postulated earlier. Pasto and Snyder have reported that β-ethoxyorganoboranes undergo *trans* elimination in the presence of boron trifluoride.[17]

Addition of boron trifluoride etherate to the β-organoboranes derived from hydroboration of Δ^2-dihydropyran, 2,3- and 2,5-dihydrofuran, and 2-methyl-4,5-dihydrofuran with diborane resulted in formation of the corresponding unsaturated alcohols as predicted. The experimental results are summarized in Table IV.

TABLE IV

UNSATURATED ALCOHOLS OBTAINED BY ADDITION OF BF_3 ETHERATE AT 25° TO THE TRIALKYLBORANES IN TETRAHYDROFURAN SOLUTION DERIVED FROM HYDROBORATION OF Δ^2-DIHYDROPYRAN AND VARIOUS DIHYDROFURANS

Organoborane derived from	Ratio of BF_3: olefin	Reacn time, hr	Product	Yield, %[a]
Δ^2-Dihydropyran	...	12	3-Hydroxytetrahydropyran	81
			4-Penten-1-ol	0
	1:10	12	3-Hydroxytetrahydropyran	36
			4-Penten-1-ol	50
	1:1	12	3-Hydroxytetrahydropyran	1
			4-Penten-1-ol	81
2,5-Dihydrofuran	1:1	2	3-Buten-1-ol	71
2,3-Dihydrofuran	1:1	2	3-Buten-1-ol	70
2-Methyl-4,5-dihydrofuran	1:1	1	*trans*-3-Penten-1-ol	88

[a] Yields by glpc analysis.

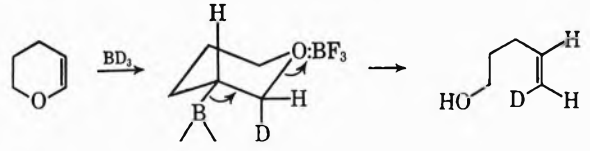
(16) J. Kollonitsch, *J. Amer. Chem. Soc.*, **83**, 1515 (1961).

(17) D. J. Pasto and S. R. Snyder, *J. Org. Chem.*, **31**, 2777 (1966).

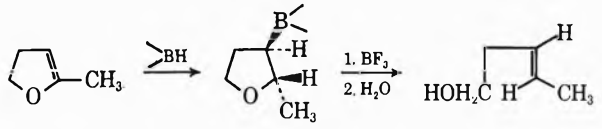
(18) A similar explanation was offered by Brown and Knights regarding the greater stability of the *trans* β adducts derived from hydroboration of 3-cyclopentene derivatives with disiamylborane: H. C. Brown and E. F. Knights, *J. Amer. Chem. Soc.*, **90**, 4439 (1968).

It should be noted that boron trifluoride acts catalytically, since a 1:10 ratio of BF_3 to olefin afforded a 50% yield of 4-penten-1-ol. Consequently, the hydroboration of olefins containing functional groups that are prone to undergo elimination must be carried out with diborane which is free of boron trifluoride.[19]

The catalytic role of boron trifluoride in these reactions can be depicted as facilitating the breaking of the carbon–oxygen bond, and resultant loss of boron, by coordination with the oxygen. Based on stereoelectronic considerations, one would predict, as mentioned earlier, that the elimination should proceed in a *trans* manner. This prediction was confirmed by the observation that *cis*-5-*d*-4-penten-1-ol was obtained after work-up from the β-organoborane derived from hydroboration of Δ^2-dihydropyran with deuterioborane



(BD_3). Also, hydroboration of 2-methyl-4,5-dihydrofuran with diborane, followed by subsequent addition of boron trifluoride, afforded only *trans*-3-penten-1-ol.



It was pointed out in the preceding discussion that the reaction of Δ^2-dihydropyran with excess diborane affords a 43:57 mixture of 1,4- and 1,5-diols, whereas hydroboration of 4-penten-1-ol gives a 12:88 distribution. Therefore, a combination of the hydroboration–elimination–rehydroboration sequence should convert Δ^2-dihydropyran mainly into 1,5-pentanediol. Treatment of Δ^2-dihydropyran with the stoichiometric amount of diborane, followed by addition of boron trifluoride etherate and rehydroboration of the unsaturated intermediate with diborane, yielded after oxidation 72% 1,5-pentanediol and only 9% 1,4 isomer. This 11:89 distribution of 1,4- to 1,5-diols is similar to the ratio of diols obtained from the hydroboration of 4-penten-1-ol.

Experimental Section

Materials.—Tetrahydrofuran, diglyme, and boron trifluoride etherate were purified as described previously.[20] Sodium borohydride (98% pure) and lithium deuteride (98% D) were obtained from Metal Hydrides, Inc. Diborane was generated from boron trifluoride etherate and sodium borohydride,[19] and was bubbled through a solution of sodium borohydride in diglyme before being passed into freshly distilled tetrahydrofuran. Likewise, diborane-d_6, prepared as described previously,[20] was bubbled through a suspension of lithium deuteride in diglyme before being passed into tetrahydrofuran. The preparation of disiamylborane in tetrahydrofuran has been previously described.[21]

Commercial samples of Δ^2-dihydropyran (Matheson Coleman and Bell), 2-ethoxy-4,5-dihydrofuran (K & K), 2,5-dihydrofuran (Aldrich), and 2-methyl-4,5-dihydrofuran (Aldrich) were puri-

(19) To ensure the absence of traces of boron trifluoride, which could catalyze the elimination reaction, the diborane generated from BF_3 etherate and $NaBH_4$ was bubbled through a solution of $NaBH_4$ in diglyme before being passed into freshly distilled tetrahydrofuran.

(20) G. Zweifel and H. Arzoumanian, *ibid.*, **89**, 291 (1967).

(21) G. Zweifel, K. Nagase, and H. C. Brown, *ibid.*, **84**, 190 (1962).

fied before use by fractional distillation. Δ^3-Dihydropyran[22] and 2,3-dihydrofuran[23] were prepared according to published procedures.

Stoichiometry and Product Studies.—In a typical experiment, 4.4 ml of a 2.0 *M* solution of borane in tetrahydrofuran (26.4 mequiv of hydride) was added to 2.1 g (25 mmol) of Δ^2-dihydropyran in 20 ml of tetrahydrofuran at 25°. After the reaction mixture had been stirred for a given period of time, 1:1 glycerol–water was added and the hydrogen evolved was measured volumetrically with a gas buret. The organoborane was oxidized at 30–50° by adding 5 ml of 3 *N* sodium hydroxide, followed by dropwise addition of 3 ml of 30% hydrogen peroxide. The reaction mixture was saturated with potassium carbonate ($K_2CO_3 \cdot 1^1/_2H_2O$), and the organic layer formed was separated. The aqueous phase was extracted twice with ether, and the combined organic layers were dried ($MgSO_4$). The yields of 3-hydroxytetrahydropyran, 1,4-pentanediol, and 1,5-pentanediol were determined by glpc using internal standards as references. The experimental results are summarized in Table I.

3-Hydroxytetrahydropyran.—To 8.4 g (0.10 mol) of Δ^2-dihydropyran in 60 ml of tetrahydrofuran was added 17.5 ml of a 2.0 *M* solution of borane in tetrahydrofuran (0.105 equiv of hydride) at 0–5°. After the reaction mixture had been stirred at 0° for 3 hr, the temperature was raised to 25° and the mixture was stirred at this temperature for an additional 2 hr. The organoborane formed was oxidized at 30–50° by adding 18 ml of 3 *N* sodium hydroxide followed by dropwise addition of 12 ml of 30% hydrogen peroxide. After the reaction mixture had been stirred for 1 hr at room temperature, sodium chloride was added and the upper phase formed was separated. The aqueous phase was extracted with ether and the combined extracts were dried ($MgSO_4$). Distillation yielded 7.1 g (70%) of 3-hydroxytetrahydropyran, bp 90° (21 mm), $n^{21}D$ 1.4572. The 3,5-dinitrobenzoate derivative was obtained, mp 133–134° [lit.[1] bp 92–95° (12–15 mm), $n^{21}D$ 1.4571].

2-Ethoxy-5-hydroxytetrahydropyran.—To 12.8 g (0.10 mol) of 2-ethoxy-3,4-dihydropyran in 60 ml of tetrahydrofuran was added 18.5 ml of a 1.9 *M* solution of borane in tetrahydrofuran (0.105 equiv of hydride) at 25°. After the reaction mixture had been stirred at room temperature for 5 hr, the organoborane formed was oxidized at 30–50° by adding 15 ml of 3 *N* sodium hydroxide and 12 ml of 30% hydrogen peroxide. After the mixture had been stirred for 1 hr, the aqueous phase was saturated with potassium carbonate ($K_2CO_3 \cdot 1^1/_2H_2O$) and the organic layer formed was separated. The aqueous phase was extracted twice with 35-ml portions of tetrahydrofuran, and the combined extracts were dried ($MgSO_4$). Distillation gave 10.2 g (70%) of 2-ethoxy-5-hydroxytetrahydropyran, bp 64–66° (1 mm), $n^{22}D$ 1.4505.

Anal. Calcd for $C_7H_{14}O_3$: C, 57.49; H, 9.65. Found: C, 57.42; H, 9.70.

***trans*-2-Methyl-3-hydroxytetrahydrofuran.**—To 2.1 g (25 mmol) of 2-methyl-4,5-dihydrofuran in 20 ml of tetrahydrofuran was added 3.6 ml of a 2.42 *M* solution of borane in tetrahydrofuran (26.4 mequiv of hydride) at 0°. After the mixture had been stirred at this temperature for 2 hr, it was oxidized by adding 5 ml of 3 *N* sodium hydroxide and 3 ml of 30% hydrogen peroxide and was extracted repeatedly with ether. Distillation yielded 1.4 g (55%) of *trans*-2-methyl-3-hydroxytetrahydrofuran, bp 91° (21 mm), $n^{22}D$ 1.4420. The 3,5-dinitrobenzoate derivative was obtained, mp 113–114°.

Anal. Calcd for $C_{12}H_{12}N_2O_7$: C, 48.65; H, 4.08; N, 9.46. Found: C, 48.54; H, 4.14; N, 9.36.

Competitive Hydroboration Experiments.—In a typical experiment, 2.10 g (25 mmol) of Δ^2-dihydropyran, 2.05 g (25 mmol) of cyclohexene, and 1.76 g (21 mmol) of cyclohexane in 5 ml of tetrahydrofuran were placed in a 100-ml flask. To this mixture was added 22 ml of a 1.2 *M* solution of disiamylborane in tetrahydrofuran (26.4 mequiv of hydride) at 25°. Aliquots were removed after 0.5, 1.0, and 2.0 hr, quenched in an ice-cooled mixture containing 3 *N* sodium hydroxide and *n*-pentane, and analyzed by glpc for remaining olefins by using the cyclohexane as an internal standard.

The experimental results are summarized in Table II.

Elimination Reactions with Diborane.—In a typical experiment, 4.17 ml of a 2.0 *M* solution of borane in tetrahydrofuran (25 mequiv of hydride) was added to 2.3 g (27.5 mmol) of Δ^2-dihydropyran in 5 ml of tetrahydrofuran at 25°. After the mixture had been stirred for 2 hr at this temperature, an additional 12.5 ml of a 2.0 *M* solution of borane (25 mequiv) in tetrahydrofuran was added. The reaction mixture was maintained at 25° for 24 hr before being oxidized with alkaline hydrogen peroxide (5 ml of 3 *N* sodium hydroxide and 3 ml of 30% hydrogen peroxide). The yields of 3-hydroxytetrahydropyran and of the pentanediols were determined by glpc using internal standards as references. The experimental results are summarized in Table III.

Elimination Reactions with Boron Trifluoride.—In a typical experiment, 27.5 mmol of Δ^2-dihydropyran was converted into the organoborane as described above. To this was added 28 mmol of boron trifluoride etherate. The reaction mixture was stirred at 25° for 12 hr; then enough 3 *N* sodium hydroxide was added to make the mixture basic. The organoborane was oxidized at 30–50° by adding 3 ml of 30% hydrogen peroxide and the products formed were analyzed by glpc. The reaction time and amount of boron trifluoride etherate added were varied in individual experiments. The results of these investigations are summarized in Table IV.

4-Penten-1-ol.—To 9.2 g (0.11 mol) of Δ^2-dihydropyran in 60 ml of tetrahydrofuran was added 13.1 ml of a 2.55 *M* solution of borane in tetrahydrofuran (0.10 equiv of hydride) at 0–5°. The reaction mixture was maintained at 0–5° for 3 hr and then at 25° for 2 hr. To the organoborane formed was added 0.110 mol of boron trifluoride etherate. The reaction mixture was stirred at 25° for 24 hr, made basic by adding 3 *N* sodium hydroxide, and saturated with sodium chloride. Distillation yielded 5.1 g (60%) of 4-penten-1-ol, bp 70° (52 mm), $n^{21}D$ 1.4288 [lit.[24] bp 76° (60 mm), $n^{20}D$ 1.4299]. The 3,5-dinitrobenzoate derivative was obtained, mp 44–45° (lit.[25] mp 44–45°).

Hydroboration of Δ^2-Dihydropyran with BD_3 Followed by Addition of Boron Trifluoride Etherate.—To 2.3 g (27.5 mmol) of Δ^2-dihydropyran in 20 ml of tetrahydrofuran was added at 0° 6.4 ml of a 1.3 *M* solution of deuterioborane (25 mequiv of deuteride) in tetrahydrofuran. The solution was stirred for 2 hr at 0–5° and for an additional one hr at 25°. The reaction mixture was then treated with 28 mmol of boron trifluoride etherate, stirred at 25° for 24 hr, made basic by adding 3 *N* sodium hydroxide, and saturated with potassium carbonate. The organic layer was separated, dried ($MgSO_4$), filtered, and distilled to give *cis*-5-*d*-4-penten-1-ol, bp 68° (35 mm), $\delta_{TMS}^{CCl_4}$ 5.16 (d, 1, J = 11 Hz, *cis* DHC=CH) and 6.07 ppm (m, 1, *cis* DHC=CH).

1,5-Pentanediol.—In a 125-ml flask was placed 2.31 g (27.5 mmol) of Δ^2-dihydropyran in 5 ml of tetrahydrofuran. Hydroboration was achieved by dropwise addition of 4.2 ml of a 2.0 *M* solution of borane (25 mequiv of hydride) in tetrahydrofuran. The solution was stirred for 2 hr at room temperature treated with 28 mmol of boron trifluoride etherate, and stirred for 12 hr at 25°. After having been diluted with 25 ml of tetrahydrofuran followed by the addition of 4.2 ml of a 2.0 *M* solution of borane (25 mequiv of hydride) in tetrahydrofuran, the reaction mixture was stirred for 1 hr at 25°. The organoborane formed was oxidized at 30–40° by adding 5 ml of 3 *N* sodium hydroxide followed by dropwise addition of 3 ml of 30% hydrogen peroxide. The reaction mixture was stirred for an additional 1 hr and then saturated with potassium carbonate ($K_2CO_3 \cdot 1^1/_2H_2O$), and the organic phase was separated and dried ($MgSO_4$). Analysis by glpc on a silicone–sorbitol column revealed the formation of 72% 1,5-pentanediol and 9% 1,4-pentanediol.

Registry No. 3-Hydroxytetrahydropyran, 19752-84-2; 2-ethoxy-5-hydroxytetrahydropyran, 23062-30-8; *trans*-2-methyl-3-hydroxytetrahydrofuran, 23061-82-7; *trans*-2-methyl-3-hydroxytetrahydrofuran 3,5-dinitrobenzoate, 23061-83-8; *cis*-5-*d*-4-penten-1-ol, 23061-84-9.

(22) J. Cologne and R. Boisde, *Bull. Soc. Chim. Fr.*, 824 (1956).
(23) R. Paul, M. Fluchaire, and G. Collardeau, *ibid.*, 668 (1950).
(24) M. S. Kharasch and C. F. Fuchs, *J. Org. Chem.*, **9**, 359 (1944).
(25) H. P. Thomas and C. L. Wilson, *J. Amer. Chem. Soc.*, **73**, 4803 (1951).

Tautomerism of 2-Ethoxy-4-pyrimidinone

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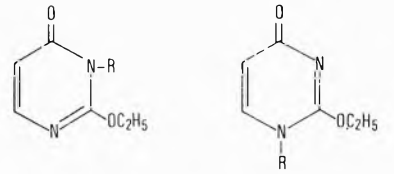
Received July 22, 1969

The fine structure of 2-ethoxy-4-pyrimidinone was studied by comparing its ultraviolet spectrum with that of its N-alkyl derivative. In aqueous solution, both *o*- (**1a**) and *p*-quinonoid (**2a**) forms are equally represented. In chloroform the *ortho* form predominates; this conclusion is further supported by the value of the stretching vibration of the NH bond.

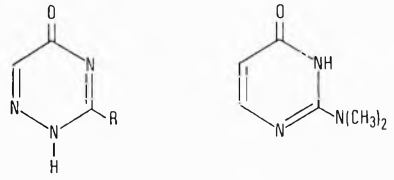
The tautomeric equilibria involving *o*- and *p*-quinonoid forms (*e.g.*, **1a** and **2a**, respectively) are generally less one-sided than other tautomeric equilibria in heterocycles. In this work 2-ethoxy-4-pyrimidinone (**1a**–**2a**) was studied, and the results together with data from the literature are used for a modification of Mason's rule[1,2] covering ν_{NH} frequencies in similar compounds. The tautomerism of 2-ethoxy-4-pyrimidinone has been previously studied briefly by Shugar and Fox[3] and by Waring and Katritzky;[4] the compound is clearly in the oxo form[4] and the value of ν_{NH} in chloroform[4,5] indicates the predominance of the form **1a** by application of Mason's rule.

Derivatives with fixed and unequivocal *o*- and *p*-quinonoid structures were required for this study. The unsubstituted **1a**–**2a**, by reaction with diazomethane in ether, gave 2-ethoxy-3-methyl-4-pyrimidinone (**1b**), the structure of which was established by hydrolysis to 3-methyluracil. 2-Ethoxy-4-methoxypyrimidine is another product of the reaction; the structure follows from the methylation by methyl iodide, which gives 1-methyl-4-methoxy-2-pyrimidinone by the Hilbert–Johnson reaction.[6] So-called cyclouridines are compounds of type **2**, but apparently caution is necessary, as strains in these heterocycles change the uv spectrum considerably. Thus $O^2:5'$ cyclo derivatives of uridine have one band,[7,8] at *ca.* 237 mμ; $O^2:2'$ derivatives have two bands,[9,10] at *ca.* 250 and 225 mμ. These strains should be lower in O^2-alkyluridine derivatives. These absorb[9] at *ca.* 250 and 230 mμ. In our study we used 2′,3′-O-isopropylidine-O^2-ethyluridine (**2c**). We also tried to prepare simpler derivatives of type **2**, starting directly from the unsubstituted **1a**–**2a**. Alkylations under different conditions did not give the desired derivative, but led to substitution on the oxygen atom followed by nitrogen alkylation to give derivatives of 2-pyrimidinone; other products were of the *o*-quinonoid type **1**. Eventually we found that vinylation of **1a**–**2a** with vinyl acetate, catalyzed by mercuric acetate and sulfuric acid, gives 1-vinyl-2-ethoxy-4-pyrimidinone. The structure of this compound was established by hydrogenation and hydrolysis, which ultimately led to 1-ethyl-5,6-dihydrouracil. Partial hydrogenation of the vinyl compound then gave 1-ethyl-2-ethoxy-4-pyrimidinone (**2b**) with uv maxima at 256 and 225 mμ. Comparison of uv spectra of **1b** and **2b** confirms the observation that *o*-quinonoid compounds adsorb[11] at longer wavelengths than the *para* isomers.



1 a, R=H
b, R=CH_3

2 a, R=H
b, R=C_2H_5
c, R=2′,3′-O-isopropylidene-1-β-D-ribofuranosil



3 a, R=SCH_3
b, R=$N(CH_3)_2$

4

5

Uv spectra of **1a**–**2a**, **1b**, and **2c** in chloroform[12] (Figure 1) show clearly that the *o*-quinonoid form **1a** predominates over **2a**. In the ir spectrum (same solvent), **1a**–**2a** has ν_{NH} as a singlet at 3387 cm^{-1}, indicating that only one form is present; variation of temperature (20–55°) failed to bring about the appearance of any new band which could be attributed to **2a**. The situation in neutral aqueous solutions is quite different. Compound **1a**–**2a** displays a large spectral shift from 273 mμ in chloroform to 258 mμ in water solution; comparison of the spectra in Figure 2 shows that both forms **1a** and **2a** are now present. Graphical matching (system **1** and **2**, **a** and **b**) suggests approximately equal proportions of **1a** and **2a**; the tautomeric constant is then *ca.* 1; if the temperature is raised the proportion of **1a** increases. The apparent explanation of this solvent dependence of the tautomeric equilibrium lies in

(1) A. R. Katritzky and L. M. Lagowski, *Advan. Heterocycl. Chem.*, **1**, 339 (1963).
(2) S. F. Mason, *J. Chem. Soc.*, 4874 (1957).
(3) D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1952).
(4) A. R. Katritzky and A. J. Waring, *J. Chem. Soc.*, 1540 (1962).
(5) The value of ν_{NH} in the present paper is different by 42 cm^{-1} from the published[4] one.
(6) G. E. Hilbert and T. B. Johnson, *J. Amer. Chem. Soc.*, **52**, 2001 (1930).
(7) All spectral data given in this paper correspond to neutral forms.
(8) D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, 868 (1957).
(9) D. M. Brown, A. R. Todd, and S. Varadarajan, *ibid.*, 2388 (1956).
(10) J. J. Fox and I. Wempen, *Tetrahedron Lett.*, 643 (1965).
(11) J. A. Berson, *J. Amer. Chem. Soc.*, **75**, 3521 (1953).
(12) All data on chloroform solutions were measured under dilutions where intermolecular association is negligible, as checked by ir.

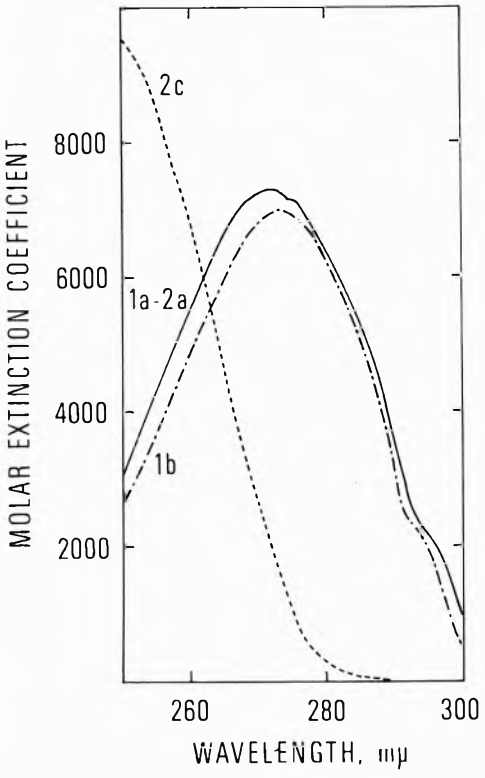


Figure 1.—Ultraviolet spectra in chloroform solution; each curve is labeled by the corresponding formula number.

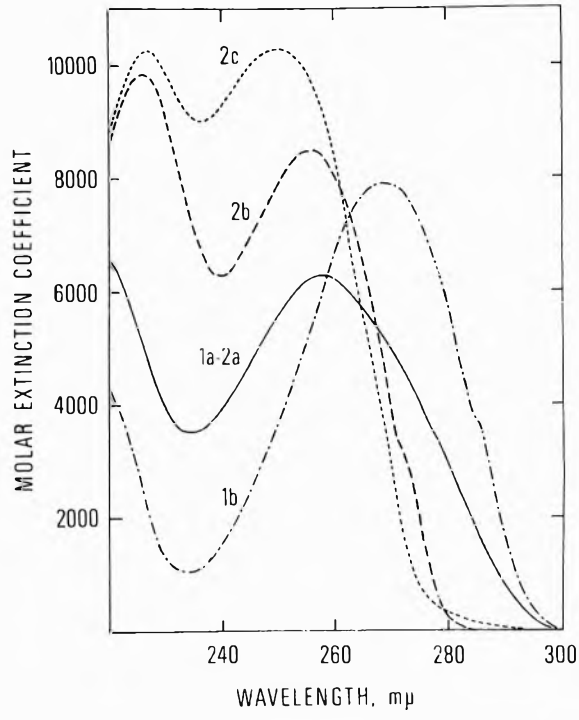


Figure 2.—Ultraviolet spectra of neutral molecules in aqueous buffer; each curve is labeled by formula numbers.

the different solvation energies; the more polar form **2a** is favored in the more polar solvent.

Our observations on the **1a**–**2a** tautomeric system both in water and nonpolar solvents are comparable with similar results[13–15] with 2-amino-4-pyrimidinone; the situation apparently is not changed by the difference in substitution of position 2. On the other hand, the low energetic difference between the *ortho* and *para* forms enables changes, similar to those induced by solvent, to be effected also by a proper ring substitution. Thus, in **3a** and **3b** the *ortho* form would have the hydrogen atom in the 3 position, which has a lower electron density and therefore a higher acidity in 6-aza analogs of pyrimidines; in both cases the *para* forms are predominant.[16–18]

For the study of *o*–*p*-quinonoid tautomerisms in nonpolar solutions, a useful rule was formulated by Mason.[1,2] He observed ν_{NH} of *o*-quinonoid forms to be generally lower (3360–3420 cm^{-1}) than ν_{NH} of *p*-quinonoid forms (3415–3445 cm^{-1}). 2-Ethoxy-4-pyrimidinone has ν_{NH} at 3387 cm^{-1}, indicating that only the *ortho* form **1a** is present in chloroform solutions and at 20–50°, the conditions under which the spectra were measured.

It is interesting to note that compounds **1a**, **3b**, and **4** have ν_{NH} values in accordance with the rule (3387, 3445, and 3405 cm^{-1}, respectively[19]), while the value for **3a** is clearly too low[16,17] (3401 cm^{-1}) and forms the only known exception to the rule. This unusual decrease could be explained by the proximity of the colinear lone electron pair to the NH bond, as illustrated in structure **5**; such a geometrical arrangement is known[20] to lower ν_{NH} considerably (10–30 cm^{-1}). In contrast, the closely similar **3b** absorbs as predicted by the rule; the only lone electron pair of the exocyclic nitrogen is conjugated with the ring and so, being in the perpendicular rather than colinear position, does not decrease the frequency of the NH bond.

Experimental Section

Melting points were determined on a hot stage and are not corrected. Uv spectra were measured with a Cary 14 spectrophotometer. For aqueous solution, phosphate buffers and 10-mm cells were used; chloroform spectra were measured using spectro quality solvent and 2-mm cells. The temperature dependence of uv spectra was recorded on a Gilford Model 2400 recording spectrophotometer. Infrared spectra were measured with a Beckman IR-12 spectrophotometer. For identification purposes the potassium bromide technique was used. Stretching vibrations of NH bonds were studied in chloroform solutions as concentrations of *ca.* 1 mg/ml; 10-mm Infrasil cells with thermostated jackets were used.

2-Ethoxy-4-pyrimidinone.—For spectral study the compound[21] was recrystallized six times from water; the ir spectrum remained constant after the second recrystallization.

Reaction of 2-Ethoxy-4-pyrimidinone with Diazomethane.—2-Ethoxy-4-pyrimidinone (1 g) was dissolved in 50 ml of dry tetrahydrofuran; an excess of diazomethane in ether was then added and the solution was left for 4 days at 5°. The solvent was then evaporated *in vacuo*, the resulting crystals were dissolved in ether, and the solution was extracted with 1 *N* NaOH. The ethereal solution was dried with magnesium sulfate and evaporated; a mixture of crystals and oil resulted. The crystals were purified by three recrystallizations from cyclohexane, followed by sublimation *in vacuo* (0.05 mm). The final yield was 190 mg (15%), mp 59–60°.

Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.57; H, 6.56; N, 18.11.

(13) H. Morita and S. Nagakura, *Theor. Chim. Acta*, **11**, 279 (1968).
(14) C. Heléne and P. Douzou, *Compt. Rend.*, **259**, 4387, 4853 (1964).
(15) D. J. Brown and T. Teitei, *Aust. J. Chem.*, **18**, 559 (1965).
(16) J. Jonas and J. Gut, *Collect. Czech. Chem. Commun.*, **27**, 1886 (1962).
(17) M. Horak and J. Gut, *ibid.*, **28**, 3392(1963).
(18) J. Pitha, P. Fiedler, and J. Gut, *ibid.*, **31**, 1964 (1966).
(19) The spectrum of compound 4 was measured in chloroform solution; variation of temperature (20–50°) failed to cause appearance of a new band corresponding to the other tautomeric form. The value for **3b** was published previously.[18]
(20) J. Pitha and S. Vasickova, *Collect. Czech. Chem. Commun.*, **30**, 1792 (1965).
(21) G. E. Hilbert and E. F. Jansen, *J. Amer. Chem. Soc.*, **57**, 552 (1935).

This substance is 2-ethoxy-3-methyl-4-pyrimidinone, as its hydrolysis (1 *N* hydrochloric acid, 1 hr boiling) gave 3-methyluracil; the identity was established by paper chromatography and ir spectra. The mother liquor from the recrystallizations from cyclohexane were evaporated, dissolved in ligroin, and left at 0° overnight. The crystals which formed were separated, the liquid was evaporated, the residue was distilled *in vacuo* (80° bath temperature, 10 mm); and 120 mg of oily distillate resulted, which remained as a liquid even after long standing at room temperature.

Anal. Calcd for $C_7H_{10}N_2O_2$: N, 18.17. Found: N, 17.88.

This substance is apparently 2-ethoxy-4-methoxypyrimidine, as reaction with excess methyl iodide at room temperature gave 1-methyl-4-methoxy-2-pyrimidinone. The identity of the product was established by the ir spectrum.

Preparation of 1-Vinyl-2-ethoxy-4-pyrimidinone.—A solution of 0.1 ml of concentrated sulfuric acid in 2 ml of ethyl acetate was added to a suspension of 0.5 g of mercuric acetate in 250 ml of vinyl acetate in a pressure flask. A clear solution resulted; 1.5 g of 2-ethoxy-4-pyrimidinone was then added. Nitrogen was bubbled through the solution and kept in a 50° bath for 2 days. Dry sodium acetate was then added, and the solution was stirred for 10 min and filtered. The filtrate was evaporated *in vacuo* and the residue was dissolved in chloroform. The chloroform solution was extracted five times with cold 1 *N* NaOH; the emulsion formed was separated by centrifugation. After drying, the chloroform fraction was evaporated *in vacuo;* yellow crystals and an oil remained. The crystals were first recrystallized from carbon tetrachloride and then from a large volume of cyclohexane, and sublimed *in vacuo* (0.05 mm). White crystals were obtained (200 mg, 10%): mp 97–99°; λ_{max} (0.05 *M* phosphate buffer, pH 7) 266 mμ (ε 12,800) and 240 (side band, 10,400); λ_{min} 222 mμ.

Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.81; H, 6.05; N, 16.88.

Hydrogenation of 1-Vinyl-2-ethoxy-4-pyrimidinone.—The vinyl compound (150 mg) was dissolved in 15 ml of ethanol and 15 ml of water, 75 mg of catalyst (5% Pd on carbon) was added, and the solution was hydrogenated at room temperature and atmospheric pressure. After 70 min, hydrogen corresponding approximately to one double bond had been consumed. The mixture was then filtered with Celite and the solution was evaporated, yielding crystals, mp 81–93° after recrystallization from a small volume of carbon tetrachloride and vacuum sublimation. Spectral properties indicated that 1-ethyl-2-ethoxy-4-pyrimidinone was the main component, but further purification was difficult. Attempted separation of impurities by extraction with alkali gave low yields, apparently owing to hydrolysis. Gas–liquid partition chromatography separation requires a high temperature (200°, Hewlett–Packard 700 laboratory chromatograph, 10% silicon fluid S-96 column), causing a partial isomerization. Finally, a pure compound was obtained through fractional vacuum sublimation. At 0.1-mm pressure and 65° (bath temperature) the sublimed fractions were monitored by disappearance of the ir band at 1680 cm^{-1}, which represents an impurity subliming before the desired compound. Fractions not having this absorption (60%), mp 94–97°, were recrystallized from tetrahydrofuran and resublimed, mp 99.5–100°; these operations did not change the ir spectrum.

Anal. Calcd for $C_8H_{12}N_2O_2$: N, 16.66. Found: N, 16.50.

Hydrogenation and Hydrolysis of 1-Vinyl-2-ethoxy-4-pyrimidinone.—The vinyl compound was hydrogenated in the same way as in the previous experiment. The residue after evaporation was dissolved in 10 ml of 1 *N* hydrochloric acid and left overnight. The solution was evaporated and the residue was resublimed *in vacuo* (0.05 mm), yielding 70 mg of white crystals, mp 130–140°, apparently a mixture. This product was dissolved in 80 ml of water, 40 mg of catalyst (5% Rh on Al_2O_3) was added, and the solution was hydrogenated in the same way as described earlier. After filtration, the solution was evaporated and the resulting crystals were sublimed *in vacuo*, giving 50 mg of sublimate which, according to the ir spectrum, is identical with 1-ethyl-5,6-dihydrouracil.

Registry No.—**1b,** 20541-38-2; **2b,** 23220-30-6; 2-ethoxy-4-methoxypyrimidine, 23220-28-2; 1-vinyl-2-ethoxy-4-pyrimidinone, 23220-29-3.

Acknowledgment.—This work was made possible through the kind interest and support of Dr. G. L. Eichhorn. Further, I would like to thank Dr. D. M. Brown and Dr. D. J. Brown for samples **2c** and **4**, respectively, and Dr. J. J. Butzow, Dr. J. J. Fox, Dr. P. J. Krueger, and Dr. C. H. Robinson for comments on the manuscript.

Cycloaddition Reactions of Thiete 1,1-Dioxides. The Preparation of 2-Thiabicyclo[2.2.0]hexane Derivatives[1]

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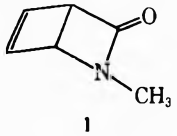
Received September 16, 1969

The reaction of thiete 1,1-dioxide and its 2,2-dimethyl derivative with typical enamines, ynamines, and dienamines has been studied. Cycloaddition resulted in the examples reported to give derivatives of the previously unknown 2-thiabicyclo[2.2.0]hexane system and of 7-thiabicyclo[4.2.0]oct-3-ene. Such condensations provide a ready synthetic entry to such molecules. The nmr spectra of the adducts are discussed.

In contrast with the recent surge of interest in bicyclo[2.2.0]hexane chemistry,[3] little attention has been paid to monoheteroatomic analogs of this strained bicyclic ring system. The only successful synthesis of a 2-azabicyclo[2.2.0]hexane derivative (**1**) was reported by Corey and Streith[4] in 1964. 1-Azabicyclo[2.2.0]-hexane (**2**) is recognized at this time only as a transitory intermediate.[5] Several 2-oxabicyclo[2.2.0]hexanes, such as **3**[4] and **4**,[6] are recognized to result from



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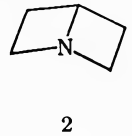

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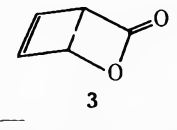

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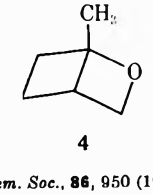


4

(1) Unsaturated Heterocyclic Systems. LXVIII. For the previous paper in this series, see L. A. Paquette, T. Kakihana, and J. F. Hansen, *Tetrahedron Lett.*, in press.

(2) NDEA Fellow, 1967–present.

(3) K. B. Wiberg, *Advan. Alicycl. Chem.*, **2**, 185 (1968).

(4) E. J. Corey and J. Streith, *J. Amer. Chem. Soc.*, **86**, 950 (1964).

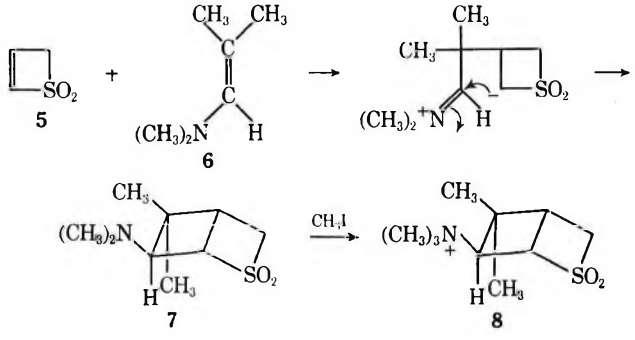
(5) C. A. Grob and V. Krasnobajew, *Helv. Chim. Acta*, **47**, 2145 (1964); I. N. Nazarov, N. S. Postakov, N. N. Mikhelva, and N. A. Tradkina, *J. Gen. Chem. USSR*, **29**, 2573 (1959); V. Prelog, E. Cerkovnikov, and G. Ustricev, *Justus Liebigs Ann. Chem.*, **535**, 37 (1938).

(6) R. Srinivasan, *J. Amer. Chem. Soc.*, **82**, 775 (1960).

certain intramolecular photochemical cycloadditions.[7]

With the twofold objective of preparing simple derivatives of the unknown 2-thiabicyclo[2.2.0]hexane system and of exploring further the cycloadditive propensity of thiete 1,1-dioxides, we have briefly investigated the reactions of **5** and **12** with a number of different types of electron-rich olefins. It was anticipated that the proven dienophilic capability of thiete 1,1-dioxides[8] would be increasingly evident in such condensations.

Enamines.—When thiete 1,1-dioxide (**5**) and 2-methyl-1-dimethylamino-1-propene (**6**) were refluxed in benzene solution for 24 hr, the 1:1 crystalline adduct **7** was obtained in 60% yield. That this substance was

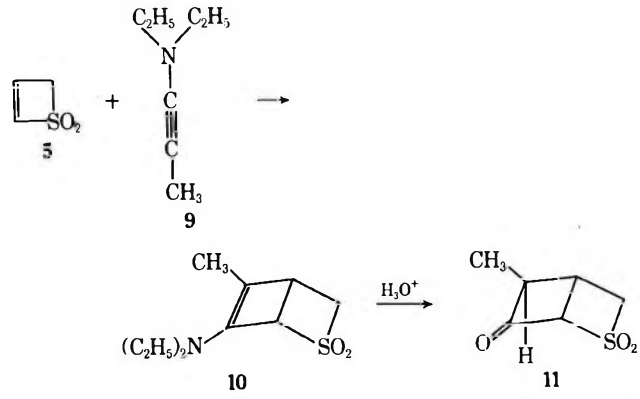


a 2-thiabicyclo[2.2.0]hexane derivative was clearly revealed by its nmr spectrum. Thus, in addition to the two six-proton singlets at δ 1.20 and 2.10 due to the methyl groups bonded to C_5 and nitrogen, respectively, there was seen a multiplet at 2.17–2.47 assigned to the H_4 proton, a doublet (J = 6 Hz) centered at 3.00 due to H_6, and a second multiplet at 3.87–4.42 ascribed to the three α-sulfonyl protons. Alternative structures for this product can be eliminated since they would be expected to exhibit either vinyl absorption or fewer α-sulfonyl protons.

The *exo* orientation of the dimethylamino group in **7** was assigned initially on the basis of the customary minimization of nonbonded steric interactions expected in the transition state for C_1C_6 bond formation. Substantiation of this assignment is seen in the magnitude of the H_1H_6 coupling constant (6 Hz) which is convincingly accommodated by the existing dihedral angle.[6,7a]

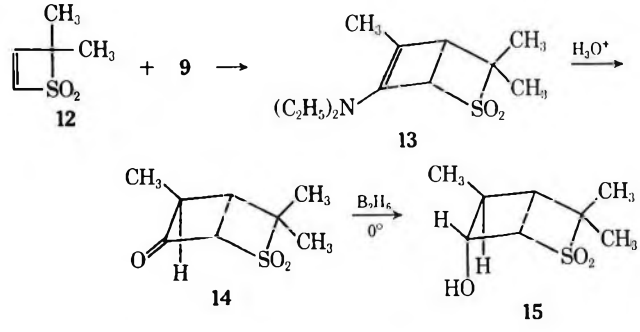
Although **7** readily afforded a methiodide (**8**), attempts to degrade this quaternary salt under a variety of Hofmann elimination conditions failed to yield a characterizable product.

Ynamines.—A similar condensation of **5** with diethyl-1-propynylamine (**9**) in refluxing benzene led in this instance to the unsaturated 2-thiabicyclo[2.2.0]hexane derivative **10**. However, this cycloaddition product was not characterized *per se* because of its instability in air. Instead, the residual enamine moiety in **10** was hydrolyzed in acid and keto sulfone **11** could be isolated consistently in 45% overall yield. This substance



exhibited principal infrared peaks in chloroform solution at 1785 (C=O), 1332, and 1145 cm^{-1} (SO_2). In its nmr spectrum ($CDCl_3$), the methyl group is seen as a doublet (J = 7.5 Hz) at δ 1.37 and H_1 appears at δ 5.68 as a quartet of triplets ($J_{1,4}$ = 7.0 Hz; $J_{1,5}$ = 3.0 Hz; $J_{1,3}$ = 1.0 Hz); the complex multiplet ascribed to the two remaining α-sulfonyl protons is centered at δ 4.42, whereas the complex patterns due to H_4 and H_5 are seen at δ 3.40 and 3.90, respectively. The stereochemical assignment of the 5-methyl group in **11** derives principally from the strong *exo* preference anticipated from this substituent under the equilibrating conditions employed and from the nmr coupling constants, but depends further upon recognition of the fact that there exists a very close spectral correlation with **14** (see below) in which an *endo*-5-methyl group is considered very unlikely because of prohibitive steric crowding.

Ynamine **9** also underwent 2 + 2 cycloaddition to 2,2-dimethylthiete 1,1-dioxide (**12**). Acid hydrolysis of the intermediate enamine **13** led in this instance (43% overall yield) to keto sulfone **14** which likewise exhibited



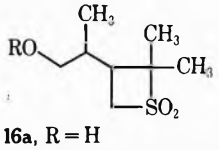
an intense cyclobutanone carbonyl stretching mode at 1795 cm^{-1}. As expected, the nmr spectrum of **14** was considerably simplified relative to that of **11** because of the presence of the *gem*-dimethyl groups at C_3 (sharp singlets at δ 1.62 and 1.72). Thus, whereas both H_1 ($J_{1,4}$ = 7.0 Hz; $J_{1,5}$ = 2.5 Hz) and H_4 ($J_{1,4}$ = 7.0 Hz; $J_{4,5}$ = 4.5 Hz) appear as doublets of doublets at δ 5.47 and 2.53, respectively, H_5 is seen as a pair of overlapping quartets centered at δ 3.80 and the 5-methyl substituent as an upfield doublet (δ 1.23; J = 7.5 Hz).

Diborane reduction of the carbonyl group in **14** proceeded readily and in high yield to give *endo* hydroxy sulfone **15**. The latter displayed strong hydroxyl absorption in the infrared at 3450 cm^{-1} and an nmr spectrum in full agreement with the assigned structure (see Experimental Section). This secondary alcohol proved to be labile to bases, *e.g.*, aluminum isopropoxide, etc.,

(7) For other examples of intramolecular bicyclic oxetane formation, see (a) H. Morrison, *J. Amer. Chem. Soc.*, **87**, 932 (1965); (b) N. C. Yang, M. Nussim, and D. R. Coulson, *Tetrahedron Lett.*, 1525 (1965); (c) J. K. Crandall and C. F. Mayer, *J. Org. Chem.*, **34**, 2814 (1969).

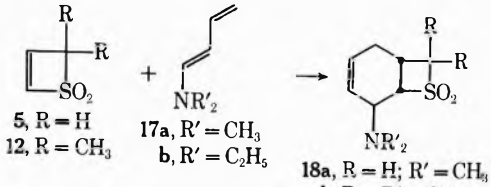
(8) (a) D. C. Dittmer and M. E. Christy, *J. Amer. Chem. Soc.*, **84**, 399 (1962); (b) D. C. Dittmer and N. Takashina, *Tetrahedron Lett.*, 3809 (1964); (c) L. A. Paquette, *J. Org. Chem.*, **30**, 629 (1965); (d) L. A. Paquette and T. R. Phillips, *ibid.*, **30**, 3883 (1965).

even under mild conditions. For example, upon standing overnight at room temperature in the presence of diborane, **15** undergoes reductive cleavage to **16a**. This behavior is not unexpected since it derives considerable driving force from the relief of ring strain and the transient intervention of an α-sulfonyl carbanion. Alcohol **16a** was further characterized as its crystalline tosylate **16b**.



16a, R = H
b, R = $SO_2C_6H_4CH_3$-*p*

Dienamines.—Preparation of 7-thiabicyclo[4.2.0]-oct-3-enes was effected by a related cycloaddition of dienamines to thiete 1,1-dioxides. 1-Dimethylamino-1,3-butadiene (**17a**) was subjected to reaction with both **5** and **12** to give adducts **18a** and **18b**, respectively.



5, R = H
12, R = CH_3

17a, R′ = CH_3
b, R′ = C_2H_5

18a, R = H; R′ = CH_3
b, R = R′ = CH_3
c, R = CH_3; R′ = C_2H_5

As observed earlier, **12** is more sluggish to react than **5** because of the steric effect generated by the *gem*-dimethyl functionality on the adjacent sp^2 carbon atom which, in this instance, is a neopentyl center. 1-Diethylamino-1,3-butadiene (**17b**) behaved similarly.

The nmr spectra of adducts **18a–c** were in complete agreement with the assigned structures. In these examples, however, it did not prove possible unequivocally to assign stereochemistry to the dialkylamino group.

In conclusion, the present research reveals that simple cycloaddition reactions of electron-rich olefins to thiete 1,1-dioxides provide a ready means of preparing derivatives of 2-thiabicyclo[2.2.0]hexane and 7-thiabicyclo[4.2.0]octane. However, preliminary studies have also indicated that 1,1-di(1-piperidinyl)ethylene, N,N-dimethyl-2-phenylethynylamine, and N,N,N′,N′-tetramethyl-1,3-butadiene-1,4-diamine do not react with **5** and **12**. Therefore, this particular cycloaddition is not entirely general.

Experimental Section

Melting points are corrected. The microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark. The nmr spectra were determined with a Varian A-60 spectrometer using tetramethylsilane as internal standard.

5,5-Dimethyl-6-*exo*-dimethylamino-2-thiabicyclo[2.2.0]hexane 2,2-Dioxide (7).—A solution of 3.0 g (0.039 mol) of thiete 1,1-dioxide (**5**)[9] and 3.9 g (0.039 mol) of 2-methyl-1-dimethylamino-1-propene (**6**)[10] in 5 ml of dry benzene was refluxed for 24 hr under a nitrogen atmosphere. Chromatography of the concentrated reaction mixture on neutral alumina afforded, on elution with ether–petroleum ether (1:3), 3.5 g (60%) of **7**: mp 102–103° further recrystallization from ether–petroleum ether did not improve the melting point); $\nu_{max}^{CCl_4}$ 1335, 1220, 1210, 1185, and 1145 cm^{-1} (SO_2); $\delta_{TMS}^{CDCl_3}$ 1.20 [s, 6 H, $C(CH_3)_2$], 2.10 [s, 6 H, $N(CH_3)_2$], 2.17–2.47 (m, H_4), 3.00 (d, J = 6.0 Hz, H_6), and 3.87–4.42 (m, 3 H, α-sulfonyl).

Anal. Calcd for $C_9H_{17}NO_2S$: C, 53.17; H, 8.43; S, 15.77. Found: C, 53.43; H, 8.45; S, 15.76.

A methiodide of **7** was prepared in the usual way in 83% yield. Recrystallization from methanol–ether gave pure **8**, mp 225° dec.

Anal. Calcd for $C_{10}H_{20}INO_2S$: C, 34.79; H, 5.84; S, 9.29. Found: C, 34.86; H, 5.86; S, 8.90.

***exo*-5-Methyl-2-thiabicyclo[2.2.0]hexan-6-one 2,2-Dioxide (11).**—A solution of 8.73 g (0.087 mol) of **5** and 12.0 g (0.107 mol) of diethyl 1-propynylamine (**9**, Fluka) in 150 ml of dry benzene was heated at reflux under nitrogen for 24 hr. The benzene was evaporated and the residual red oil was dissolved in 100 ml of 6 *M* HCl and extracted continuously with ether overnight. Evaporation of the dried ether solution yielded 6.30 g (45%) of **11** which was twice recrystallized from benzene–hexane: mp 75–78°; $\nu_{max}^{CHCl_3}$ 1785 (C=O), 1332, 1188, and 1144 cm^{-1} (SO_2); $\delta_{TMS}^{CDCl_3}$ 1.37 (d, J = 7.5 Hz, methyl), 3.40 (m, H_4), 3.90 (m, H_5), 4.42 (m, 2 H), (remaining α-sulfonyl), and 5.68 (q of t, J = 7.0, 3.0, and 1.0 Hz, H_1).

Anal. Calcd for $C_6H_8O_3S$: C, 45.00; H, 5.00; S, 20.02. Found: C, 44.90; H, 5.08; S, 19.74.

***exo*-3,3,5-Trimethyl-2-thiabicyclo[2.2.0]hexan-6-one 2,2-Dioxide (14).**—A solution of 7.0 g (0.053 mol) of 2,2-dimethylthiete 1,1-dioxide (**12**)[10] and 7.0 g (0.063 mol) of **9** in 100 ml of dry benzene was refluxed under nitrogen for 48 hr. The benzene was evaporated and the residual red oil was hydrolyzed as above to give 4.23 g (42.5%) of **14**: mp 118–119° after two recrystallizations from benzene–hexane; $\nu_{max}^{CHCl_3}$ 1795 (C=O), 1325, 1170, and 1115 cm^{-1} (SO_2); $\delta_{TMS}^{CDCl_3}$ 1.23 (d, J = 7.5 Hz), 1.62, 1.72 (s, *gem*-dimethyl), 2.53 (d of d, J = 7.0 and 4.5 Hz, H_4), 3.80 (overlapping quartets, H_5), and 5.47 (d of d, J = 7.0 and 2.5 Hz, H_1).

Anal. Calcd for $C_8H_{12}O_3S$: C, 51.07; H, 6.38; S, 17.04. Found: C, 51.18; H, 6.49; S, 16.86.

***exo*-3,5,5-Trimethyl-*endo*-4-hydroxy-2-thiabicyclo[2.2.0]hexane 2,2-Dioxide (15).**—Into a solution of 2.87 g (0.015 mol) of **14** in 200 ml of anhydrous tetrahydrofuran cooled to 0° under nitrogen was introduced gaseous diborane, generated externally by dropping 15 g (0.11 mol) of boron trifluoride etherate into a solution of 1.5 g (0.04 mol) of sodium borohydride in 50 ml of diglyme. After completion of the diborane generation (30 min), the mixture was stirred for an additional 2 hr at 0°. Dilute hydrochloric acid (50 ml) was added cautiously, the tetrahydrofuran was evaporated, and the aqueous layer was continuously extracted overnight with ether. The dried ether solution was evaporated to afford 2.15 g (75.5%) of **15**: mp 54–55.5° (from benzene–hexane); $\nu_{max}^{CHCl_3}$ 3450 (OH), 1312, 1287, 1125, and 1110 cm^{-1} (SO_2); $\delta_{TMS}^{CDCl_3}$ 1.21 (d, J = 7.0 Hz, 5-methyl), 1.51, 1.53 (s, *gem*-dimethyl), 1.82 (t, J = 7.0 Hz, H_4), 2.85 (m, H_5), 3.85 (broad s, H_1 and H_6), and 4.80 (broad, OH).

Anal. Calcd for $C_8H_{14}O_3S$: C, 50.53; H, 7.36; S, 16.87. Found: C, 50.51; H, 7.41; S, 16.98.

Ring Opening of 15.—A 2.50-g sample of **14** was reduced in the above manner with diborane. The reaction mixture was allowed to stir at room temperature overnight. After the same work-up, 1.59 g (63%) of **15a**, a viscous oil, was obtained. This material was molecularly distilled at 100° (0.5 mm): $\nu_{max}^{CHCl_3}$ 3510, 3400 (OH), 1305, 1153, and 1120 cm^{-1} (SO_2); $\delta_{TMS}^{CDCl_3}$ 0.98 (d, J = 6.5 Hz, methyl), 1.54 (s, *gem*-dimethyl), 2.00 (m, 2 H, H_3 and adjacent proton), 3.05 (s, OH), 3.42 (d, J = 4.8 Hz, OCH_2), and 3.83 (AB, J = 10.0 and 2.5 Hz, α-sulfonyl).

This alcohol was converted into its tosylate (**16b**) with tosyl chloride in pyridine at 0°. The crystalline sulfonate ester was obtained as white prisms, mp 124.5–125.5° (from ethanol).

Anal. Calcd for $C_{15}H_{22}O_5S_2$: C, 52.02; H, 6.35; S, 18.52. Found: C, 52.26; H, 6.58; S, 18.34.

5-Dimethylamino-7-thiabicyclo[4.2.0]oct-3-ene 7,7-Dioxide (18a).—A mixture of 6.35 g (0.061 mol) of **5** and 6.0 g (0.062 mol) of 1-dimethylamino-1,3-butadiene (**17a**)[11] in 10 ml of dry benzene was left at room temperature under nitrogen for 6 days. The black solution was concentrated *in vacuo* and the residue was chromatographed on neutral alumina. Elution with petroleum ether–ether (9:1) gave 8.8 g (71.5%) of **18a** as a yellow oil. Purification through its hydrochloride salt gave a colorless oil

(9) D. C. Dittmer and M. E. Christy, *J. Org. Chem.*, **26**, 1324 (1961).

(10) W. E. Truce, J. R. Norell, J. E. Richman, and J. P. Walsh, *Tetrahedron Lett.*, 1677 (1963).

(11) Z. Arnold, *Collect. Czech. Chem. Comm.*, **25**, 1308 (1960).

with no change in spectral properties: $\nu_{max}^{CCl_4}$ 1325, 1200, 1175, and 1130 cm^{-1} (SO_2); $\delta_{TMS}^{CCl_4}$ 1.90–2.83 (m, H_1 and H_2), 2.20, 2.34 (s, $N(CH_3)_2$), 3.33–3.74 and 4.00–4.62 (m, 2 H each, H_5 and α-sulfonyl), and 5.86 (broad s, 2 H, vinyl).

A methiodide of **18a** was obtained in 78% yield, mp 191° dec (methanol–water).

Anal. Calcd for $C_{10}H_{18}INO_2S$: C, 34.99; H, 5.29; N, 4.08. Found: C, 34.92; H, 5.35; N, 3.93.

5-Dimethylamino-8,8-dimethyl-7-thiabicyclo[4.2.0]oct-3-ene 7,7-Dioxide (18b).—A mixture of 5.0 g (0.038 mol) of **12** and 4.0 g (0.041 mol) of **17a** in 10 ml of dry benzene was left at room temperature under nitrogen for 1 week and then refluxed for 2 hr. The black solution was worked up and chromatographed as above to give an oily solid, recrystallization of which from ether–petroleum ether afforded 1.7 g (19.5%) of **18a**, mp 45–48°. An analytical sample was prepared through the hydrochloride salt, mp 215° dec (from methanol–ether), and regeneration of the free base: mp 59°; $\nu_{max}^{CCl_4}$ 1315, 1175, 1153, and 1112 cm^{-1} (SO_2); $\delta_{TMS}^{CDCl_3}$ 1.40 and 1.65 (s, *gem*-dimethyl), 2.28 (s, $N(CH_3)_2$), 2.17 (m, 2 H, H_2), 3.65–3.86 (m, H_5), 4.25–4.60 (m, H_6), and 5.88 (broads, 2 H, vinyl).

Anal. Calcd for $C_{11}H_{19}NO_2S$: C, 57.61; H, 8.35; N, 6.10; S, 13.98. Found: C, 57.62; H, 8.42; N, 5.99; S, 13.84.

A methiodide salt of **18b** was prepared, mp 211° dec (methanol–water).

Anal. Calcd for $C_{12}H_{22}INO_2S$: C, 38.82; H, 5.97; S, 8.64. Found: C, 38.62; H, 5.92; S, 8.42.

5-Diethylamino-8,8-dimethyl-7-thiabicyclo[4.2.0]oct-3-ene 7,7-Dioxide (18c).—A mixture of 1.0 g (7.6 mmol) of **12** and 0.94 g (7.6 mmol) of 1-diethylamino-1,3-butadiene (**17b**)[12] in 5 ml of dry xylene was refluxed under nitrogen for 12 hr. The dark reaction mixture was concentrated and the residue was chromatographed on Florisil. Elution of the column with petroleum ether containing increasing amounts of ether gave a yellow crystalline solid. Recrystallization of this substance from petroleum ether afforded 0.4 g (9.5%) of **18c**: mp 64°; $\nu_{max}^{CCl_4}$ 1312, 1165, 1150, and 1110 cm^{-1} (SO_2). Approximately one-fourth of the starting quantity of **12** was recovered.

Anal. Calcd for $C_{13}H_{23}NO_2S$: C, 60.66; H, 9.01; N, 5.44; S, 12.46. Found: C, 60.39; H, 8.88; N, 5.40; S, 12.36.

Registry No.—**7**, 23431-18-7; **8**, 23430-88-8; **11**, 23430-89-9; **14**, 23430-90-2; **15**, 23430-91-3; **16a**, 23431-19-8; **16b**, 23431-20-1; **18a**, 23430-92-4; **18a** (methiodide), 23430-93-5; **18b**, 23430-94-6; **18b** (methiodide), 23465-13-6; **18c**, 23430-95-7.

Acknowledgment.—This work was financed in part by the National Science Foundation, Grant GP5977, whom we thank.

(12) S. Hunig and H. Kahanek, *Chem. Ber.*, **90**, 238 (1957).

The Reaction of 6,6-Dibromobicyclo[3.1.0]hexane with Methyllithium. Efficient Trapping of 1,2-Cyclohexadiene by Styrene[1]

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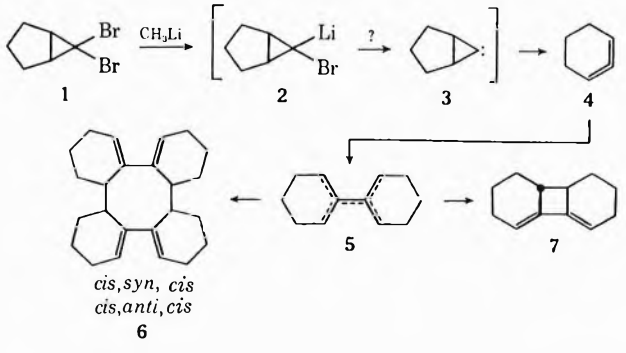
Received August 8, 1969

The reaction of 6,6-dibromobicyclo[3.1.0]hexane (**1**) with methyllithium in styrene affords a 76% yield of *exo*- and *endo*-7-phenylbicyclo[4.2.0]oct-1-ene (**8a** and **8b**) in a ratio of 2.2:1. The structures of **8a** and **8b** have been established by spectral methods, oxidative degradation, and hydrogenation to *exo*- and *endo*-7-phenylbicyclo[4.2.0]octane, which were synthesized independently. The formation of **8a** and **8b** is interpreted in terms of the generation of 1,2-cyclohexadiene, which adds to styrene to form a singlet biradical that closes to **8a** and **8b**.

The reaction of 6,6-dibromobicyclo[3.1.0]hexane (**1**) with methyllithium gives no evidence of products derived from carbene **3** (Scheme I). Rather, at −80°

SCHEME I



the major products are the stereoisomers **6**, while in refluxing ether diene **7** is formed in good yield.[3] We have interpreted[3] these results in terms of the generation of 1,2-cyclohexadiene (**4**) from either **2** or **3** (or both) and have suggested that dimerization of **4** first gives a diallylene **5**, which either cyclizes to **7** at "high" temperatures or dimerizes to **6** at low temperatures (Scheme I). In order to gain insight into the nature of 1,2-cyclohexadiene, we have investigated intercepting it with various reagents. In this paper we report the trapping of **4** with styrene and a rigorous proof of the structures of the adducts.

The reaction of **1** with methyllithium in isobutylene, cyclohexene, and furan under a variety of conditions produced the same products, **6** and **7**, observed when ether was employed as the sole solvent; no evidence for any "trapping products" was obtained. However, addition of methyllithium in ether to a solution of **1** in pure styrene at −15° gave, after distillation, a 76% yield of a 1:1 styrene–C_6H_8 adduct **8**. A small amount (4–5%) of **7** was formed and the total distillation residue, *ca.* one-tenth the weight of **8**, was found to consist of **6** (along with small amounts of "trimeric" material[3]). No evidence was found for the formation of any styrene polymer. The product composition was the same with methyllithium made from methyl bromide or methyl iodide. Dilution of the styrene in ether lowered the yield of **8** somewhat.

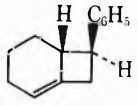
The trapping product **8** was shown by glpc to be a mixture of two compounds, in a ratio of 2.2:1. Based on the detailed evidence presented below, the major product has been shown to be *exo*-7-phenylbicyclo-

(1) Supported in part by the National Science Foundation (Grant GP-1306) and the Petroleum Research Fund administered by the American Chemical Society (Grant 1549-A4).

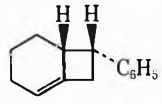
(2) National Institutes of Health Predoctoral Fellow, 1960–1964.

(3) W. R. Moore and W. R. Moser, *J. Amer. Chem. Soc.*, in press.

[4.2.0]oct-1-ene (**8a**) and the minor product to be *endo*-7-phenylbicyclo[4.2.0]oct-1-ene (**8b**). The major product **8a** could be isolated in a pure state by spinning-band distillation; the minor compound **8b** was isolated



8a



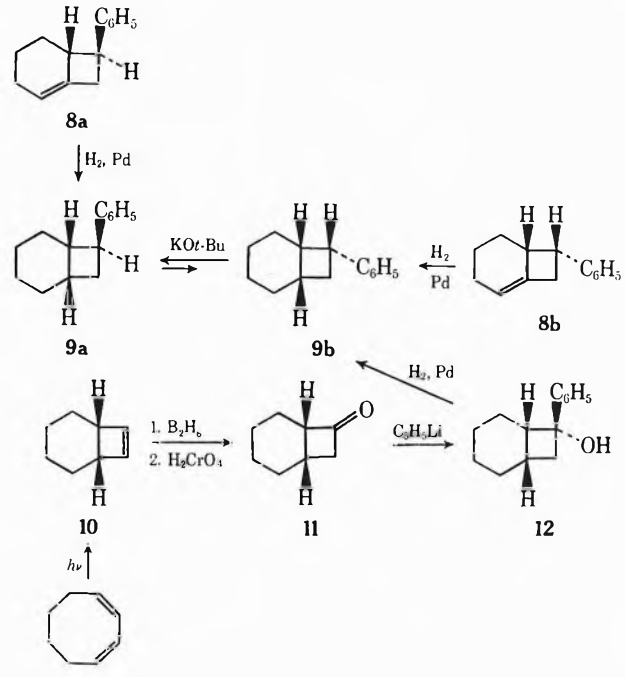
8b

by preparative glpc. Elemental analysis and mass spectra established that both compounds were $C_{14}H_{16}$. Both showed infrared absorption characteristic of a monosubstituted benzene. The nmr spectra established that both compounds have five aromatic and one olefinic proton. The upfield portions of the spectra differ: **8a** shows four protons in a relatively sharp band at δ 2.99 with six protons in a broad band at δ 0.55–2.3; **8b** shows one proton as a triplet of doublets at δ 3.70 overlapping a complex three-proton pattern at δ 2.5–3.9 and six protons in a broad band at δ 0.35–2.5. These nmr differences serve as a basis for a structural and stereochemical assignment (below), confirmed by degradation.

Quantitative hydrogenation of **8a** over palladium on carbon established the presence of one double bond and gave a single product **9a** (no **9b**). Similarly, **8b** gave a single product **9b** (no **9a**) upon absorption of 1 mol of hydrogen. The two compounds, $C_{14}H_{18}$ by analysis and mass spectra, had similar, but different, ir and nmr spectra and the same glpc retention times on all columns employed except Craig polyester succinate. Heating either **9a** or **9b** with potassium *t*-butoxide in dimethyl sulfoxide[4] caused equilibration to a mixture of the two compounds containing about 90% **9a**, establishing that this isomer is the more stable. A similar mixture resulted from treatment of **9a**,**b** with potassium amide in liquid ammonia.

The structures **9a** and **9b** were established by the synthetic sequence outlined in Scheme II. *cis*-Bicyclo[4.2.0]oct-7-ene (**10**), prepared by photolysis of *cis*,*cis*-1,3-cyclooctadiene,[5,6] was hydroborated and oxidized with chromic acid[7] to give *cis*-bicyclo[4.2.0]octan-7-one (**11**). Ketone **11** prepared in this way was shown to be identical with the ketone obtained by chromic acid oxidation of bicyclo[4.2.0]octan-7-ol.[8] Treatment of **11** with phenyllithium gave an 87% yield of 7-phenylbicyclo[4.2.0]octan-7-ol (**12**), which appeared to be a single epimer. Since the phenyl group should enter the molecule from the less hindered side, we assign the *exo*-phenyl configuration to **12**. Hydrogenolysis of **12** over palladium on carbon in acetic acid at 60° afforded only **9b**. The fact that base-catalyzed equilibration, which can only affect the configuration at the benzylic C-7 position, converts **9b** into **9a** establishes the structure of the latter. The assignment of the

SCHEME II

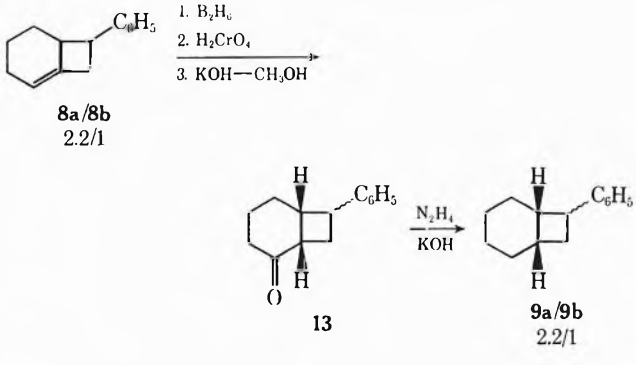


stereochemistry follows from consideration of the relative stabilities of these two isomers. An *endo*-phenyl group clearly suffers nonbonded repulsions absent in the *exo* isomer. Hence the less stable isomer, **9b**, must have the *endo*-phenyl configuration.

The hydrogenolysis of alcohol **12** thus proceeded with overall inversion of configuration at C-7. This result might be due to backside displacement of the protonated hydroxyl on the catalyst surface, but it is probable that the alcohol was catalytically dehydrated to 7-phenylbicyclo[4.2.0]oct-7-ene, which was then hydrogenated from the less hindered side, leading to the *endo* configuration for the phenyl group.

The data at this point established the carbon skeleton of **8a** and **8b** but not the position of the double bond. A 2.2/1 mixture of **8a**/**8b** was hydroborated and oxidized with chromic acid and the product was treated with dilute potassium hydroxide in methanol to ensure that only the more stable *cis*-fused bicyclic system was in hand. Since the resultant ketone **13** (Scheme III)

SCHEME III



showed carbonyl absorption at 1710 cm^{-1} only, the keto group had to be in the six-membered ring. Wolff–Kishner reduction of **13** gave a 2.2/1 mixture of **9a** and **9b**. This sequence confirmed the *cis* ring fusion in **9a**

(4) D. J. Cram, C. A. Kingsbury, and B. Rickborn, *J. Amer. Chem. Soc.*, **83**, 3688 (1961).

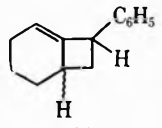
(5) (a) W. G. Dauben and R. L. Cargill, *J. Org. Chem.*, **27**, 1910 (1962). (b) S. F. Chappell and R. F. Clark, *Chem. Ind.* (London), 1198 (1962). (c) Both the direct[6a] and the photosensitized[6b] photolyses apparently involve *cis*,*trans*-1,3-cyclooctadiene. In both systems we observed quick formation of a glpc peak which apparently was this strained olefin.

(6) (a) W. J. Nebe and G. J. Fonken, *J. Amer. Chem. Soc.*, **91**, 1249 (1969); (b) R. S. H. Liu, *ibid.*, **89**, 112 (1967).

(7) H. C. Brown and C. P. Garg, *ibid.*, **83**, 2951 (1961).

(8) A. C. Cope and R. W. Gleason, *ibid.*, **84**, 1928 (1962).

and **9b** and narrowed the possible alternate structures for **8a** and **8b** to the epimers of 8-phenylbicyclo[4.2.0]-oct-1-ene (**14**). Based on model compounds, we esti-

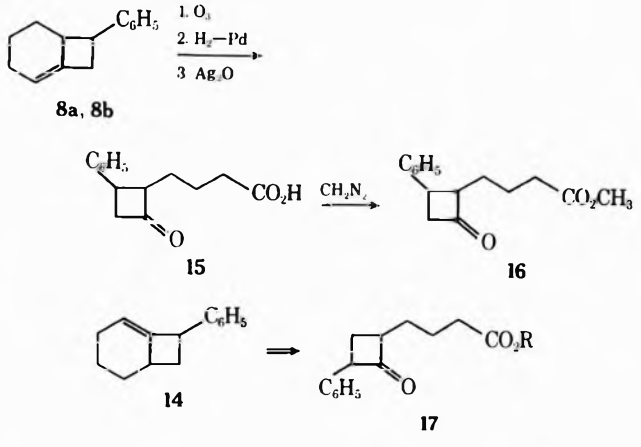


14

mate that both epimers of **14** should show nmr signals for the benzylic proton (at C-8) at *ca.* δ 4.3.[9] Similarly, for **8b** we predict a value of *ca.* δ 3.5 for the benzylic proton (at C-7), close to the value of δ 3.70 observed. Molecular models show clearly that owing to the puckering of the four-membered ring the corresponding benzylic proton in **8a** lies in the shielding region of the double bond and consequently must fall upfield from the δ 3.70 signal of **8b**. This predication is confirmed by the observation that the signal from the C-7 proton of **8a** must fall in the band at δ 2.99 (along with the other three cyclobutane protons).[10] In addition, the C-7 proton of **8b** appears as a triplet of doublets ($J_1 = J_2 \cong 9$ Hz, $J_3 \cong 3$ Hz), a pattern consistent with structure **8b** ($J_{cis} \cong 9$ Hz, $J_{trans} \cong 3$ Hz), but totally inconsistent with structure **14**.

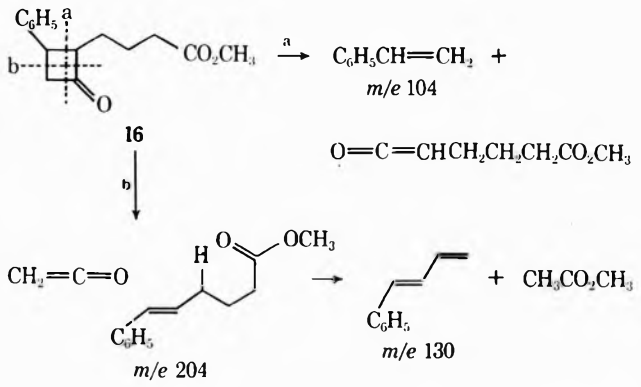
To confirm the spectral assignment of the position of the double bond, we investigated the oxidative degradation of **8a,b**. Ozonation of a 2.2:1 mixture of **8a,b** at −80° followed by catalytic hydrogenation of the ozonide and oxidation of the resultant aldehyde with silver oxide afforded keto acid **15** (71%) which was converted into the keto ester **16** with diazomethane (Scheme IV).

SCHEME IV



Both **15** and **16** show strong carbonyl absorption at 1780 cm^{-1} in the infrared, characteristic of cyclobutanones. The mass spectrum of the keto ester established that it was **16** and not the isomeric keto ester **17** which would result from **14**. Major fragments are found at *m/e* (rel intensity) 204 (13), 130 (60), and 104 (100). The base peak at *m/e* 104 represents styrene and supports either structure, but the *m/e* 204 and 130 peaks can come only from **16** and not from **17** (Scheme V).

SCHEME V

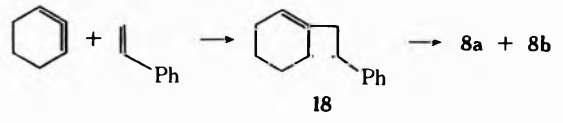


Further evidence supporting structure **16** rather than **17** came from deuterium-exchange studies. Keto acid **15** was treated with potassium carbonate in deuterium oxide for 17 hr and then washed with water to regenerate the CO_2H group, resulting in the incorporation of an average of 2.6 atoms of deuterium per molecule. Treatment of the deuterated **15** with diazomethane gave keto ester **16**, with the same deuterium content. Although the exchange had not quite reached the maximum for **15**, which has three protons adjacent to the keto group (protons adjacent to a carboxylate group do not exchange under these conditions), the observed incorporation of 2.6 atoms of deuterium per molecule clearly excludes structure **17**, which can incorporate a maximum of two atoms of deuterium per molecule.

Discussion

The formation of the adducts **8a** and **8b** in high yields substantiates our arguments[3] for the intermediacy of 1,2-cyclohexadiene. Although small amounts of **6** and **7** are formed, styrene clearly is an efficient trap. The orientation in this addition is similar to that observed for addition of normal allenes to activated olefins,[11] but, because **4** is by no means a normal allene, we felt that it was essential to provide unequivocal evidence for the structures of **8a** and **8b**.

Obviously the addition of **4** to styrene, a (2 + 2) cycloaddition, is very fast. A concerted thermal (2 + 2) cycloaddition must be suprafacial–antarafacial (*cis–trans*).[12] Since 1,2-cyclohexadiene can be looked upon as simply a badly twisted allene, any addition to it can be regarded as antarafacial. Yet the mode of dimerization of **4** (see Scheme I and ref 3) suggests that the addition of **4** to styrene is not concerted. We believe that this addition reaction is a two-step process involving formation of a biradical intermediate **18** which subsequently closes to both **8a** and **8b**.[13]



18

Addition of **4** to styrene to form **18** should occur with the plane of **4** approximately perpendicular to planar

(9) The C-8 proton is on a cyclobutane ring, tertiary, allylic, and benzylic —all features causing a downfield shift.

(10) Models also suggest that the preferred rotational conformations of the phenyl group will lead to deshielding of the C-7 proton of **8b** but shielding of the C-7 proton of **8a**.

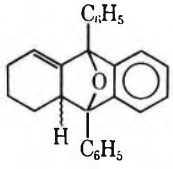
(11) (a) J. D. Roberts and C. M. Sharts, *Org. Reactions*, **12**, 1 (1962); (b) D. R. Taylor, *Chem. Rev.*, **67**, 317 (1967).

(12) R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968).

(13) Based on the relative stabilities of **9a** and **9b** we assume that **8a** is more stable than **8b**.

styrene and oriented to minimize steric repulsions as depicted in Figure 1 (I). If closure follows from this conformation, models suggest that there should be at least a slight preference for formation of **8b** [closure along b, Figure 1 (I)] over **8a** [closure along a, Figure 1 (I)], but, if the biradical rotates to the sterically preferred conformation shown in Figure 1 (II), the two direct modes of closure are equivalent and give only **8a**. The fact that **8a** does predominate (2.2:1), provides some, if not compelling, support for the proposed intermediacy and mode of reaction of **18**.

Wittig and Fritze[14] have reported trapping 1,2-cyclohexadiene with 1,3-diphenylisobenzofuran and isolating a 4:1 ratio of adducts **19**. Based on infrared



19

spectra, the major isomer was assigned the *endo* configuration. While this addition may be concerted, examination of models indicates that if a biradical were formed in this case, an analysis similar to that above predicts that formation of the *endo* isomer would be favored.

Finally, we wish to comment on the fact that, in the reactions which afforded **8a,b**, there was *no* polymerization of styrene (the solvent). Thus, if **18** is an intermediate, it cannot be a triplet; triplet **18** should be a highly efficient initiator for polymerization. Since triplet **4** would generate triplet **18**, it is clear that 1,2-cyclohexadiene, as generated from **1**, must be a singlet.

Experimental Section[15]

exo-**7-Phenylbicyclo[4.2.0]oct-1-ene** (**8a**) and *endo*-**7-Phenylbicyclo[4.2.0]oct-1-ene** (**8b**).—A solution of 65.6 g (0.273 mol) of 6,6-dibromobicyclo[3.1.0]hexene[3] (**1**) in 500 ml of styrene was cooled to −15° and 0.33 mol of 1 *M* methyllithium (prepared from methyl bromide and lithium) in ether was added dropwise with rapid stirring. After 15 min the mixture was warmed to room temperature and worked up in the usual way. Distillation afforded 36.1 g (74%) of olefins **8a,b**, bp 78° (0.04 mm), $n^{25}D$ 1.5561, and a residue of 3.9 g. Glpc analysis (5% EGA, 150°) showed a ratio of **8a:8b** of 2.2:1. The distillation forerun showed 4.6% **7** and the residue (SE-30) was shown to consist of **6** along with small amounts of trimeric[3] material. A subsequent run gave a 76% yield of **8a,b**. The **8a,b** mixture showed only weak uv absorption (ethanol) at 250 mμ (log ε 2.51) which was due to the phenyl group, and the infrared spectrum showed bands which were due to **8a** and **8b** only.

Anal. Calcd for $C_{14}H_{16}$: C, 91.25; H, 8.75. Found: C, 91.08; H, 8.68.

Distillation through a 90-cm spinning-band column gave a pure sample of **8a** and a fraction enriched in **8b** from which **8b** was obtained by preparative glc (20% EGA, 140°).

Compound **8a** gave the following data: ir (neat) 3070, 3050, 3020, 1603, 1498, 770, 750, and 700 cm^{-1}; nmr (CCl_4) δ 7.31 (sharp, 5 H, C_6H_5), 5.41 (br, 1 H, C=CH), 2.99 (narrow, 4 H, C-6, C-7, C-8), and 0.5–2.3 (complex, 6 H, $CH_2CH_2CH_2$); mass spectrum *m/e* 184 (M^+).

Anal. Calcd for $C_{14}H_{16}$: C, 91.25; H, 8.75. Found: C, 91.34; H, 8.76.

Compound **8b** gave the following data: ir (neat) 3070, 3050, 3020, 1603, 1498, 765, and 700 cm^{-1}; nmr (CCl_4) δ 7.32 (sharp, 5 H, C_6H_5), 5.46 (br, 1 H, C=CH), 2.5–3.9 (complex, 4 H, C-6, C-7, C-8, including a triplet of doublets at 3.70, C-7), and 0.4–2.5 (complex, 6 H, $CH_2CH_2CH_2$); mass spectrum *m/e* 184 (M^+).

Anal. Calcd for $C_{14}H_{16}$: C, 91.25; H, 8.75. Found: C, 91.27; H, 8.79.

When the reaction was carried out using equal volumes of styrene and ether at −40° and methyllithium (made from methyl iodide) the ratio **8a:8b** was unchanged but the yield decreased.

exo-**7-Phenylbicyclo[4.2.0]octane** (**9a**).—Hydrogenation (25°, 1 atm) of 98.1 mg of **8a** over 30% palladium on carbon resulted in the rapid uptake of 1 equiv of hydrogen. Short-path distillation gave 94.2 mg (95%) of **9a**: ir (neat) 3070, 3050, 3020, 1603, 1498, 765, and 700 cm^{-1}; nmr (CCl_4) δ 7.37 (sharp, 5 H, C_6H_5), 3.55 (complex, 1 H, C-7), and 0.7–3.0 (complex, 12H); mass spectrum *m/e* 186 (M^+). Glpc on several columns showed only **9a** and no **9b**.

Anal. Calcd for $C_{14}H_{18}$: C, 90.26; H, 9.74. Found: C, 90.33; H, 9.69.

Bicyclo[4.2.0]oct-7-ene (**10**).[5a]—Photolysis of 70 g of *cis,cis*-1,3-cyclooctadiene in 2.9 l. of anhydrous ether using a 500-W Hanovia high-pressure mercury arc (quartz probe) for 152 hr afforded 17 g (24%) of **10**, bp 129–135°, which was found to be 95% pure by glpc (12% TEG-12% C-20 M, 91°). Purification by preparative glpc (S-550, 104°) gave 11.6 g of pure **10** with infrared and nmr spectra identical with those obtained by Dauben and Cargill.[5a,16]

In the above photolysis as well as in an acetophenone-sensitized reaction, an unidentified peak (with a retention time 1.2 times that of 1,3-cyclooctadiene, TEG-C-20 M, 90°) appeared shortly after the photolysis began. Its concentration remained *ca.* one-third that of 1,3-cyclooctadiene during the remainder of the photolysis. This material apparently was *cis,trans*-1,3-cyclooctadiene.[6]

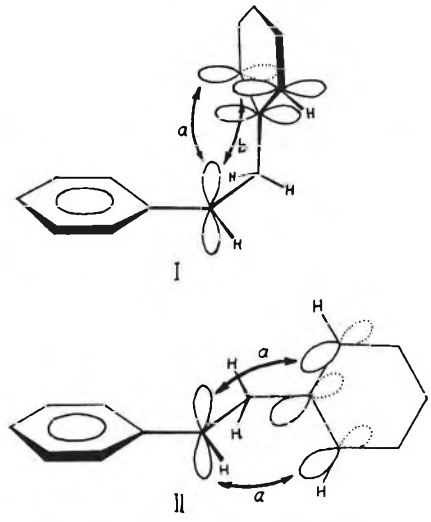


Figure 1.—Cyclization of the proposed biradical formed on addition of 1,2-cyclohexadiene to styrene: I, initial conformation; II, conformation after rotation. Closure in mode a gives **8a**, in mode b gives **8b**.

(14) G. Wittig and P. Fritze, *Angew. Chem.*, **78**, 905 (1966); *Justus Liebigs Ann. Chem.*, **711**, 82 (1968). 1-Bromocyclohexene was treated with potassium *t*-butoxide in dimethyl sulfoxide in the presence of the isobenzofuran. The two adducts were formed in 41% combined yield.

(15) Spectral measurements were determined with the following instruments: ir, Perkin-Elmer Models 21, 237, and 337 spectrophotometers; nmr, Varian A-60 spectrometer: uv, Cary Model 14 spectrophotometer; mass spectrum, Consolidated Electrodynamics Model 21-130 mass spectrometer (ionizing potential of 70 eV). Glpc columns were generally 0.5 × 200 cm and 1.5 × 200 cm (homemade apparatus, thermal conductivity detector) or 0.2 × 150 cm and 0.2 × 300 cm (Wilkens A-600 flame ionization) employing acidic, basic, or neutral Chromosorb P or W and the following liquid phases: Carbowax 20M (C-20 M), silicone oil 550 (S-550), silicone oil 710 (S-710), tetraethylene glycol (TEG), SE-30 silicone rubber (SE-30), ethylene glycol adipate (EGA), Versamid 900 (V-900), silicone nitrile XF-1150 (XF-1150), silicone nitrile XE-60 (XE-60), and Craig polyester succinate (CPS). Internal standards were employed using appropriate response factors; peak areas were measured with a planimeter. Melting points are corrected and boiling points are uncorrected. All reactions employing organometallic reagents, active metals, alkoxides, hydrides, photolysis, pyrolysis, and diborane were conducted under a nitrogen atmosphere.

(16) We wish to thank Professor Dauben for providing spectra.

Bicyclo[4.2.0]octan-7-one (11).—Olefin **10** (7.3 g, 0.068 mol) was treated with a solution of 0.049 mol of diborane[17] in 85 ml of tetrahydrofuran at 0°. After addition of water and evaporation of most of the solvent, a solution of 16.5 g of sodium dichromate and 12 ml of concentrated sulfuric acid in 60 ml of water and 50 ml of ether were added. After 8 hr at 25° the usual work-up gave 5.0 g (60%) of **11**, bp 65° (6.5 mm), n^{25}D 1.4742. The infrared spectrum was identical with that obtained by Cope and Gleason.[8]

Oxidation of bicyclo[4.2.0]octan-7-ol[8] in ether with chromic acid gave an 89% yield of **11** identical in every way with the sample prepared above.

7-Phenylbicyclo[4.2.0]octan-7-ol (12).—Addition of 28 mmol of phenyllithium in ether to 2.72 g (21.9 mmol) of **11** in ether at −80° followed by the usual work-up and short-path distillation (110°, 0.02 mm) gave 3.86 g (87%), n^{25}D 1.5513, of **12** as a colorless liquid, n^{25}D 1.5513. Glpc (15% V-900 at 220°, 2% EGA at 180°) showed only a single peak which appeared to be a single compound (based on plate values). Spectral data follow: ir (neat) 3400 (br), 3070, 3050, 3020, 1603, 1498, 765, and 700 cm^{-1}; nmr (CCl_4) δ 7.50 (5 H, C_6H_5) and 0.5–3.0 (complex, 13 H, OH at 2.20).

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.08; H, 9.21.

***endo*-7-Phenylbicyclo[4.2.0]octane (9b). A. From 12.**—Alcohol **12** (161 mg) was stirred over 30% palladium on carbon in acetic acid at 58° under 1 atm of hydrogen. Hydrogen uptake was fairly rapid (25 min) up to 1 equiv and then became very slow, at which point the mixture was worked up to afford on short-path distillation 124 mg (84%) of **9b** as a colorless liquid, n^{25}D 1.5332. Glpc analysis (CPS at 120°, EGA at 150°, XE-60) showed that the compound was pure and contained no **9a**. Spectral data follow: ir (neat) 3070, 3050, 3020, 1603, 1498, 760, and 700 cm^{-1}; nmr (CCl_4) δ 7.29 (5 H, C_6H_5), 3.55 (1 H, br, complex, C-7), and 0.5–2.9 (12 H, complex); mass spectrum *m/e* 186 (M^+).

Anal. Calcd for $C_{14}H_{18}$: C, 90.26; H, 9.74. Found: C, 90.30; H, 9.69.

B. From 8b.—Hydrogenation of **8b** over 30% palladium on carbon in ethanol at 25° resulted in the rapid uptake of 1 equiv of hydrogen. Short-path distillation afforded a colorless liquid with glpc retention times (CPS, EGA, XE-60) and an infrared spectrum identical with that of **9b** prepared above. No **9a** was formed.

Equilibration of 9a and 9b.—Hydrocarbon **9b** (46 mg) was heated in a solution of potassium *t*-butoxide (prepared by adding 40 mg of potassium to anhydrous *t*-butyl alcohol followed by evaporation of the alcohol, ultimately at 0.01 mm for 8 hr) in 2 ml of anhydrous dimethyl sulfoxide at 58° for 19 hr. Glpc analysis (CPS, 120°, relative retention times **9a**, 1.05, **9b**, 1.00) established that **9a** and **9b** were present in a ratio of 86:14. The compounds were identified by glpc retention times and infrared spectra.

Hydrocarbon **9a** was treated in the same way, but heating was continued at 58° for 10 days. Glpc and infrared analysis established that **9a** and **9b** were present in a ratio of 90:10. Because of the much longer time, 90:10 must be closer to the equilibrium content than 86:14.

A sample of **8a** and **8b** (2.2:1) was stirred for 12 hr with 0.1 *M* potassium amide in liquid ammonia. The usual work-up yielded a mixture of **8a** and **8b** with an infrared spectrum nearly identical with that of the 90:10 mixture above.

Oxidative Hydroboration of 8a and 8b.—A 2.2:1 mixture of **8a** and **8b** (75 mg) was hydroborated in tetrahydrofuran with a 50% excess of diborane.[17] After 12 hr, water was added followed by a 25% excess of chromic acid in water and ether. After 48 hr at 25°, work-up yielded a ketone which showed a strong ir band at 1710 cm^{-1} only. This material was stirred with 10% potassium hydroxide in methanol at 25° for 40 hr. An aliquot showed only a 1710-cm^{-1} ir band. Diethylene glycol (25 ml) was added, the methanol was removed by distillation, and 4 ml of 68% aqueous hydrazine was added. The mixture was refluxed for 5 hr, the water was removed by distillation, and the mixture was then refluxed for 43 hr. Work-up and glpc analysis established that only **9a** and **9b** were present in a ratio of 2.2:1.

Ozonization of 8a,b.—A 2.2:1 mixture of **8a** and **8b** (2.2 g) was ozonized in 20 ml of ethyl acetate at −80°. The ozonide was hydrogenated in the same solvent over 5% palladium on carbon at 25° (90% of theoretical uptake). Filtration and evaporation of the solvent left a colorless oil: ir (neat) 1785, 1710, and 700 cm^{-1}; nmr (CCl_4) δ 9.67 (1 H, CHO), 7.28 (s, 5 H, C_6H_5), 2.59–3.75 (complex, 4 H, $C_6H_5CHCH_2COCH$), 2.32 (br, 2 H), and 1.70 (br, 4 H). The oil was treated with 2.0 g of silver oxide and 2.0 g of sodium hydroxide in 200 ml of 1:1 water–ethanol at 25° for 8 hr. The basic solution was filtered and washed with ether, affording 0.28 g of neutral material, ir (CCl_4) 3400 and 1780 cm^{-1} (no other carbonyl band). Acidification of the basic solution and extraction with ether afforded 1.95 g (71%) of **2-(3-carboxypropyl)-3-phenylcyclobutanone (15)** as a colorless oil, ir ($CHCl_3$) 1780 and 1710 cm^{-1} with a typical carboxyl band in the 3-μ region. This material could not be distilled without decomposition. Tlc and nmr of **15** and glpc of **16** indicated that **15** was at least 93% pure: ir (CCl_4) 1785, 1710, 1603, 1498, and 700 cm^{-1}; nmr ($CDCl_3$) δ 9.53 (s, 1 H, CO_2H), 6.90 (s, 5 H, C_6H_5), 3.03 (s, 2 H, $C_6H_5CHCHC{=}O$), 1.9–2.83 (complex, 4 H, t at 2.58, CH_2CO, broad band at *ca.* 2.1, CH_2CO_2H), and 1.58 (br, 4 H, CH_2CH_2). Keto acid **15** was treated with a slight excess of diazomethane in ether. Short-path distillation (0.08 mm, bath temperature 125°) left no residue and gave 2.05 g of an oil. Glpc analysis (2% EGA) showed one major and three minor peaks. The major peak (93%) was collected by glpc (10% EGA, 220°) and short-path distilled, giving **2-(3-carbomethoxypropyl)-3-phenylcyclobutanone (16)** as a colorless oil: n^{25}D 1.5237; ir (CCl_4) 3070, 3050, 3020, 1785, 1740, 1140, 1175, and 700 cm^{-1}; nmr (CCl_4) δ 7.29 (s, 5 H, C_6H_5), 3.60 (s, 3 H, OCH_3), 3.21 (br s, 2 H, $C_6H_5CHCHC{=}O$), 1.92–3.05 (complex, 4 H, $CH_2C{=}O$ and $CH_2CO_2CH_3$), and 1.2–1.96 (br, 4 H, CH_2CH_2); mass spectrum *m/e* (rel intensity), 204 (13), 130 (60), 117 (13), 104 (100), 91 (16), 78 (26), 77 (24), no M^+ peak.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 73.21; H, 7.23.

Keto acid **15** (85 mg) was dissolved in 25 ml of deuterium oxide containing 0.3 g of potassium carbonate. After 18 hr at 25°, the mixture was acidified with an acetic acid–sodium acetate buffer. The solution was washed with ether and the ether extract was washed with water. The solvent was evaporated under reduced pressure, leaving the deuterated keto acid **15**. Nmr analysis indicated a minimum of 2.6 atoms of deuterium per molecule. Treatment of the deuterated **15** with diazomethane gave deuterated **16**, which showed the same deuterium content as **15**.

Reaction of 1 with Methyllithium in the Presence of Isobutylene, Furan, and Cyclohexene.—Addition of methyllithium (1 *M* in ether) to 1 in 1:1 isobutylene–ether at −80°, 1:1 cyclohexene–ether at −80°, and furan (freshly distilled from sodium) at −80° followed by the usual work-up and glpc analysis (S-710, C-20 M, SE-30) showed no new products and also showed that the product composition was essentially the same[3] (**6** was the major peak) as that observed in the absence of the olefins.

Addition of 8 mmol of 1 to 10 ml of 1 *M* methyllithium in ether and 50 ml of isobutylene at −18° gave only products formed in the absence of the olefin. The yield of compound **7** was 21%.

Addition of 9 mmol of 1 in 10 ml of ether to 15 ml of 1 *M* methyllithium in 20 ml of cyclohexene at reflux gave a 60% of **7** and no new products.

Isomerization of 8a,b.—High-surface sodium on alumina, which has been utilized for isomerization of methylene cyclobutanes to cyclobutenes,[18] was prepared by shaking molten sodium (1 part) with anhydrous alumina (5 parts, Alcoa grade F) at 200° (0.1 mm). A 60 × 1.2 cm tube was packed with this sodium–alumina and maintained at 200° while a slow stream of nitrogen was passed through the tube. Passage of a 2.2:1 mixture of **8a** and **8b** through the pyrolysis tube gave a 50% recovery of a white solid. Glpc analysis (C-20M, 209°) showed four peaks, with relative retention times (per cent composition) of 0.61 (10), 0.71 (9), 1.00 (5), and 1.20 (76). The material with relative retention time 1.00 was shown to be starting material. The major component was identified as 1,2-diphenylethane by glpc retention times, melting points, and infrared spectra.

Registry No.—1, 2568-36-7; **8a**, 23115-89-1; **8b**, 23068-83-9; **9a**, 23068-84-0; **9b**, 23068-85-1; **12**, 23068-86-2; **15**, 23074-17-1; **16**, 23074-18-2; methyllithium, 917-54-4; 1,2-cyclohexadiene, 14847-23-5; styrene, 100-42-5.

(17) H. C. Brown and P. A. Tierney, *J. Amer. Chem. Soc.*, **80**, 1552 (1958).

(18) E. Gil-Av and J. Herling, *Tetrahedron Lett.*, 27 (1961).

Configurational Study of Some 9-Substituted 3-Oxabicyclo[3.3.1]nonanes by Nuclear Magnetic Resonance

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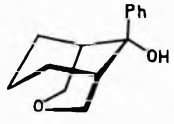
Received May 27, 1969

Several 9-substituted 3-oxabicyclo[3.3.1]nonanes were synthesized and their configurations and conformations were assigned by nmr spectroscopy.

When 1-phenylcyclohexene was subjected to the Prins reaction, two diastereoisomeric products were obtained.[1] It was possible to assign to them structures **1** and **2** by chemical means, which, however, did not establish their configurations.[2]



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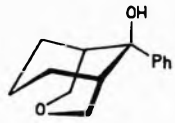

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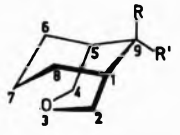
An nmr study of the two compounds and of a series of analogs appeared as the most promising approach to the determination of the configuration and possibly of the conformations of the two rings in the molecule. To this purpose, the compounds reported in Table I were prepared.

TABLE I



Compd	R	R′	Compd	R	R′
1	Ph	OH	2	OH	Ph
3	Ph	H	4	H	Ph
5	C_6H_{11}	OH	6	OH	C_6H_{11}
7	C_6H_{11}	H	8	H	C_6H_{11}
9	H	OH	10	OH	H
11	H	H			

Compounds **3** and **4** were obtained from **1** and **2**, respectively, by hydrogenolysis, compounds **5**, **6**, **7**, and **8**, from **1**, **2**, **3**, and **4**, respectively, by catalytic hydrogenation of the phenyl to cyclohexyl group in the presence of rhodium on alumina.

Compounds **9** and **10** were prepared by reduction of 3-oxabicyclo[3.3.1]nonan-9-one and separated by column chromatography.

We thus have two correlated series of compounds, *i.e.*, the series **1**, **3**, **5**, and **7**, and the series **2**, **4**, **6**, and **8**, besides the two products **9** and **10** and the parent compound **11**.

(1) G. Lippi and B. Macchia, *Chim. Ind.* (Milan), **50**, 697 (1968).

(2) The configuration of the substituents at C-9 of 3-oxabicyclo[3.3.1]-nonane is indicated following the convention adopted for the description and the representation of the steroids [*J. Amer. Chem. Soc.*, **82**, 5577 (1960)]. Using the the C–O–C bridge as a reference group, the substituent which is oriented on the same side as the oxygen with respect to the general plane of the cyclohexane ring is denoted by β, and the substituent with opposite configuration, *i.e.*, located on the opposite side with respect to the reference group, is called α. The hydrogen atoms are indicated with the number of the carbon atom to which they are bonded and with the designation "a" or "e" according to whether they are axial or equatorial with respect to the ring to which they belong.

TABLE II

CHEMICAL SHIFTS AND COUPLING CONSTANTS RELATIVE TO THE 2 AND 4 PROTONS[a]

Compd	τ'	τ''	$J_{2,2'}$,	$J_{2e,9\alpha}$	$J_{2a,8a}$
1	5.60 (a)	6.20 (e)	10.9	...	*b*
2	6.21	6.34	10.9	...	...
3	5.87 (e)	6.12 (a)	11.2	...	*b*
4	6.14 (a)	6.32 (e)	11.4	1.0[c]	...
5	5.81 (a)	6.34 (e)	10.9	...	*b*
6	6.09	6.21	11.6	...	...
7	6.02 (e)	6.36 (a)	10.9	...	*b*
8	6.12	6.36	11.2	...	...
9	5.93 (a)	6.39 (e)	10.9	0.8	...
10	6.03 (e)	6.31 (a)	11.2	...	*b*
11	6.11 (e)	6.26 (a)	10.9	...	...

[a] Chemical shifts (τ' and τ'', τ' being less than τ'') were measured directly from spectra determined at a sweep width of 500 cps with a scanning time of 500 sec and are expressed in parts per million; J values are in cycles per second and were measured using a sweep width of 250 cps and the same scanning time. The letters "a" and "e" in parentheses indicate axial and equatorial protons. [b] The lines of the axial 2,4 protons after double resonance on the 1 and 5 protons are appreciably broader with respect to the equatorial ones. No quantitative measurements have been made, but the order of magnitude of the coupling is <0.5 cps. [c] The coupling is between the benzylic proton and the high-field 2 and 4 protons.

Stereochemical assignments of these compounds could not be made by chemical means, using the technique followed by House, *et al.*,[3] for analogous compounds having an NCH_3 group in place of the oxygen atom.

The only compound for which a configuration had been proposed is **10**.[4] However, such an assignment, though plausible, cannot be confirmed by the absence of an OH–O bond in the infrared spectrum of **10**, as admitted by the authors themselves,[4] since the ir spectra of **9**, **5**, and **6** also show no evidence for an OH–O bond, but only the free OH bands at 3623 cm^{-1} for **9** and **10**, and at 3619 cm^{-1} for **5** and **6**. On the contrary, in the spectra of **1** and **2** there is a shift of the OH stretching band toward longer wavelengths attributable to OH–π bonding.[5] Therefore infrared spectroscopy does not give useful data for solving the problem.

Results

Table II reports the chemical shifts and, when present, the coupling constants relative to the hydrogens at

(3) H. O. House, H. C. Muller, C. G. Pitt, and P. P. Wickham, *J. Org. Chem.*, **28**, 2407 (1963); H. O. House and W. M. Bryant, III, *ibid.*, **30**, 3634 (1965).

(4) A. T. Blomquist and J. Wolinsky, *J. Amer. Chem. Soc.*, **79**, 6025 (1957).

(5) M. Tichý in "Advances in Organic Chemistry. Methods and Results," Vol. 5, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1965, Chapter 4; B. Macchia, F. Macchia, and L. Monti, unpublished data, 1968.

positions 2 and 4. The assignments of the peaks to the axial or equatorial protons is justified later. Actually, all spectra show some couplings between the relevant protons and those at position 1 and 5. Such couplings have not been directly measured but were systematically eliminated by double resonance.

Discussion

The presence of the phenyl substituent in the α or β position would be expected to influence differently the chemical shifts of the methylene protons of the cyclohexane ring, as well as of those in position 2 and 4. In particular, since the molecules in question are presumably rigid, it is possible to estimate with a fair approximation, using Johnson and Bovey tables,[6] the differences between the chemical shifts of the various protons for the more probable conformation. Let us first consider the cyclohexyl ring protons. When the phenyl group is in the β position, the ring protons should be on the average deshielded, and also the substituent effects should be very similar for the various protons. On the contrary, the effects of an α-phenyl group will be notably different because of the different positions of the protons with respect to the benzene ring (compare, for example, protons 1 and 5 with respect to 6, 7, and 8). The expected cyclohexyl proton spectrum of the α-phenyl compounds should therefore be more diffuse than that of the β-phenyl ones, with the center of gravity strongly shifted toward low field. If this is true, this would enable us to assign configuration to **3** and **4** and would also give information about **1** and **2**, which are the respective starting products. Actually, it is not certain that the hydrogenolysis of the hydroxyl group takes place with retention of configuration; this is the usual course of the Raney nickel hydrogenolysis of benzylic hydroxyl groups,[7] but apparent exceptions caused by equilibration of the products under the reaction conditions have been reported.[8]

From an examination of the spectra it is evident that the spectra of compounds **3** and **4** agree with the expectation for the α- and β-phenyl derivatives, respectively. In fact, the cyclohexyl envelope is much broader in **3** than in **11** and with the center of gravity practically unchanged, whereas in **4** there is a clear shift toward low field.

The nmr spectra of compounds **1** and **2** are complicated by the effect of the dipole moment of the hydroxyl group, which can affect the chemical shifts.[9] Moreover, even if the presence of a OH–π bond indicates a preferential conformation of the hydroxyl group, the weight of such a conformation is obviously not known. It may be assumed that the effect of the hydroxyl group will be the same as in cyclohexanols.[10] Particularly if the hydroxyl group is α, the two axial protons 6 and 8 should experience its deshielding action (*ca.* 0.5 ppm[10]), whereas the other protons should be less affected. If, instead, the hydroxyl group is β, the effect of the lone-pair electric dipole of oxygen should be much smaller. The effect on protons 1 and 5 is, of course, identical in both cases.

The spectra of compounds **1** and **2** are in good agreement with these expectations about the effects of the hydroxyl and the phenyl groups. The signals for protons 1 and 5 are at the same position ($J \cong 7.7$) in both spectra, but in the spectrum of **2** they are overlapped by those of two other protons, *i.e.*, axial 6 and 8, for which a deshielding of about 0.5 ppm by the α-hydroxyl group can be expected.[10] The center of gravity of the spectrum of compound **1** is very little shifted. The fact that expectations have been confirmed suggests that the reduction of hydroxyl group[1] has taken place with retention of configuration.

The spectrum of the cyclohexyl protons in **10** has the center of gravity shifted toward low field with respect to the unsubstituted compound **11**, whereas the center of gravity of the spectrum of protons 2 and 4 is almost unchanged. On the contrary, compound **9** has the center of gravity of the cyclohexyl protons almost unchanged, whereas that of protons 2 and 4 is shifted toward low field. Furthermore, two of these protons, namely those at higher field, are coupled with the hydrogen in **9**. All this is in full agreement with the assignment given for **10** by Blomquist.[4]

Attention should now be paid to the spectra of the four protons, chemically equivalent in pairs, in positions 2 and 4. The corresponding peaks are isolated from the other ones and therefore their chemical shifts and couplings constants with other protons can be measured easily and accurately. Moreover, in these molecules small long-range couplings are possible,[11] which are particularly sensitive to configuration and conformation. A tentative interpretation is possible if we suppose that the contributions of each substituent to the chemical shifts of these protons are additive. First of all, it is necessary to assign, in each spectrum, the lines of the AB doublets (sometimes split by "long-range" couplings) freed through double resonance from the effect of the coupling with protons 1 and 5.

Compounds **11**, **1**, **3**, **5**, **7**, and **9** carry the 9-phenyl or 9-cyclohexyl substituents in the α position and the hydroxyl one in the β position. It must be pointed out that, if we assume a chair–chair conformation, which is rather likely on the basis of the results obtained with similar compounds,[12] a long-range coupling is expected between the α hydrogen at C-9 and the equatorial protons at C-2 and C-4. Moreover, each axial proton at C-2 and at C-4 should be coupled with an axial proton of the cyclohexyl ring. Now, if we exclude **11** and **9**, all mentioned compounds have the α position substituted, and therefore equatorial 2 and 4 protons should not show any long-range coupling. One can expect a coupling of the axial protons 2 and 4, respectively, with the axial protons 8 and 6; this provided a method for the assignments reported in Table II. A clear coupling of 0.8 cps is observed in **9**,

(6) C. E. Johnson, Jr., and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).
(7) S. Mitsui, Y. Senda, and K. Konno, *Chem. Ind.* (London), 1354 (1963); S. Mitsui and Y. Kudo, *ibid.*, 381 (1965), and references cited therein.
(8) J. A. Zderic, M. E. C. Rivera, and D. C. Limón, *J. Amer. Chem. Soc.*, **82**, 6373 (1960); E. W. Garbisch, Jr., *J. Org. Chem.*, **27**, 3363 (1962).
(9) P. Bucci, *J. Amer. Chem. Soc.*, **90**, 252 (1968).
(10) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry. Illustrations from the Steroid Field," Holden-Day, Inc., San Francisco, Calif., 1964, p 183.
(11) Reference 10, p 115.
(12) M. Dobler and J. D. Dunitz, *Helv. Chim. Acta*, **47**, 695 (1964); W. A. C. Brown, G. Eglinton, J. Martin, W. Parker, and G. A. Sim, *Proc. Chem. Soc.*, 57 (1964); I. Laszlo, *Rec. Trav. Chim. Pays-Bas*, **84**, 251 (1965); N. W. J. Pumphrey and M. J. T. Robinson, *Chem. Ind.* (London), 1903 (1963); H. O. House and W. M. Bryant, III, *J. Org. Chem.*, **31**, 3482 (1966); J. E. Douglass and T. B. Ratliff, *ibid.*, **33**, 355 (1968).

which may be attributed to $J_{2e,9\alpha}$ and $J_{4e,9\alpha}$, since its value is greater than $J_{2a,8a}$, which in general could not be measured but only observed as a line broadening. The assignments of the protons of **11** is not possible on the basis of the single spectrum, since the two chemical shifts are very similar (their difference is only 8.7 cps). In cyclohexane the axial proton chemical shifts are at higher fields, but this consideration is useless here because of the presence of the oxygen atom and the substitution of two CH axial bonds with the second cycle. Our assignment will therefore be uniquely based on the best agreement obtained with the additivity of the substituents effects.

The α-phenyl group may either assume, with respect to the rest of the molecule, the position shown in Figure 1a (the most probable one, under those steric conditions), or rotate freely. In the former case, we may expect[6] changes in chemical shift of -0.11 and -0.16 ppm for the equatorial and axial protons near to the oxygen, respectively. In the latter case, a good estimate of the changes is obtained by averaging the above values with those obtainable when the plane of the benzene ring is orthogonal to the previous position (Figure 1b). They are, respectively, -0.08 and -0.14, with a mean value of -0.095 and -0.15. If we adopt for **11** the assignment reported in Table II, one obtains, respectively, shifts equal to -0.24 and -0.14 ppm. The poor agreement may be caused by various factors (substitution of the C–H dipole with the C–Ph group, differences in solvent interaction, etc.). The significant fact is, however, that both protons are deshielded by not very different amounts. On the basis of the assignment of the spectrum of **11** we may obtain the contributions of cyclohexyl in the α position and of the hydroxyl group in β position reported in Table III.

TABLE III

Group	Position	H_{2a} and H_{4a}	H_{2e} and H_{4e}
Phenyl	α	-0.14	-0.24
Cyclohexyl	α	$+0.10$	-0.09
Hydroxyl	β	-0.33	$+0.27$

By means of these contributions we can calculate the expected shifts for compounds **1** and **5**. They are -0.47 and $+0.03$ (compound **1**) and -0.23 and $+0.18$ (compound **5**), respectively, for axial and equatorial protons. The experimental values are -0.66 and $+0.09$ (**1**) and -0.45 and $+0.23$ (**5**). The agreement in order of magnitude and sign is good, especially if we consider that we have neglected the probably notable interactions between two geminal substituents (for example, the OH–π bond in **1**, which is easily observed in the ir spectra).

The chemical-shift changes induced by the hydroxyl group (toward low field for the axial protons, smaller and toward high field for the equatorial protons) can easily be rationalized; in fact, the electric field generated by the "lone pairs," directed along the C–H_a direction, causes a charge shift from the axial hydrogen to the carbon atom and, to a lesser extent, from the carbon to the equatorial hydrogen. All assumptions made so far fully agree with the configurations assigned to compounds **1**, **3**, **5**, **7**, and **9**, and also with the supposed chair–chair conformation.

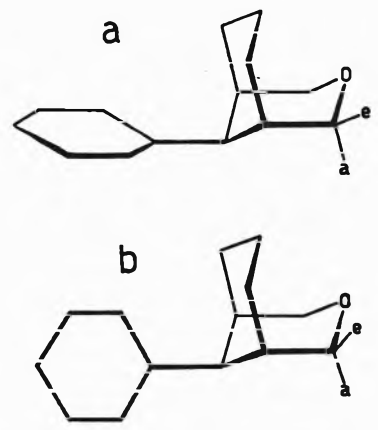


Figure 1.—Conformations of the 9α-benzene ring.

We shall now consider the series **11**, **2**, **4**, **6**, **8**, and **10**. Most interesting is the spectrum of **4**. In fact, it is possible to observe here a clear coupling between the benzylic 9α proton and two of the protons in 2 and 4. By triple resonance (*i.e.*, by simultaneously irradiating protons 1 and 5 and proton 9) it has been possible to assign unambiguously such coupling. On the basis of the presence of a long-range coupling, which causes a broadening of the corresponding peaks, we have assigned the spectrum of **10**. The changes in chemical shift (-0.08 and $+0.05$ for equatorial and axial protons, respectively) are here not significant and indicate the small effect of the hydroxyl group in the α configuration.

An analysis of the data, carried out on the same basis as that applied to the previous series of compounds, gave contradictory results. In fact, it is not possible, within reasonable limits of error, to establish any additivity of substituent effect or to explain the chemical shifts observed when β phenyl or β cyclohexyl are present. A possible explanation for this fact is the nonvalidity of the assumption of the chair–chair conformation when a bulky substituent is on the side of the tetrahydropyrane ring. It may, in fact, be assumed that, owing to the smaller steric requirements of the oxygen atom with respect to a methylene group,[13] the boat conformation of the tetrahydropyrane ring is preferred because of its smaller interaction with the substituent. Such a hypothesis, or at least the presence of a rapid equilibrium between the two forms, can explain the broadness of the peaks relative to one of the two hydrogen types in position 2 and 4 in the cyclohexyl derivatives. Such broadness indicates a much greater coupling with the protons in positions 1 and 5 than that observed in all other examined spectra. In fact, the band at lower field is *ca.* 5 cps broad, against the usual 2.5–3.5 cps. This fact is not observed in the spectra of the corresponding compounds with the phenyl group in the β position. In this case, assuming a chair–chair conformation and a suitable assignment, changes of -0.12 and $+0.21$ are obtained for the chemical shift of the axial and equatorial protons, respectively, caused by the phenyl substituent in **4**. Such values, which are found almost unchanged in the spectrum of **2**, are not consistent with the calculated ones, assuming as before the free rotation of the phenyl group, *i.e.*, -0.02 and -0.05 ppm.

(13) E. L. Eliel and S. M. C. Knoeber, *J. Amer. Chem. Soc.*, **88**, 5347 (1966).

The experimental values, which are actually not very large, might be due to changes in the solvation of the oxygen atom because of steric hindrance.

From the previous considerations, the assignment of the configurations to the relevant compounds is largely demonstrated. The configuration of **10** agrees with that already assigned.[4] It is also almost certain, in accordance with the results for analogous compounds found in the literature,[12] that the chair–chair conformation is the most stable, with the exception of the β-cyclohexyl derivatives, for which there is some evidence of a different situation.

Experimental Section[14]

9-Phenyl-3-oxabicyclo[3.3.1]nonan-9β-ol (1) and **9-phenyl-3-oxabicyclo[3.3.1]nonan-9α-ol** (2) were obtained[1] by the sulfuric acid catalyzed reaction of 1-phenylcyclohexene with formaldehyde in acetic acid solution: **1**, mp 141–142°, ir[15] 3608 cm^{-1}; **2**, mp 147–148°, ir[15] 3608 cm^{-1}.

9α-Phenyl-3-oxabicyclo[3.3.1]nonane (3) and **9β-phenyl-3-oxabicyclo[3.3.1]nonane** (4) were prepared[1] by hydrogenolysis with Raney nickel of alcohols 1 and 2, respectively: **3**, mp 54–55°; **4**, mp 46–48°.

9-Cyclohexyl-3-oxabicyclo[3.3.1]nonan-9β-ol (5).—A suspension of 0.300 g (1.37 mmol) of 1 and 0.300 g of 5% rhodium on alumina in 15 ml of water was shaken under hydrogen at room temperature and atmospheric pressure. When the absorption stopped, the mixture was extracted with ether. Evaporation of the dried ether extract gave 0.302 g of **5**, mp 172–174° (from petroleum ether), ir[15] 3616 cm^{-1}.

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.92; H, 10.69.

9-Cyclohexyl-3-oxabicyclo[3.3.1]nonan-9α-ol (6).—A suspension of 0.150 g (0.68 mmol) of **2** and 0.150 g of 5% rhodium on alumina was hydrogenated under the conditions used above. The residue (0.147 g) was dissolved in petroleum ether and chromatographed through a 1.0 × 15 cm column of neutral alumina (grade II). Elution with 8.5:1.5 petroleum ether–benzene yielded 0.110 g of **6**, mp 114° [from petroleum ether (bp 30–50°)], ir[15] 3619 cm^{-1}.

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.85; H, 10.89.

9α-Cyclohexyl-3-oxabicyclo[3.3.1]nonane (7).—Reduction of 0.300 g of **3** as described above gave 0.297 g of **7**, which was crystallized from ethanol, mp 88–90°.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.60; H, 11.46.

9β-Cyclohexyl-3-oxabicyclo[3.3.1]nonane (8).—Hydrogenation of 0.071 g of 4 as above yielded a crude residue which was dissolved in petroleum ether (bp 30–50°) and chromatographed through a 1.0 × 15 cm column of neutral alumina (grade II). Elution with petroleum ether (bp 30–50°) gave 0.046 g of pure **8** as an oil, $n^{25}D$ 1.49489.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.90; H, 11.73.

3-Oxabicyclo[3.3.1]nonan-9α-ol (10).—This compound was prepared according to the procedure of Blomquist and Wolinsky,[4] mp 205–207° (sealed capillary), ir[15] 3624 cm^{-1} (lit.[4] mp *ca.* 205°).

3-Oxabicyclo[3.3.1]nonan-9-one.—A solution of 1.50 g of **10** in 40 ml of acetone was treated dropwise with 2.75 ml of Jones reagent,[16] left for 3 min at room temperature, diluted with water, and extracted with ether. The ether extract was washed with 10% aqueous sodium carbonate, dried, and evaporated to give 1.40 g of the product, which after sublimation melted at 155–157° (lit.[4] mp 154–157°).

3-Oxabicyclo[3.3.1]nonan-9β-ol (9).—To a mixture of 2.30 g (0.10 g-atom) of sodium and 50 ml of boiling toluene was added rapidly a solution of 1.40 g (0.01 mol) of 3-oxabicyclo[3.3.1]-nonan-9-one in 23 ml of absolute ethanol. The mixture was refluxed for 1 hr, cooled, and diluted with ether. Evaporation of the resulting washed and dried solution gave a crude mixture of alcohols 9 and 10, which was chromatographed through a 1.5 × 35 cm column of neutral alumina (grade II). Elution with 6:4 petroleum ether–benzene gave 0.41 g of **10**, and further elutions with increasing amounts of benzene yielded 0.11 g of a mixture of 9 and 10 and finally 0.37 g of pure **9**. After crystallization from petroleum ether (bp 30–50°), **9** melted at 209–210° (sealed capillary), ir[15] 3624 cm^{-1}.

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.40; H, 9.75.

3-Oxabicyclo[3.3.1]nonane (11).—A sample kindly provided by Dr. E. L. Wittbecker,[17] after sublimation, melted at 135–138° (sealed capillary) (lit.[17] mp 135–138°).

Registry No.—**1**, 23328-19-0; **2**, 23328-20-3; **3**, 23328-21-4; **4**, 23328-22-5; **5**, 23328-23-6; **6**, 23328-24-7; **7**, 23328-25-8; **8**, 23328-26-9; **9**, 23328-27-0; **10**, 23328-28-1; **11**, 280-71-7.

Acknowledgments.—This work was supported by a contribution from the Consiglio Nazionale delle Ricerche. The authors would like to thank Professor G. Bertè for many useful discussions and Dr. M. Pannocchia for help in the experimental work.

(14) Melting points were determined on a Kofler hot stage, unless stated otherwise, and are uncorrected. Infrared spectra for comparisons between compounds were taken with a Perkin-Elmer Model 137 Infracord and those for determination of hydroxyl stretching bands with a Perkin-Elmer Model 237 grating spectrophotometer. Nuclear magnetic resonance spectra were determined on *ca.* 7% solutions in chloroform with a Varian DA-60 IL spectrometer using tetramethylsilane as an internal standard. Petroleum ether refers to the fraction boiling at 40–70°. Magnesium sulfate was used as the drying agent.

(15) Infrared spectra were determined in dried carbon tetrachloride, using the indene band at 3110 cm^{-1} as a calibration standard. A quartz cell of 2-cm optical length was employed, and the concentration of the solutions was *ca.* 3×10^{-3} *M*.

(16) R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 457 (1953).

(17) E. L. Wittbecker, H. K. Hall, Jr., and T. W. Campbell, *J. Amer. Chem. Soc.*, **82**, 1218 (1960).

The Preparation of 4-Substituted 1-Methoxycarbonylbicyclo[2.2.2]octanes, Substituted 1-Phenylbicyclo[2.2.2]octanes, 4-Substituted 1-*p*-Nitrophenylbicyclo[2.2.2]octanes, and 1,4-Disubstituted Bicyclo[2.2.2]octanes

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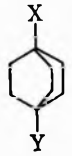
Received September 8, 1969

The preparation of several 1,4-disubstituted and 1-substituted bicyclo[2.2.2]octanes is described, including the following new compounds: 4-X-1-methoxycarbonylbicyclo[2.2.2]octane (X = H, Me, Et, Ph, Br, OH, or CO_2H), 4-X-1-phenylbicyclo[2.2.2]octane (X = H, Me, Et, *i*-Pr, or Ph), 4-X-1-*p*-nitrophenylbicyclo[2.2.2]octane (X = Et, *i*-Pr, Br, OMe, CN, or CO_2Me), 1-X-bicyclo[2.2.2]octane (X = *o*-, *m*-, *p*-nitrophenyl, *p*-aminophenyl, *p*-acetamidophenyl, 4-acetamido-3-nitrophenyl, 4-amino-3-nitrophenyl, 2,4-dinitrophenyl, or 4-amino-2-nitrophenyl), 1-X-4-Y-bicyclo[2.2.2]octane (X = OH, Y = *i*-Pr or isopropenyl; X = OMe, Y = isopropenyl; X = Br, Y = isopropenyl). An efficient preparation of dimethyl cyclohexa-1,3-diene-1,4-dicarboxylate is also reported.

In a 1,4-disubstituted bicyclo[2.2.2]octane (**1**) there will be a steric effect at a reaction site, Y, arising from

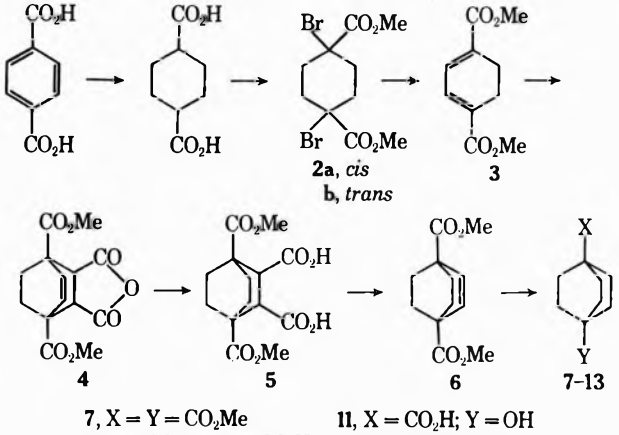


1

the bulk of the bicyclic system but, apart from any ponderal effect, independent of X, and so changing the substituent X will allow the nonconjugative polar effect of X to be studied in suitable reactions. Roberts, *et al.*,[2,3] Holtz and Stock,[4,5] Ritchie, *et al.*,[6,7] and Wilcox, *et al.*,[8,9] have used this system in investigations of polar and solvent effects. We wished to extend previous work on the kinetics of alkaline ester hydrolysis to 4-substituted 1-methoxycarbonylbicyclo[2.2.2]octanes, and to study electrophilic aromatic substitution in 4-substituted 1-phenylbicyclo[2.2.2]octanes, so that the nonconjugative polar effect of the substituent on the *ortho*, *meta*, and *para* positions of the benzene ring could be examined, steric effects being constant. We now describe the preparation of the compounds required for this investigation.

The reaction plan outlined in Scheme I was followed, despite reports that attempts to synthesise **6** by this sequence had failed.[10] The mixed *cis*- and *trans*-cyclohexane-1,4-dicarboxylic acid chlorides were brominated and were then converted into the mixed esters (**2**). The *cis* and the *trans* isomer can easily be separated at this stage, since the *cis* isomer is more soluble in methanol. Various conditions for the dehydrobromination of **2** were tried, but, as reported by Smith, *et al.*,[10] and Kauer, *et al.*,[11] the yields of **3** were variable. By using pyridine as solvent and as base for the dehydrobromination, the diene **3** was obtained from the mixed esters **2** in 80% yield; also hydrolysis of the esters was avoided and hence the need to reesterify the product. Ainbinder[12] recently reported a convenient six-stage synthesis of **3** from hydroquinone, and although this synthesis may be better than those described by Kauer, *et al.*,[11] Guha and Hazra,[13] von Baeyer,[14] Smith, *et al.*,[10] and Baker and Stock,[15] even better methods are that reported by Prinzbach, *et al.*,[16] and the method described here.

Scheme I



7, X = Y = CO_2Me
8, X = CO_2Me; Y = CO_2H
9, X = CO_2Me; Y = Br
10, X = CO_2Me; Y = Ph
11, X = CO_2H; Y = OH
12, X = CO_2Me; Y = OH
13, X = CO_2Me; Y = H

Oxidative bisdecarboxylation of **5** with lead tetraacetate had been reported to fail by Humber, *et al.*,[17] and by Smith, *et al.*,[10] but we found that the reaction occurs smoothly in dimethyl sulfoxide or dioxane as solvent at room temperature.[18] Kauer, *et al.*,[11] have since found that **5** can be decarboxylated with lead tetraacetate in refluxing benzene. The Cristol–Firth method of brominative decarboxylation[19,20] was applied to **8** with 1,2-dibromoethane as solvent and gave

(1) S. Sotheeswaran, Ph.D. Thesis, University of Hull, England, 1967. Department of Chemistry, University of Ceylon, Peradeniya, Ceylon.
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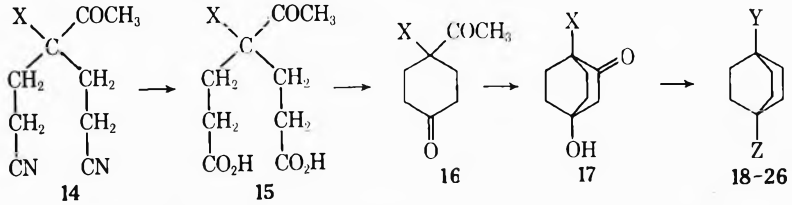
SCHEME II



14 **15** **16** **17** **18-26**

14-17a, X = Me
b, X = Et
c, X = Ph
d, X = *i*-Pr
e, X = isopropenyl

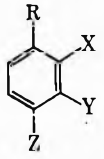
18, Y = OH; Z = X
19, Y = OMe; Z = X
20, Y = Br; Z = X
21, Y = Ph; Z = H
22, Y = Z = Ph
23, Y = CN; Z = Ph
24, Y = CO_2H; Z = X
25, Y = CO_2Me; Z = X
26, Y = Ph; Z = X

X as above

yields of **9** comparable with those obtained by the Hunsdiecker reaction,[21] but in the latter method unreacted acid was recovered; the Cristol–Firth reaction in petroleum ether (bp 60–70°) as solvent failed.

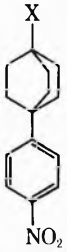
The synthesis of **13** we employed is essentially a modification of the method of Grob, *et al.*[22] In the preparation of 1-diethylaminobutadiene we used a solvent (ether) of lower boiling point than that used by Grob, *et al.*, so that the solvent could be removed more quickly before the final distillation, and consistent yields (60–65%) were obtained, without polymerization of the product.

By modifications of the methods of Bruson and Riener,[23,24] Colonge and Vuillemey,[25] and Holtz and Stock,[4] several 1,4-disubstituted bicyclo[2.2.2]octanes were prepared *via* the 4-substituted 1-hydroxybicyclo[2.2.2]-octan-3-ones (**17**) (Scheme II). Holtz and Stock[4] reduced the ketones **17a–17c** in 30–40% yields; we studied the reduction of the carbonyl group of **17c** in more detail and we used improved methods to reduce the carbonyl groups in **17a–17e**. The Huang-Minlon[26] modification of the Wolff–Kishner reduction of **17c** give a 20% yield of **18c**, but by using Grob's[27] modification of the Wolff–Kishner reduction a 40% yield was obtained. The yield was further improved by increasing the time taken for the formation of the hydrazone and by maintaining a slow distillation of hydrazine hydrate during 2 hr. The compound **18c** was consistently obtained in 65–70% yield by using these conditions, and 70–75% yields of **18a** or **18b** were obtained. However, only 10 and 25% yields of **18d** and **18e**, respectively were obtained, and the use of acidic conditions,[27] in the hope of increasing the yield of the hydrazone, gave no improvement. Further work with **17e** revealed that the reduction gave satisfactory yields if the hydrazone was isolated, anhydrous conditions were maintained in the decomposition of the hydrazone, and redistilled hydrazine hydrate was added to the mixture of pure hydrazone, potassium hydroxide and diethylene glycol to ensure a gradual rise in temperature as the hydrazine hydrate distilled off. In this way a 55% yield of **18e** was obtained. Another method tried for the reduction of **17e** was *via* the tosylhydrazone according to Caglioti and Grasselli;[28] a 27% overall yield was obtained.



27-35a, R = 1-bicyclo[2.2.2]octyl
b, R = *t*-butyl

27, X = Y = H; Z = NO_2
28, X = Y = H; Z = NH_2
29, X = Y = H; Z = $NHCOCH_3$
30, X = H; Y = NO_2; Z = $NHCOCH_3$
31, X = H; Y = NO_2; Z = NH_2
32, X = Z = H; Y = NO_2
33, X = Z = NO_2; Y = H
34, X = NO_2; Y = H; Z = NH_2
35, X = NO_2; Y = Z = H



36, X = Br
37, X = CO_2Me
38, X = OMe
39, X = Et
40, X = *i*-Pr
41, X = CN

The compound **23** was prepared from **20c** as described previously.[4] However, it proved difficult to isolate the product from the complex reaction mixture, and therefore Friedmann and Schechter's[29] extraction procedure was used.

The method we describe for the Koch–Haaf carboxylation[30] of **20a** or **20b** is an improvement on the one reported by Holtz and Stock.[4] The reaction involves the formation of a bridgehead carbonium ion, and although the formation of the 1-bicyclo[2.2.2]octyl carbonium ion is more difficult than, for example, the formation of the 1-adamantyl or *t*-butyl carbonium ion,[31,32] the formation of a 1-bicyclo[2.2.2]octyl carbonium ion is still conveniently easy.

The Friedel–Crafts alkylation of benzene with 1-bromoadamantane gave a high yield under mild conditions.[33,34] Likewise, we found that alkylations of benzene with **20a–20d** or **9** proceed easily and in good

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(22) C. A. Grob, M. Ohta, E. Renk, and A. Weiss, *Helv. Chim. Acta*, **41**, 1191 (1958).
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(25) J. Colonge and R. Vuillemey, *Bull. Soc. Chim. Fr.*, 2235 (1961).
(26) Huang-Minlon, *J. Amer. Chem. Soc.*, **71**, 3301 (1949).
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(28) L. Caglioti and P. Grasselli, *ibid.*, 153 (1964).
(29) L. Friedman and H. Schechter, *J. Org. Chem.*, **26**, 2522 (1961).
(30) H. Koch and W. Haaf, *Angew. Chem.*, **72**, 628 (1960).
(31) R. C. Fort and P. von R. Schleyer, *Advan. Alicycl. Chem.*, 283 (1966).
(32) G. J. Gleicher and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **89**, 582 (1967).
(33) R. C. Fort and P. von R. Schleyer, *Chem. Rev.*, **64**, 277 (1964).
(34) H. Stetter, M. Schwarz, and A. Hirschhorn, *Chem. Ber.*, **92**, 1629 (1959).

yield. For **20a** or **20b** the reaction with anhydrous ferric chloride as catalyst gave almost pure **26a** or **26b**. The compounds were purified by crystallization (**26a**) or by column chromatography (**26b**). For **20d** the crude product was less pure and purification proved difficult. With anhydrous aluminium chloride as catalyst the reaction was faster, and the impurities (*ca.* 15%) were removed by one crystallization from ethanol. The alkylation of benzene by using **9** or **20c** and anhydrous aluminium chloride gave **10** or **22** in 83 or 78% yield, respectively, and no by-products were formed in the reaction.

The nitration of **21** to obtain **27a** in different media and under different conditions was studied to find the optimum conditions for the mononitration. In glacial acetic acid a considerable excess of fuming nitric acid was necessary to achieve nitration (see method 2); the use of longer reaction times or greater amounts of nitric acid gave lower yields of **27a**. Addition of **21** in glacial acetic acid to fuming nitric acid in concentrated sulfuric acid gave variable results, probably because of the difficulty in controlling the temperature. With a mixture of glacial acetic acid and acetic anhydride as solvent and a threefold excess of nitric acid in sulfuric acid, a reasonable yield of **27a** was obtained (see method 1). In the most convenient preparation we used acetic anhydride as solvent and fuming nitric acid as nitrating agent, at room temperature (see method 3).

The compounds **32a** and **35a** were prepared by a modification of the method described by Wepster, *et al.*,[35] for the preparation of *o*- and *m*-*t*-butylnitrobenzene.

Experimental Section

Melting points and boiling points are uncorrected. Ir spectra were recorded with a Unicam SP200 instrument. Uv spectra were recorded at 25° with a Unicam SP700 spectrophotometer; the wavelength values quoted refer to maxima and the molecular extinction coefficients are given in parentheses. Nmr spectra were recorded with a Varian HA-100 spectrometer, with tetramethylsilane as internal standard and deuteriochloroform as solvent.

Cyclohexane-1,4-dicarboxylic Acids.—The mixture of acids was obtained by hydrogenating terephthalic acid in aqueous alkali, with a Raney nickel catalyst.[36]

Dimethyl 1,4-Dibromocyclohexane-1,4-dicarboxylate (**2**).—The above acids (172 g, 1 mol) in redistilled thionyl chloride (450 ml) were heated under reflux with stirring until the solution became clear (3–4 hr). Bromine (341.0 g, 2.135 mol) was added dropwise during 4–6 hr. The mixture was heated under reflux for 2 days in a dry atmosphere and for the last 24 hr the mixture was irradiated with a 100-W tungsten lamp. The excess of bromine and thionyl chloride was distilled off, anhydrous methanol (400 ml) was added to the residue cooled in ice, and the mixture was heated under reflux for a further 3 hr. Methanol (200 ml) was added to dissolve the dimethyl *cis*-1,4-dibromocyclohexane-*cis*-1,4-dicarboxylate. The residual solid was filtered off and recrystallized from 1:1 methanol–acetone to give dimethyl *trans*-1,4-dibromocyclohexane-*trans*-1,4-dicarboxylate (**2b**), yield 155 g, mp 148–150° (lit.[13] mp 150°).

The methanol was evaporated from the filtrate and the residue was distilled under reduced pressure [bp 120–128° (2 mm)] to give the *cis,cis* ester **2a**, yield 143.9 g, mp 61–63° (lit.[13] mp 68°). The overall yield of mixed esters was 83%.

Dimethyl Cyclohexa-1,3-diene-1,4-dicarboxylate (**3**). **Method 1. Dehydrobromination with Cold Methanolic Potassium Hydroxide.**—Compound **2** was dehydrobrominated with ice-cold potassium hydroxide in 95% aqueous methanol (1:2 w/w) for 48–50 hr. The mixture was then acidified with dilute hydrochloric acid, and the precipitated acid was reesterified. The product was crystallized from petroleum ether (bp 60–80°) to give **3**, mp 73–76°. Starting from **2a** the yield was 8.96 g (32%); and from **2b**, 0.924 g (3.3%).

Method 2. Dehydrobromination with Methanolic Potassium Hydroxide at 50–60°.—The method was the same as that just described except that the mixture was heated at 50–60° for 3–4 hr; compound **3** was produced, mp 75–77°. Starting from **2a** the yield was 5.60 g (20%); from **2b**, 5.32 g (19%).

Method 3. Dehydrobromination with Pyridine.—The diester **2** (118 g, 0.33 mol) was heated under reflux with an excess of pure, dry pyridine (150 ml) for 12–15 hr. The mixture was cooled and diluted with water (1 l.). The precipitate was filtered off, dried ($CaCl_2$) *in vacuo*, and recrystallized from petroleum ether to give **3**: mp 81–83° (lit.[13,14] mp 83–85°,[10] 84–85°,[16] 83–84°,[37] 81°); nmr τ 2.93 (s, 2 H), 6.21 (s, 6 H), and 7.46 (s, 4 H); λ_{max} (EtOH) 309 nm (ϵ 10,950). Starting from **2a** the yield was 43 g (66.5%); from **2b**, 59 g (91%).

1,4-Dimethoxycarbonylbicyclo[2.2.2]oct-2-ene-5,6-dicarboxylic Anhydride (**4**).—The ester **3** (19.6 g, 0.1 mol) was heated with maleic anhydride (29.4 g, 0.3 mol) at 100° for 1 hr and then at 170° for 1 hr. The mixture was cooled and the gummy solid was recrystallized four times from petroleum ether (bp 100–120°)–xylene (3:1) to give **4** (16.2 g, 55%), mp 181–183° (lit.[10] mp 191.5°,[17] 183–185°,[11] 188–188.6°).

1,4-Dimethoxycarbonylbicyclo[2.2.2]octane-2,3-dicarboxylic Acid (**5**).—The anhydride **4** (29.4 g, 0.1 mol) was treated with a solution of potassium bicarbonate (20 g, 0.2 mol) in deionized water (100 ml) and the mixture was heated on a steam bath for 20 min. 10% palladium on carbon (2–3 g) was added to the cold product, and the mixture was hydrogenated at atmospheric pressure. The catalyst was filtered off and the filtrate was acidified and cooled. The precipitated solid was recrystallized from water to give **5** (30 g, 95%), mp 166–168° (lit.[10] mp 177–178°,[17] 190–192°,[11] 210° dec).

1,4-Dimethoxycarbonylbicyclo[2.2.2]oct-2-ene (**6**).—This compound was prepared as described previously.[18] On a larger scale **6** was prepared[38] by heating **3** at 165° with ethylene under 1000 atm pressure in a silver-lined autoclave as reported by Kauer.[39] The crude product was recrystallized from hexane to give **6** (67%), mp 73–75° (lit.[39] mp 75–76°).

1,4-Dimethoxycarbonylbicyclo[2.2.2]octane (**7**).—The diester **6** was hydrogenated in methanol with a 10% palladium on carbon catalyst. The product was recrystallized from hexane to give **7** (90%), mp 98–100° (lit.[11] mp 100–101°).

4-Carboxy-1-methoxycarbonylbicyclo[2.2.2]octane (**8**).—The diester **7** (9.04 g, 0.04 mol), potassium hydroxide (2.24 g, 0.04 mol) in methanol (42.5 ml), and water (4.25 ml) were heated under reflux for 5–7 hr. The mixture was cooled and poured into water, and the product was shaken with ether. The organic phase was washed with water and dried ($MgSO_4$); evaporation of the solvent gave the recovered diester **7** (2.6 g). The aqueous phase was heated to drive off dissolved ether and was then acidified. The precipitated acids were washed with chloroform (3 × 50 ml) and the aqueous phase was filtered to remove any insoluble dicarboxylic acid. The chloroform layer was chilled, and any dicarboxylic acid which separated was filtered off. The filtrate was dried ($MgSO_4$) and the solvent was evaporated. The residue was crystallised from benzene to give the acid **8** (4.0 g, 66% allowing for the recovered diester): mp 180–182°; ir (KCl) 3000 (OH), 2950, 2875 (CH_3, CH_2), 1720, 1680 (C=O), 1240, and 1080 cm^{-1} (CO).

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.09; H, 7.59.

1,4-Dicarboxybicyclo[2.2.2]octane (1.4 g) had a melting point of 360–370° (lit.[2] mp >360°).

4-Bromo-1-methoxycarbonylbicyclo[2.2.2]octane (**9**).—The acid **8** (4 g, 0.0189 mol) was dissolved in acetone (30 ml) and neutralized (phenolphthalein) with aqueous 1 *N* sodium hydroxide. Silver nitrate (3.4 g, 0.020 mol) in water (5 ml) was added dropwise with stirring, and the gray-white precipitate was filtered off and washed with water, acetone, and ether. The residue was dried ($CaCl_2$) *in vacuo* for 24 hr and then at 100° under high vacuum for 2 days. The yield of silver salt was 4.3 g (71%) and of recovered acid was 0.13 g (3%).

(35) H. J. B. Biekart, H. B. Dessens, P. E. Verkade, and B. M. Wepster, *Rec. Trav. Chim. Pays-Bas*, **71**, 321 (1952).

(36) R. G. Cooke and A. K. MacBeth, *J. Chem. Soc.*, 1245 (1939).

(37) R. H. Burnell and W. I. Taylor, *ibid.*, 3636 (1954).

(38) We thank I. C. I., Mond Division, England, for carrying out this reaction.

(39) J. C. Kauer, *Chem. Abstr.*, **59**, 6276*g* (1963).

The dry silver salt (4.3 g, 0.0135 mol) was made into a paste with dry petroleum ether (bp 40–60°, 50 ml). Pure, dry bromine (2.16 g, 0.0135 mol) was added dropwise to the vigorously stirred suspension under dry nitrogen. The mixture was stirred for a further 30 min and was then heated under reflux for 30 min. The product was filtered off and the residue was washed with ether. The filtrate and the ethereal washings were repeatedly washed with aqueous 1 *N* sodium carbonate and dried ($MgSO_4$). The solvent was evaporated and the residue was crystallized from methanol–water (10:1) to give the ester **9** (2.0 g, 60% based on the silver salt): mp 75–76°; ir (KCl) 2920, 2850 (CH_3, CH_2), 1719 (C=O), 1252, and 1080 cm^{-1} (CO).

Anal. Calcd for $C_{10}H_{13}O_2Br$: C, 48.60; H, 6.12; Br, 32.33. Found: C, 48.40; H, 6.06; Br, 32.65.

The yield of **8** recovered was 0.45 g (11%).

1-Methoxycarbonyl-4-phenylbicyclo[2.2.2]octane (10).—The bromo compound **9** (0.65 g, 0.00263 mol) in dry benzene (25 ml) was added during 15 min to a stirred solution of sublimed anhydrous aluminium chloride (1.3 g, 0.00975 mol) in benzene (20 ml) at −10° under dry nitrogen. For 1 hr the temperature was kept below 10° and the mixture was stirred vigorously. The temperature was then allowed to rise to room temperature during 1 hr. Stirring was continued overnight and the mixture was heated at 50–60° for 4 hr. The reaction mixture was cooled and poured into ice–hydrochloric acid, and the product was washed with ether. The ethereal layer was washed with aqueous sodium carbonate and water and dried ($MgSO_4$). The solvent was evaporated to give a brownish solid (0.6 g). The crude solid was dissolved in petroleum ether (bp <40°) and the solution was passed down a column (50 × 2 cm) of alumina. The solute was eluted with petroleum ether–acetone (99:1), and was crystallized from methanol to give the ester **10** (0.53 g, 83%): mp 89–91°; ir (KCl) 3020, 1590, 1490 (aromatic) 2900, 2800 (CH_3, CH_2), 1705 (C=O), 1240, 1070 (CO), 750, and 695 cm^{-1} (monosubstituted benzene); nmr τ 2.65–2.90 (complex, 5 H), 6.34 (s, 3 H), 8.11 (narrow peak, 12 H, $W_{1/2}$ = 1.5 cps).

Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.74; H, 8.00.

1-Carboxy-4-hydroxybicyclo[2.2.2]octane (11).—Compound **9** was hydrolyzed with sodium hydroxide by using a method similar to that described by Roberts, *et al.*,[2] for the hydrolysis of the ethyl ester. The yield of **11** was 68%, mp 221–223° (lit.[2] mp 222.9–225°).

4-Hydroxy-1-methoxycarbonylbicyclo[2.2.2]octane (12).—The acid **11** (1.7 g) in ether was treated with an ethereal solution of diazomethane until the yellow colour persisted. The ethereal solution was dried ($MgSO_4$) and the ether was evaporated. The residue was crystallized three times from hexane to give the ester **12** (51%): mp 61–63°; ir (KCl) 3300 (OH) 2975, 2875 (CH_3, CH_2), 1720 (C=O), 1240, and 1065 cm^{-1} (CO).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.25; H, 8.97.

1-Diethylaminobutadiene.—This compound was prepared (62%) by a modification of the method of Hünig and Kahanek,[40] by using ether instead of benzene as solvent; with benzene as solvent we frequently obtained yields of 20–30%. The diolefin had a boiling point of 70–80° (11 mm) [lit.[40] bp 60–70° (12 mm)].

1-Ethoxycarbonyl-2-diethylaminocyclohex-3-ene.—This compound was prepared (88%) as described by Hünig and Kahanek:[40] bp 85–95° (4.5 mm) [lit.[40] bp 80–83° (0.2 mm)].

1-Ethoxycarbonylcyclohexa-1,3-diene {52%, bp 68–78° (4 mm) [lit.[22] bp 90–92° (11 mm)]} and **1-ethoxycarbonylbicyclo[2.2.2]oct-2-ene-5,6-dicarboxylic anhydride** [91%, recrystallized three times from petroleum ether (bp 60–80°)–benzene (3:1), mp 84–85° (lit.[22] mp 86.5–87°)], were prepared as described by Grob, Ohta, Renk, and Weiss.[22]

1-Ethoxycarbonylbicyclo[2.2.2]octane-2,3-dicarboxylic Acid.—This compound was prepared from the above anhydride by the method described for the preparation of **5** (92%, from water), mp 143–146° (lit.[22] mp 135–147°).

1-Ethoxycarbonylbicyclo[2.2.2]oct-2-ene.—This compound was prepared as described previously,[18] bp 95–99° (10 mm) [lit.[22] bp 95–96° (10 mm)].

1-Ethoxycarbonylbicyclo[2.2.2]octane.—The above olefin was hydrogenated in ethanol with a 10% palladium on carbon catalyst and the residue was distilled (90%), bp 88–90° (4.5 mm) [lit.[22] bp 75–76° (3 mm)].

(40) S. Hünig and M. Kahanek, *Chem. Ber.*, **90**, 238 (1957).

1-Carboxybicyclo[2.2.2]octane.—The above ester was hydrolyzed with ethanolic potassium hydroxide solution. The acidified solution gave the acid (89%, from acetone), mp 139–140° (lit.[2] mp 140.8–141.3°).

1-Methoxycarbonylbicyclo[2.2.2]octane (13).—The above acid in ether was treated with ethereal diazomethane until the yellow color persisted. The solvent was evaporated and the residue was chromatographed on an alumina column (20 × 1.3 cm); elution with petroleum ether (bp <40°) gave the pure ester. Evaporation of the solvent from the light petroleum eluates and distillation of the residue gave the ester **13** (57%): bp 54–56° (4 mm); mp 37–39°; ir (CCl_4) 2940, 2860, 1460, 1438 (CH_3, CH_2), 1720 (C=O), 1240, and 1065 cm^{-1} (CO).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.25; H, 9.25.

3-Acetyl-1,5-dicyano-3-X-pentanes (14a–14e).—These compounds were prepared by modification of the methods of Bruson and Riener.[23,24] Acrylonitrile (1 mol) was added slowly to a vigorously stirred solution of a ketone (0.5 mol) in *t*-butyl alcohol (100 g) containing a suitable base. The base, stirring time, and temperature used are given, respectively, after the ketone. Butan-2-one (30% methanolic potassium hydroxide, 3 g, 4–6 hr, 0–5°) gave **14a** (67%), mp 66–67° from benzene (lit.[23] mp 67°); pentan-2-one (Triton "B," 2 g, 4–6 hr, 10–15°) gave **14b** (42%), mp 107–109° from ethanol [lit.[23] mp 109°]; 3-phenylpropan-2-one (Triton "B," 5 g, 3 hr, 20–25°) gave **14c** (87%), mp 109° from ethanol (lit.[23] mp 109–110°); 4-methylpentan-2-one (10% methanolic potassium hydroxide, 2.5 g, 4–6 hr, 0–5°) gave **14d** (10.7%), bp 202–210° (2 mm) [lit.[23] bp 200–205° (2 mm)], mp 98–100° from ethanol (lit.[23] mp 101°); mesityl oxide (10% methanolic potassium hydroxide to give pH 10–10.5, 18–20 hr, 20–25°) gave **14e** (61%), mp 115–116° from methanol (lit.[24] mp 116–117°).

3-Acetyl-3-X-pentane-1,5-dicarboxylic Acids (15a–15e).—The compounds **14a–14e** were each hydrolyzed with aqueous sodium hydroxide, heated with decolorizing charcoal, and then acidified. The acid precipitated from the cold mixture was filtered off and crystallized from 1,2-dichloroethane to give **15a** (71%), mp 122–123° (lit.[23] mp 125°), or from water to give **15b** (76%), mp 112–113° (lit.[23] mp 112–113°); **15c** (90%), mp 168–170° (lit.[23] mp 171–172°); **15d** (85%), mp 146–148° (lit.[23] mp 148°); and **15e** (80%), mp 128–131° (lit.[24] mp 136–137°).

4-Acetyl-4-X-cyclohexanones (16a–16e).—These compounds were prepared by a modification of the method described by Colonge and Vuillemey:[25] **16a** (58%), bp 133–136° (15 mm) [lit.[25] bp 133° (15 mm)]; **16b** (72%), bp 140–147° (17 mm) [lit.[25] bp 144° (18 mm)]; **16c** (55%), mp 76–77° (lit.[25] mp 78°), bp 163–166° (2 mm) [lit.[25] bp 163–165° (2 mm)]. The reaction using **15d** produced two fractions. The first fraction was 4-acetyl-4-isopropylcyclohexanone (**16d**, 40%): bp 108–118° (2 mm); ir (KCl) 2950, 2880 (CH_3, CH_2), 1705, and 1690 cm^{-1} (C=O); nmr τ 9.10 (d, 6 H, J = 6.6 cps) and 7.5–8.5 (m, 12 H).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 71.99; H, 10.10.

The second fraction was 3-acetyl-3-isopropylpentane-1,5-dicarboxylic anhydride (2%), bp 194–204° (2 mm).

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 64.01; H, 7.99.

Potassium bicarbonate solution hydrolyzed this product to give **15d**.

The reaction using **15e** produced an unidentified fraction, bp 120–180° (1 mm), and 4-acetyl-4-isopropenylcyclohexanone (**16e**, 45%): bp 80–83° (1 mm); ir (KCl) 2930, 2900 (CH_3, CH_2), 1705, 1695 (C=O), 1630, and 910 cm^{-1} (C=CH_2).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.85; H, 8.85.

When potassium acetate (0.30 mol/1 mol of **15e**) was added to the reaction mixture, the yield of **16e** was 58%.

1-Hydroxy-4-X-bicyclo[2.2.2]octan-3-ones (17a–17e).—These compounds were prepared as described by Colonge and Vuillemey:[25] **17a** (85%), bp 143–147° (15 mm) [lit.[25] bp 147° (18 mm)], mp 58–59° (lit.[25] mp 60°); **17b** (80%), bp 158–160° (15 mm) [lit.[25] bp 157° (16 mm)], mp 49–51° (lit.[25] mp 50°); **17c** (72%), crystallized from ethanol–water (2:1), mp 180–183° (lit.[25] mp 183°). 1-Hydroxy-4-isopropylbicyclo[2.2.2]octan-3-one (**17d**, 85%) had a melting point of 69–71° from cyclohexane, ir (KBr) 3300 (OH), 2950, 2850 (CH_3, CH_2), and 1710 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.88; H, 9.67.

1-Hydroxy-4-isopropenylbicyclo[2.2.2]octan-3-one (**17e**, 80%) had a melting point of 96–98° from cyclohexane; ir (KCl) 3200 (OH), 2910, 2840 (CH_3, CH_2), 1700 (C=O), 1630, and 895 cm^{-1} (C=CH_2).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.58; H, 9.21.

1-Hydroxy-4-X-bicyclo[2.2.2]octanes (18a–18e). Method 1.—The ketones **17a–17e** (0.02 mol) were each heated under reflux with hydrazine hydrate (25 ml of 98–100% w/w) for 5 hr; the mixture was cooled and potassium hydroxide (0.1 mol) and diethylene glycol (35 ml) were added. The apparatus was then arranged for distillation and the bath temperature was maintained at 160° for 1 hr and then raised to 220°. Nitrogen was evolved and the temperature was kept at 220° until the nitrogen evolution ceased (2 hr). The reaction mixture was cooled, poured into water, and washed with ether; the apparatus was washed out with ether, and the distillate was neutralized with 2 *N* hydrochloric acid and shaken with ether. The combined ethereal solutions were washed with 2 *N* hydrochloric acid and water and dried ($MgSO_4$). Evaporation of the ether left either a solid, **18a–18c** or **18e**, or a liquid, **18d**. Compound **18a** (70%) was sublimed at 70–80° (20 mm) [lit.[4] 70° (25 mm)], mp 98–101° (lit.[4] mp 103–104°); **18b** (75%) was sublimed at 80–90° (2 mm) [lit.[4] 70° (25 mm)], mp 101–103° (lit.[4] mp 104.5–106°); **18c** (69%) was crystallized from cyclohexane, mp 115–117° (lit.[4] mp 122–123°). The liquid from **17d** on distillation at 100–110° (1 mm) gave a solid, which was crystallized from cyclohexane to give 1-hydroxy-4-isopropylbicyclo[2.2.2]octane (**18d**, 10%): mp 124–127°; ir (KCl) 3250 (OH), 2900, and 2820 cm^{-1} (CH_3, CH_2).

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.34; H, 11.62.

Compound **18d** was also prepared by hydrogenating **18e** in methanol with a 10% palladium-on-carbon catalyst.

The solid from **17e** gave 1-hydroxy-4-isopropenylbicyclo[2.2.2]-octane (**18e**, 25%): mp 110.9–112° from cyclohexane; ir (KCl) 3280 (OH), 2905, 2810 (CH_3, CH_2), 1625, and 892 cm^{-1} (C=CH_2).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.31; H, 10.88.

Method 2 for 18e.—The ketone **17e** (1.8 g, 0.01 mol) was heated under reflux with hydrazine hydrate (4 ml of 98–100% w/w) for 3 hr. The crude hydrazone, mp 128–145°, was precipitated by cooling the reaction product, and showed no carbonyl absorption in its infrared spectrum. This hydrazone (1.55 g, 0.008 mol), potassium hydroxide (3 g, 0.0535 mol), diethylene glycol (17 ml), and hydrazine hydrate (7 ml) were slowly heated and the procedure was then as given in method 1: yield 0.73 g, 55%.

Method 3 for 18e.—Compound **17e** (0.9 g, 0.005 mol), toluene-*p*-sulfonhydrazide (1.4 g, 0.0075 mol), and dry ethanol (40 ml) were heated under reflux for 4 hr and then cooled. The solid was filtered off and recrystallized from ethanol to give 1-hydroxy-4-isopropenylbicyclo[2.2.2]octan-3-one toluene-*p*-sulfonylhydrazone (1 g, 57%): mp 198–200° dec; ir (KCl) 3450 (NH, OH), 2925, 2850 (CH_3, CH_2), 1635, 885 (C=CH_2), 1590 (C=N), 1330, 1155 (S=O), and 820 cm^{-1} (1,4-disubstituted benzene).

Anal. Calcd for $C_{18}H_{24}N_2O_3S$: C, 62.04; H, 6.94; N, 8.04. Found: C, 62.18; H, 7.07; N, 8.50.

The tosyl hydrazone (0.664 g, 0.002 mol) was dissolved in freshly distilled dioxane (25–30 ml), sodium borohydride (2.22 g, 0.0587 mol) was added, and the mixture was heated under reflux for 8 hr. The mixture was cooled, poured into water, and shaken with ether and the solution was dried ($MgSO_4$). The solid left after evaporation of the ether was crystallized from cyclohexane to give **18e** (0.15 g, 47%); the overall yield from **17e** was 27%.

1-Methoxy-4-X-bicyclo[2.2.2]octanes (19c or 19e).—The alcohols **18c** or **18e** were methylated by using the method described by Holtz and Stock.[4] The product in either case was about 90% pure as indicated by glpc analysis. From **18c** chromatographic separation on an alumina column (30 × 1.3 cm) and elution with petroleum ether followed by petroleum ether–ether (92:8) gave **19c** (61%), bp 138–142° (5 mm) [lit.[41] bp 121° (0.8 mm)], mp 44–46° (lit.[41] mp 44°). From **18e** elution with petroleum ether gave 4-isopropenyl-1-methoxybicyclo[2.2.2]octane (**19e** 62.5%): bp 103–110° (8 mm); ir (liquid film) 2950, 2875, 2825 (CH_3, CH_2), 1635, 895 (C=CH_2), and 1110 cm^{-1} (CO).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.28; H, 11.24.

1-Bromo-4-X-bicyclo[2.2.2]octanes (20a–20d).—These compounds were prepared as described by Holtz and Stock.[4] The bromide **20a** (85%) was sublimed at 80–90° (12 mm) [lit.[4] 70° (1 mm)], mp 90–93° (lit.[4] mp 92–94°); **20b** (85%) was sublimed at 50–60° (12 mm) [lit.[4] 70° (1 mm)], mp 34–36° (lit.[4] mp 34–35°); **20c** (90%) was crystallized from ethanol, mp 107–108° (lit.[4] mp 109–110°). The product from **18d** was sublimed at 75–80° (5 mm) to give 1-bromo-4-isopropylbicyclo[2.2.2]-octane (**20d**, 87%): mp 36–38°; ir (liquid film) 2925, 2850 (CH_3, CH_2), and 685 cm^{-1} (CBr).

Anal. Calcd for $C_{11}H_{19}Br$: C, 57.14; H, 8.30; Br, 34.55. Found: C, 57.19; H, 8.31; Br, 34.10.

1-Phenylbicyclo[2.2.2]octane (21). Method 1.—The compound **20c** (13.2 g, 0.05 mol) in ethanol (500 ml) was added to a suspension of Raney nickel (15 g) in ethanolic sodium ethoxide (12 g of sodium in 100 ml of ethanol). The mixture was stirred at room temperature in an atmosphere of hydrogen until the calculated volume was absorbed (9–12 hr). The catalyst was filtered off, water was added, and the mixture was shaken with ether. The ethereal solutions were washed with water and dried ($MgSO_4$). The ether was evaporated and the residue was crystallized from ethanol–water (2:1) to give **21** (8 g, 86%): mp 78–80°; ir (KCl) 2910, 2825 (CH_3, CH_2), 1590, 1490 (aromatic), 755, and 695 cm^{-1} (monosubstituted benzene); nmr τ 2.65–2.97 (complex, 5 H) and 8.28–8.47 (br, 13 H).

Anal. Calcd for $C_{14}H_{18}$: C, 90.26; H, 9.74. Found: C, 90.23; H, 9.81.

Method 2.[42]—The compound **20c** (5.3 g, 0.02 mol) in dry tetrahydrofuran (30 ml) and *t*-butyl alcohol (2.96 g, 0.04 mol) was vigorously stirred under nitrogen, small pieces of lithium (0.694 g, 0.1 g-atom) were added, and the mixture was heated at 98° for 5–6 hr. Water was added to the cold product and the mixture was kept overnight at room temperature and then poured into water. The precipitated solid was crystallized as in method 1 to give **21** (3.27 g, 88%).

1,4-Diphenylbicyclo[2.2.2]octane (22).[43]—This compound was prepared from **20c** by the alkylation of benzene following the method described for the preparation of compound **10**. The hydrocarbon **22** (78% from ethanol) had a melting point of 210–211°; ir (KCl) 2950, 2915, 2862 (CH_2), 3090, 3060, 3022, 1598, 1498 (aromatic), 1005, 755, and 695 cm^{-1} (monosubstituted benzene); nmr τ 2.51–2.97 (complex, 10 H) and 8.05 (s, 12 H).

Anal. Calcd for $C_{20}H_{22}$: C, 91.55; H, 8.45. Found: C, 91.34; H, 8.47.

1-Cyano-4-phenylbicyclo[2.2.2]octane (23).—This compound was prepared as described by Holtz and Stock.[4] The crude reaction product (from 3.97 g of **20c**) was shaken with dimethylformamide and then poured into a solution of hydrated ferric chloride (20 g) in concentrated hydrochloric acid (5 ml) and water (30 ml). The mixture was heated at 60–70° to decompose the copper complex and then shaken successively with ether and benzene. The organic layers were washed with dilute hydrochloric acid and dried ($MgSO_4$), and the solvents were evaporated to give the crude cyanide, mp 120–135°. Glpc analysis showed the presence of the bromide **20c**. Chromatography on an acid-washed alumina column (60 × 2 cm) and elution with carbon tetrachloride removed the bromide; elution with methanol and crystallization of the product from ethanol gave **23** (0.85 g, 26.8%), mp 142–143° (lit.[4] mp 142–143.5°).

1-Carboxy-4-phenylbicyclo[2.2.2]octane (24c).—This compound was prepared as described by Holtz and Stock,[4] mp 289–291° (lit.[4] mp 293–294°).

1-Carboxy-4-X-bicyclo[2.2.2]octanes (24a or 24b).—The compound **20a** or **20b** (0.05 mol) and concentrated sulfuric acid (350 ml) were vigorously stirred at room temperature in an atmosphere of dry nitrogen. Formic acid ("AnalaR," 25 ml, 30.5 g, 0.663 mol) was added dropwise during 3–4 hr followed by silver sulfate (15.59 g, 0.05 mol) added portionwise. The mixture was stirred for a further 1 hr, silver bromide was filtered off, and the filtrate was poured onto ice. The precipitate was filtered off and washed with ether. The ethereal solution was washed with 4 *N* sodium hydroxide. The alkaline washings were heated

(41) J. Colonge, P. Francois, and R. Vuillemey, *Bull. Soc. Chim. Fr.*, 1028 (1966).

(42) P. Bruck, *Tetrahedron Lett.*, 449 (1962).

(43) Prepared in the Department of Chemistry, University of Ceylon, Peradeniya, Ceylon.

to remove dissolved ether and acidified. The precipitated acid was filtered off, heated in methanol with decolorizing charcoal, and crystallized from methanol–water. The acid **24a** (70%) had a melting point of 186–188° (lit.[4] mp 187–188°,[44] 184.2–186.0°,[45] 194–195°); **24b** (75%) had a melting point of 167–169° (lit.[4] mp 170.5–171°,[45] 178.5–179.5°).

1-Methoxycarbonyl-4-X-bicyclo[2.2.2]octanes (25a or 25b).—The acid **24a** or **24b** was esterified with ethereal diazomethane as described for **13** and the residue was distilled under reduced pressure. 1-Methoxycarbonyl-4-methylbicyclo[2.2.2]octane (**25a**, 90%) was obtained: mp 19.5–20°; bp 62–64° (3 mm); ir (liquid film) 2925, 2860, 1460, 1438 (CH_3, CH_2), 1720 (C=O), 1240, and 1065 cm^{-1} (CO).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.58; H, 10.00.

4-Ethyl-1-methoxycarbonylbicyclo[2.2.2]octane (**25b**, 95%) was also obtained: bp 119–120° (16 mm); ir (liquid film) 2925, 2850, 1460, 1438 (CH_3, CH_2), 1719 (C=O), 1240, and 1065 cm^{-1} (CO).

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.73; H, 10.13.

1-Phenyl-4-X-bicyclo[2.2.2]octanes (26a, 26b, or 26d). Method 1.[34]—Compound **20a**, **20b**, or **20d** (0.01 mol) in pure, dry benzene (30 ml) was added during 30 min to anhydrous ferric chloride (0.004 mol) in pure, dry benzene (20 ml) at room temperature and the mixture was stirred vigorously under dry nitrogen. The bath temperature was slowly raised during the addition and kept at 90–95° for 5–6 hr, and the mixture was then kept at room temperature overnight. The product was poured onto ice and hydrochloric acid and washed with ether. The organic layer was washed free of acid and dried ($MgSO_4$), and the solvent was evaporated. The purities of the residues (**26a**, **26b**, or **26d**) were shown by glpc to be 98, 95, and 85%, respectively, and the yields were 80, 78, and 74%, respectively. The crude residues were chromatographed on an alumina column (23 × 2 cm), and elution with petroleum ether removed contaminating starting material.

The material from **20a** was crystallized five times from ethanol to give 4-methyl-1-phenylbicyclo[2.2.2]octane (**26a**, 21%): mp 50–52°; ir (KCl) 2900, 2825 (CH_3, CH_2), 1375 (CH_3), 3040, 3005, 1598, 1492, 1458 (aromatic), 758, and 698 cm^{-1} (monosubstituted benzene); nmr τ 2.63–2.97 (complex, 5 H), 8.11–8.60 (symmetrical m, 12 H), and 9.17 (s, 3 H).

Anal. Calcd for $C_{15}H_{20}$: C, 89.94; H, 10.06. Found: C, 89.67; H, 10.02.

The ethyl compound (**26b**) could not be purified by repeated crystallization and the remaining impurities were removed by chromatography on a silicic acid (100 mesh) column (18 × 1.5 cm). Elution with petroleum ether gave 4-ethyl-1-phenylbicyclo[2.2.2]octane (**26b**, 23%): mp 36–38°; ir (KCl) 2900, 2825 (CH_3, CH_2), 1380 (CH_3), 3035, 3000, 1595, 1495, 1450 (aromatic), 758, and 698 cm^{-1} (monosubstituted benzene); nmr τ 2.62–2.97 (complex, 5 H), 8.10–8.61 (symmetrical m, 12 H), 8.81 (q, 2 H), and 9.20 (t, 3 H).

Anal. Calcd for $C_{16}H_{22}$: C, 89.65; H, 10.35. Found: C, 89.44; H, 10.51.

The isopropyl compound **26d** was obtained by chromatography on a silicic acid column (20 × 1.3 cm) and elution with petroleum ether followed by crystallization three times from ethanol. 4-Isopropyl-1-phenylbicyclo[2.2.2]octane (**26d**, 1.3%) was obtained: mp 60–62°; ir (KCl) 2925, 2850 (CH_3, CH_2), 3038, 3010, 1598, 1495, 1445 (aromatic), 750, and 690 cm^{-1} (monosubstituted benzene); nmr τ 2.61–2.93 (complex, 5 H), 8.12–8.59 (symmetrical m, partially overlapping the methine resonance, 13 H), and 9.09 (d, 6 H).

Anal. Calcd for $C_{17}H_{24}$: C, 89.41; H, 10.59. Found: C, 89.59; H, 10.40.

The compound **26d** (31%, from ethanol) was also prepared by using aluminium chloride as catalyst.

1-(*p*-Nitrophenyl)bicyclo[2.2.2]octane (27a). Method 1.—The hydrocarbon **21** (2.5 g, 0.013 mol) was dissolved in glacial acetic acid (50 ml) and acetic anhydride (25 ml), and the solution was cooled to 0–5°. A mixture of fuming nitric acid (1.7 ml, *d* 1.5, 0.0384 mol) and sulfuric acid (15 ml, 98%) was added with stirring, keeping the temperature below 5°. The temperature was then allowed to rise slowly and the mixture was kept at room temperature for 45 min and then poured onto ice. The solid was filtered off, washed free of acid, and crystallized from ethanol to give **27a** (1.46 g, 47%): mp 104–106°; ir (KCl) 2898, 2825 (CH_2), 1510, 1345, 850, 750 (NO_2), 3098, 1590 (aromatic), 1100, and 850 cm^{-1} (1,4-disubstituted benzene); nmr τ 1.89 (d, 2 H, J = 9 cps), 2.56 (d, 2 H, J = 9 cps), 8.25 (br peak, 13 H, $W_{1/2}$ = 4 cps); λ_{max} (isooctane) 269.3 nm (ϵ 11,930).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.36; H, 7.50; N, 6.23.

Method 2.[46]—The hydrocarbon **21** (2.5 g, 0.013 mol) was dissolved in glacial acetic acid (60 ml), and fuming nitric acid (10 ml, 0.23 mol) was added. The mixture was stirred vigorously and heated in an oil bath at 110–115° for 4 hr. The product was cooled and poured onto ice to give **27a** (1.0 g, 32%), which was purified as described in method 1.

Method 3.—The hydrocarbon **21** (0.232 g, 0.00125 mol) was dissolved in acetic anhydride (7.0 ml) and the solution was stirred at 25°. Fuming nitric acid (175 μl, *d* 1.5, 0.00396 mol) was slowly added from a micrometer syringe during 15–30 min. The mixture was stirred for 3 hr, poured into water, and shaken with ether. The ethereal layer was washed with dilute sodium carbonate and water and dried ($MgSO_4$). The ether was evaporated and the solid was crystallized from ethanol to give **27a** (0.15 g, 52%).

The following 4-substituted 1-(*p*-nitrophenyl)bicyclo[2.2.2]-octanes were prepared from the corresponding 4-substituted 1-phenylbicyclo[2.2.2]octanes by using method 3 described above and were crystallized at least four times from ethanol to give the pure *para* isomer. 4-Bromo-1-(*p*-nitrophenyl)bicyclo[2.2.2]octane (**36**, 52%) was obtained: mp 153–155°; ir (KCl) 2950, 2875 (CH_2), 1518, 1350, 855, 755 (NO_2), 3090, 1600 (aromatic), 825 (1,4-disubstituted benzene), and 695 cm^{-1} (CBr).

Anal. Calcd for $C_{14}H_{16}BrNO_2$: C, 54.19; H, 5.20; Br, 25.75; N, 4.52. Found: C, 54.25; H, 5.06; Br, 25.91; N, 4.54.

4-Methoxycarbonyl-1-(*p*-nitrophenyl)bicyclo[2.2.2]octane (**37**, 48%) was obtained: mp 142–144°; ir (KCl) 2945, 2850 (CH_2, CH_2), 1518, 1350, 858, 745 (NO_2), 1718 (C=O), 1240, 1070 (CO), 1595 (aromatic), and 858 cm^{-1} (1,4-disubstituted benzene).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.26; H, 6.66; N, 5.01.

4-Methoxy-1-(*p*-nitrophenyl)bicyclo[2.2.2]octane (**38**, 40%) was obtained: mp 51–53°; ir (KCl) 2950, 2860 (CH_3, CH_2), 1518, 1350, 850, 750 (NO_2), 1098 (CO), 3090, 1595 (aromatic), and 850 cm^{-1} (1,4-disubstituted benzene).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.73; H, 7.50; N, 5.32.

4-Ethyl-1-(*p*-nitrophenyl)bicyclo[2.2.2]octane (**39**, 51%) was obtained: mp 53–55°; ir (KCl) 2925, 2875 (CH_3,CH_2), 1518, 1350, 850, 750 (NO_2), 1598 (aromatic), and 850 cm^{-1} (1,4-disubstituted benzene).

Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.35; H, 8.15; N, 5.42.

4-Isopropyl-1-(*p*-nitrophenyl)bicyclo[2.2.2]octane (**40**, 55%) was obtained: mp 111–113°; ir (KCl) 2930, 2850 (CH_3, CH_2), 1518, 1345, 850, 750 (NO_2), 1598 (aromatic), and 850 cm^{-1} (1,4-disubstituted benzene).

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.83; H, 8.41; N, 5.16.

4-Cyano-1-(*p*-nitrophenyl)bicyclo[2.2.2]octane (**41**, 47%) was obtained: mp 158–160°; ir (KCl) 2950, 2875 (CH_2), 2225 (CN), 1520, 1342, 850, 748 (NO_2), 1595 (aromatic), and 850 cm^{-1} (1,4-disubstituted benzene).

Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.17; H, 6.20; N, 11.00.

***p*-*t*-Butylnitrobenzene (27b).**—This compound was prepared by nitrating *t*-butylbenzene:[35,47] mp 28.0° (lit.[47] mp 28.4°); bp 130–132° (14 mm) [lit.[47] bp 135° (10 mm)]; nmr τ 1.89 (d, 2 H, J = 9 cps) 2.47 (d, 2 H, J = 9 cps), and 8.64 (s, 9 H); λ_{max} (isooctane) 266.5 nm (ϵ 10,650).

1-(*p*-Aminophenyl)bicyclo[2.2.2]octane (28a) and *p*-Amino-*t*-butylbenzene (28b).—10% palladium on carbon (50 mg) was suspended in water (5 ml), sodium borohydride (0.38 g, 0.01 mol) in water (10 ml) was added,[48] and the mixture was kept under an atmosphere of nitrogen. A solution of the nitro compound **27a** or **27b** (0.005 mol) in methanol (75 ml) was added dropwise with cooling. Stirring was continued for 1–2 hr after the addition was

(44) *Chem. Abstr.*, **62**, 14529e (1965).
(45) *Ibid.*, **64**, 15772c (1966).
(46) G. W. Gray and D. Lewis, *J. Chem. Soc.*, 5156 (1961).
(47) K. L. Nelson and H. C. Brown, *J. Amer. Chem. Soc.*, **73**, 5605 (1951).
(48) T. Neilson, H. C. S. Wood, and A. G. Wylie, *J. Chem. Soc.*, 371 (1962).

complete. The catalyst was filtered off and washed with ether. The filtrate was poured into water and shaken with ether and the combined ethereal layers were washed with 2 *N* hydrochloric acid. The aqueous phase was basified with 2 *N* sodium hydroxide to give either a solid (**28a**) or an oil (**28b**). The solid was filtered off and washed free of alkali to give **28a** (90%): mp 128–132°; ir (KCl) 2900, 2825 (CH_2), 3375, 3300, 1620, 1250 (NH_2), 3025, 1519 (aromatic), and 844 cm^{-1} (1,4-disubstituted benzene). Compound **28b** was isolated by shaking the final aqueous phase with ether. The ethereal layer was washed with water; the solvent was evaporated and the residue was distilled to give **28b** (95%), bp 132–138° (28 mm) [lit.[35] bp 120–123° (15 mm)].

1-(*p*-Acetamidophenyl)bicyclo[2.2.2]octane (29a) and *p*-Acetamido-*t*-butylbenzene (29b).—The amine **28a** or **28b** (0.010 mol) was treated with acetic anhydride (0.011 mol) and acetic acid (0.011 mol) and the mixture was heated in an oil bath at 160° for 30 min. The hot solution was poured into water and the brownish-white solid was filtered off and crystallized from ethanol–water (10:1). Compound **29a** (95%) was obtained: mp 175–177°; ir (KCl) 2900, 2850 (CH_3, CH_2), 3275, 1545, 1280 (NH), 1665 (C=O), 1605 (aromatic), and 838 cm^{-1} (1,4-disubstituted benzene).

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.66; H, 8.71; N, 6.07.

Compound **29b** (81%) was obtained, mp 168–171° (lit.[35] mp 171–172°).

1-(4-Acetamido-3-nitrophenyl)bicyclo[2.2.2]octane (30a) and 4-Acetamido-3-nitro-*t*-butylbenzene (30b).—The compound **29a** or **29b** was nitrated by using the method of Wepster, *et al.*,[35] for the preparation of **30b**, and the product was crystallized from ethanol. Compound **30a** (95%) was obtained: mp 130–132°; ir (KCl) 2925, 2850 (CH_3, CH_2), 3350 (NH), 1515, 1345, 765 (NO_2), 1700 (C=O), 1620, 1580 (aromatic), and 850 cm^{-1} (1,3,4-trisubstituted benzene).

Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.64; H, 6.99; N, 9.72. Found: C, 66.70; H, 6.87; N, 9.79.

Compound **30b** (95%) was obtained, mp 104–106° (lit.[34] mp 107–107.5°).

1-(4-Amino-3-nitrophenyl)bicyclo[2.2.2]octane (31a) and 4-Amino-3-nitro-*t*-butylbenzene (31b).—The compound **30a** or **30b** (0.02 mol) and sodium methoxide (0.0324 g, 0.0006 mol) in methanol (20 ml) were heated under reflux for 2.5 hr.[49] The mixture was then cooled in the refrigerator and the reddish orange crystals which formed were filtered off and recrystallized from ethanol. Compound **31a** (95%) was obtained: mp 132–135°; ir (KCl) 2900, 2825 (CH_3, CH_2), 3450, 3325, 1635, 1245 (NH_2), 1518, 1345, 775 (NO_2), 1590, 1458 (aromatic), and 840 cm^{-1} (1,3,4-trisubstituted benzene).

Anal. Calcd for $C_{14}H_{18}N_2O_2$. C, 68.27; H, 7.37; N, 11.37. Found: C, 68.16; H, 7.42; N, 11.65.

Compound **31b** (93%) was obtained, mp 104–107° (lit.[35] mp 106–107°).

1-(*m*-Nitrophenyl)bicyclo[2.2.2]octane (32a) and *m*-*t*-Butylnitrobenzene (32b).—The amine **31a** or **31b** was deaminated by using Hodgson and Walker's method.[50] The amine **31a** or **31b** (0.005 mol) in glacial acetic acid (30–40 ml for **31a**, and 15–20 ml for **31b**) was added slowly to a solution of sodium nitrite (0.006 mol) in sulfuric acid (3.2 ml, 98%). The mixture was kept below 20° during the addition, and ethanol (10–15 ml) was added with cooling. The mixture was then heated under reflux for 4 hr, cooled, and poured into water. The mixture was shaken with ether and the ethereal layers were washed with 10% aqueous sodium hydroxide and water and dried ($MgSO_4$). The ether was evaporated, and for **32a** the residue was sublimed at 120–130° (1.0 mm) to give a solid which was crystallized from ethanol to give yellow crystals of **32a** (53%): mp 73–76°; ir (KCl) 2900, 2825 (CH_2), 1520, 1345, 738 (NO_2), 3050 (aromatic), 842, 802, and 685 cm^{-1} (1,3-disubstituted benzene); nmr τ 1.81–2.67 (4 H) and 8.23 (br peak, 13 H, $W_{1/2}$ = 5 cps); λ_{max} (isooctane) 259.2 nm (ϵ 7760).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.69; H, 7.47; N, 6.10.

For **32b**, the residue was distilled to give **32b** (70%): bp 106–110° (3 mm) [lit.[35] bp 136–137° (16 mm)]; nmr τ 1.73–2.81 (4 H) and 8.62 (s, 9 H); λ_{max} (isooctane) 257.9 nm (ϵ 8870).

1-(2,4-Dinitrophenyl)bicyclo[2.2.2]octane (33a). Method 1.—The compound **21** (2.5 g, 0.013 mol) was added to a vigorously stirred mixture of sulfuric (4 ml, 98%) and nitric acid (4 ml, *d* 1.5, 0.0905 mol) at 20–30°. The mixture was then kept at 55–60° for 2 hr, cooled, and poured onto ice. The solid was filtered off and crystallized from ethanol to give **33a** (2.9 g, 78%): mp 154–156°; ir (KCl) 2900, 2850 (CH_2), 1530, 1350, 741 (NO_2), 3075, 1595 (aromatic), and 840 cm^{-1} (1,2,4-trisubstituted benzene).

Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.64; H, 5.84; N, 10.48.

Method 2.—The hydrocarbon **21** (2.5 g, 0.013 mol) in glacial acetic acid (65 ml) was added cautiously to a mixture of fuming nitric acid (10 ml, *d* 1.5, 0.23 mol) in sulfuric acid (15 ml, 98%) below 15°. The mixture was stirred for 2 hr below 30° and worked up as described in method 1 to give **33a** (3.1 g, 83%).

1-(4-Amino-2-nitrophenyl)bicyclo[2.2.2]octane (34a).—The compound **33a** (0.55 g, 0.00199 mol), water (5 ml), and ethanol (5 ml) were stirred vigorously at 60–70°. A solution of sodium sulfide nonahydrate (0.96 g, 0.0040 mol) and sulfur (0.128 g, 0.0040 mol) in water (1.5 ml) was added during 20 min. The mixture was heated under reflux for 2 hr and then poured into water. The solid was filtered off and boiled (five or six times) with an excess of 2 *N* hydrochloric acid, and the hot solution was filtered. The combined filtrates were basified with 2 *N* aqueous sodium hydroxide and the precipitated solid was filtered off, dried, and crystallized from petroleum ether (bp 100–120°) to give pale yellow needles of **34a** (0.32 g, 65%): mp 129–132°; ir (KCl) 2900, 2850 (CH_2), 3450, 3375, 3225, 1638, 1300 (NH_2), 1530, 1370 (NO_2), 1610, 1505 (aromatic), 860, and 820 cm^{-1} (1,2,4-trisubstituted benzene).

Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.10; H, 7.17; N, 11.02.

1-(*o*-Nitrophenyl)bicyclo[2.2.2]octane (35a).—The compound **34a** (1.23 g, 0.005 mol) was dissolved in dry ethanol (4.6 ml) and 98% sulfuric acid (1.47 g, 0.015 mol), and the cooled solution was diazotised at 5–10° with a solution of sodium nitrite (0.53 g, 0.00768 mol) in water (1.0 ml). The mixture was kept for 30 min at −10°, then heated under reflux for 4–5 hr. The product was cooled, poured into water, and shaken with ether. The ethereal layer was washed with 10% aqueous sodium hydroxide and water and dried ($MgSO_4$). The ether was evaporated and the residue was sublimed at 140–150° (2 mm) and crystallized from ethanol–water (5:1) to give **35a** (0.38 g, 33%): mp 58–61°; ir (KCl) 2900, 2850 (CH_2), 1530, 1375, 843, 745 (NO_2), 3050 (aromatic), and 775 cm^{-1} (1,2-disubstituted benzene); nmr τ 2.43–2.90 (4 H) and 8.04–8.44 (symmetrical m, 13 H); λ_{max} (isooctane) 287 8 nm (ϵ 5150).

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.59; H, 7.58; N, 6.11.

***o*-*t*-Butylnitrobenzene (35b).**—This compound was prepared by Mr. J. B. Woods following the procedure of Wepster, *et al.*,[35] bp 128–132° (16 mm) [lit.[35] bp 249–250° (761 mm)], nmr τ 2.40–2.85 (4 H) and 8.65 (s, 9 H). The uv spectrum (isooctane) did not show a maximum from 249.2 to 288.7 nm.

Registry No.—**3,** 1659-95-6; **8,** 18720-35-9; **9,** 23062-51-3; **10,** 23062-52-4; **12,** 23062-53-5; **13,** 2064-04-2; **16d,** 23102-72-9; **16e,** 23062-55-7; **17d,** 23062-56-8; **17e,** 23062-57-9; **17e,** toluene-*p*-sulfonylhydrazone, 23042-25-3; **18d,** 23062-58-0; **18e,** 23062-59-1; **19e,** 23062-60-4; **20d,** 23062-61-5; **21,** 23062-62-6; **22,** 23062-63-7; **25a,** 23062-64-8; **25b,** 23062-65-9; **26a,** 23062-66-0; **26b,** 23062-67-1; **26d,** 23102-73-0; **27a,** 23062-68-2; **28a,** 23062-69-3; **29a,** 23042-12-8; **30a,** 23102-74-1; **31a,** 23042-13-9; **32a,** 23042-14-0; **33a,** 23042-15-1; **34a,** 23042-16-2; **35a,** 23042-17-3; **36,** 23042-18-4; **37,** 23042-19-5; **38,** 23042-20-8; **39,** 23042-21-9; **40,** 23042-22-0; **41,** 23042-23-1; 3-acetyl-3-isopropylpentane-1,5-dicarboxylic anhydride, 23042-24-2.

Acknowledgment.—We thank S. R. C. for financial assistance, and one of us (S. S.) thanks the Commonwealth Scholarship Commission and the British Council for a maintenance award.

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Free-Radical Additions to Dibenzotricyclo[3.3.0.0^{2,8}]-3,6-octadiene

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Received July 31, 1969

The cyclopropane ring in dibenzotricyclo[3.3.0.0^{2,8}]-3,6-octadiene (1) is opened by inversion by the trichloromethyl radical in the free-radical addition of bromotrichloromethane to 1. At higher temperatures, thiophenol adds ionically to 1 in the presence or absence of free-radical initiators. Thiophenol also hydrogenates 1 at high temperatures, apparently *via* a diradical intermediate. It is concluded from this study that cyclopropane rings are quite unreactive toward free-radical additions.

A number of studies have been devoted to the chemistry of additions to cyclopropanes. Of particular interest is the stereochemistry of these processes. Nucleophilic ring openings appear to occur always with inversion,[1] whereas electrophilic cyclopropane ring openings may occur with inversion as well as retention. Thus, electrophilic ring opening of quadricycloheptane-2,3-dicarboxylic acid by bromine occurs with inversion at both carbon atoms of the cyclopropane ring.[2] Positive bromine also opens cyclopropanols with inversion.[3] Protonation (deuteration) of cyclopropanes takes place with inversion in the case of *exo*-tricyclo[3.2.1.0^{2,4}]octane,[4] but with retention of configuration in cyclopropanols[5] and bicyclobutanes.[6] 1-Methylnortricyclene is deuterated in acetic acid-d_1 catalyzed by sulfuric acid-*d*, to give a mixture of norbornyl acetates in which the deuterium atom is 62.2% 6-*endo* (retention) and 37.8% 6-*exo* (inversion).[7] Deuterium bromide in acetic acid-d_1 opens the cyclopropane ring of the Diels–Alder adduct of cycloheptatriene–maleic anhydride with retention.[8] Theoretical calculations[9] on the structure of protonated cyclopropanes indicate that the three-membered ring should undergo electrophilic opening with retention.[10]

Free-radical ring openings are encountered far less often than their ionic counterparts. Indeed, one can find few examples of possible free-radical ring openings[12] and closures.[13] These free-radical displacements are very difficult at normal sp^3-hybridized carbon atoms[14] and appear to take place only on highly reactive carbon centers such as Dewar anthracene[15] and cyclopropanes.[12] The stereochemistry of these openings is unknown.[16] Since the stereochemistry of nucleophilic and electrophilic displacements occur in the opposite sense, *i.e.*, nucleophilic displacements (four-electron systems) occur preferentially with inversion and electrophilic displacements (two-electron systems) occur preferentially with retention, free-radical displacements (three-electron systems) should be very much of interest with respect to the stereochemical possibilities.[21]

Results and Discussion

Dibenzotricyclo[3.3.0.0^{2,8}]-3,6-octadiene (1) was chosen for the study of the stereochemistry of free-radical cyclopropane ring opening because of the relative ease of ring openings in the system[22] as well as the fact that the stereochemistry of the resulting *cis*-dibenzobicyclo[3.3.0]-2,7-octadiene could be established by pmr spectroscopy.[1d,22]

When 1 is allowed to react with refluxing (105°) bromotrichloromethane in the presence of benzoyl peroxide (no reaction in the absence of peroxides), a single product is observed in the pmr spectrum up to *ca.* 20% reaction. As the reaction proceeds, considerable darkening is observed and broad multiplets, presumably

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(10) MO calculations indicate that edge-protonated and corner-protonated cyclopropanes are of comparable energy.[11] It might very well be that edge-protonated cyclopropanes result in opening with retention while corner-protonated rings lead to opening with inversion. If this is the case, one might expect subtle changes in steric as well as electronic properties to result in changes in the stereochemistry of electrophilic cyclopropane ring openings.

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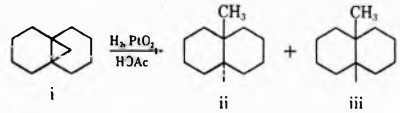
(16) Because of the geometry of the molecule, Dewar anthracene is forced to undergo ring opening with inversion.[15] Highly strained cyclopropanes undergo ring opening with benzyne[17] and maleic anhydride[18] with inversion at each carbon center. Although these latter reactions apparently involve the intermediacy of diradicals,[17,18] how much of this radical character is inherent in the transition state is not clear. Interestingly, the cyclopropane i undergoes nonstereospecific catalytic hydrogenation to give a 50:50 mixture of *cis*- and *trans*-methyldecalins ii and iii,[19] but hydrogenation of bicyclo[2.1.0]pentanes occurs with retention.[20]



i ii iii

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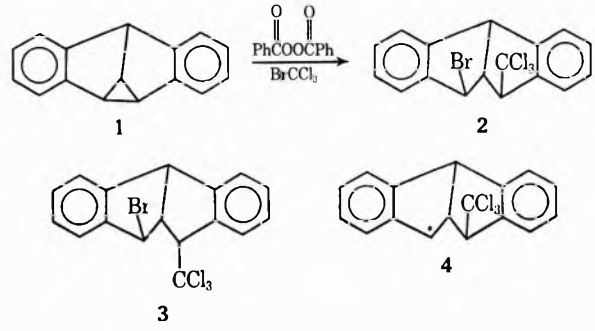
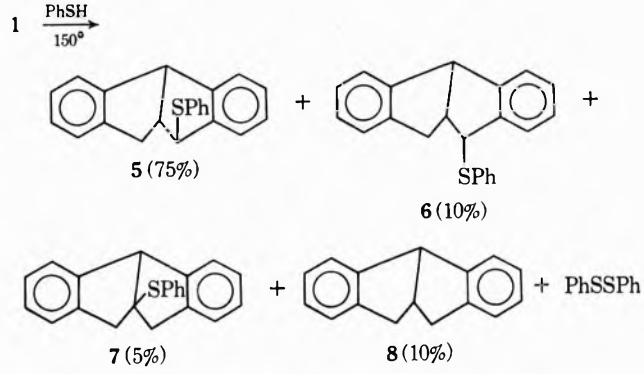
arising from decomposition products, begin appearing in the pmr spectrum. Isolation of the 1:1 adduct of **1** and bromotrichloromethane is hampered not only by these undesired materials, but the adduct itself is sensitive to such things as protic solvents and column chromatography. The most successful manner found for isolating the adduct was chromatography over Florisil (elution with Skellysolve B). The first material off the column was a dark red oil whose ir and pmr spectra, because of the nondescript peaks, were suggestive of a polymeric substance. This material was followed by a light brown oil which when crystallized from *n*-pentane gave *ca.* a 15–20% yield of *anti*-4-trichloromethyl-*anti*-6-bromo-*cis*-dibenzobicyclo[3.3.0]-2,7-octadiene (**2**). When **2** is added to the above reaction mixture at 105°, after a short time the pmr signals attributable to **2** begin to disappear. However, in refluxing bromotrichloromethane (no peroxides added), **2** appears to be stable. If the reaction is stopped after *ca.* 15–20% reaction time, chromatography over Florisil yields 70% recovered **1** and 15% **2** as the only characterizable products. The structure of **2** is supported by an elemental analysis and spectral data. The pmr spectrum is most instructive; outside the aromatic region (8 H from τ 2.3–3.0) lie three doublets (1 H each) at 4.74 (J_{56} = 5.0 Hz), 5.08 (J_{15} = 7.8 Hz), and 5.75 (J_{45} = 3.0 Hz) and a complex multiplet (1 H) from 5.92 to 6.20. The complex multiplet at τ 5.92–6.20 clearly is due to the absorption of the C-5 hydrogen, and the benzhydryl hydrogen at C-1 can be assigned the peak at 5.08, since, in all of the reported compounds in this system, this proton is found always in this region and with J_{15} = 7–8 Hz.[1d,22] The hydrogen α to the bromine atom is assigned the low field signal at τ 4.74, and the proton α to the trichloromethyl group then would be assigned that signal 1 ppm upfield at 5.75; this is consistent with previous observations[23] that the pmr signal for a proton α to a bromine atom is found *ca.* 1 ppm downfield from a proton α to a trichloromethyl group. Since the coupling constants for the *anti* C-4 and C-6 protons are observed to be >7 Hz[1d,22] and the J values for the corresponding *syn* C-4 and C-6 protons are found to be 2–6.4 Hz,[1d,22] clearly the substituents at C-4 and C-6 are in the *anti* configuration. Thus, the ring has undergone opening by the trichloromethyl radical with inversion. Although none of the corresponding *syn*-trichloromethyl epimer (**3**) was observed, conceivably small amounts of **3** could have been produced but destroyed under the conditions of the reaction. However, it is unlikely that **3** → **2** under the conditions of the reaction. Whether the stereochemistry observed in the opening is characteristic of cyclopropanes in general or whether the *anti* epimer **2** results because of favorable interaction of the aromatic ring in the transition state leading to the radical **4** is not clear. The fact that the bromine atom is transferred from bromotrichloromethane to **4** to yield the *anti*-bromide **2** probably reflects the stereoelectronic requirements of the benzylic radical **4** in the chain-transfer step as well as a definite steric preference for larger groups to occupy the *anti* position.[1d,22] When **1** in bromotrichloromethane is irradiated with uv light, the only adduct observed arises from the electrophilic addition of bromine across the 2,8 bond.[22]



Treatment of **1** with thiophenol at 150° for 1 day gives four compounds along with diphenyl disulfide. In refluxing thiophenol (170°) the ratio of **5**/**6**/**7**/**8** is



11:2:1:7. The percentage of **8** increases dramatically (from 10% at 150° to 30% at 170°). The rate and product distribution of these reactions are unaffected by the presence of free-radical initiators or oxygen. Also, no observable change in the product distribution results when **1** is treated with thiophenol at 170° in the presence of potassium thiophenoxide (heterogeneous reaction). However, the reaction was complete in a few minutes at 110° when a catalytic amount of *p*-toluenesulfonic acid was added. Under these conditions an 85:15 mixture of **5** and **6** results; no **7** or **8** is observed. The proof of structure for the thio ethers **5**–**7** is based on their reactions with Raney nickel to give **8** as well as the pmr spectra of the sulfides and the corresponding sulfones (see Experimental Section). The products from these addition reactions, **5**–**8**, are all stable under the various reaction conditions described above. The thio ethers **5** and **6** are clearly the result of ionic addition of thiophenol across the cyclopropane ring. The formation of small amounts of **7** can be rationalized in terms of protonation of the ring followed by loss of a proton to give the olefin **9**. Under the reaction conditions, **9** should easily undergo free-radical addition of thiophenol to give **7**. This explanation is consistent with the fact that **7** is observed only at high temperatures, a condition which should favor deprotonation of the intermediate carbonium ion.[24]

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Thiophenol apparently is capable of hydrogenating the cyclopropane ring of **1** since relatively large amounts of **8** and diphenyl disulfide are observed (*vide supra*). Thiols are excellent hydrogen atom donors to free radicals; thiophenol is particularly effective.[25] It appears that the 2,8 bond of the cyclopropane ring in **1** undergoes reversible homolysis at higher temperatures to give a diradical (**10**) which is then trapped, *via* hydrogen atom transfer, by thiophenol. Based on previous work of 1,2-diphenylcyclopropanes[26,27] the energy of activation for such homolysis can be expected to be *ca.* 30-35 kcal/mol, a value which is consistent with the large increase in the amount of **8** observed with increasing reaction temperatures. Poorer hydrogen atom transfer reagents are much less effective at trapping the diradical **10**. At temperatures below 200°, fluorene does not reduce **1** after several days. However, dihydroanthracene gives *ca.* 5–10% **8** and 9,9′,-10,10′-tetrahydro-9,9′-bianthryl after 2 days at 200°. Thus, as expected, dihydroanthracene is much less effective at trapping the diradical **10** than is thiophenol, but is more effective than fluorene.[28] Cyclopropanes rearrange *via* 1,2-hydrogen atom shifts in the intermediate diradical to propylenes.[29] In the case of **1** this could give rise to **9** which would then result in the formation of **7**. However, heating **1** in refluxing dimethylacetamide (bp 165°) or *n*-decane (bp 174°) for up to 50 hr gave only recovered starting material. This lack of rearrangement of **1** → **9** appears to be characteristic of 1,2-diphenylcyclopropanes.[26,27]

Treatment of **1** with thiophenol or butanethiol under the influence of uv light gave no reaction after extended periods of time. Treatment of **1** with *n*-butanethiol at 100° in the presence of benzoyl peroxide gave recovered **1** along with varying amounts of *n*-butyl phenyl sulfide. This sulfide could be isolated from the reaction of *n*-butanethiol with benzoyl peroxide in the absence of **1**.

It is clear from these data that **1** and presumably cyclopropanes in general are quite unreactive toward free-radical addition reactions. Whereas protonation of cyclopropanes appears to be somewhat more facile than protonation of the corresponding olefins,[30] free-radical additions to olefins appears to take place far more readily than these additions to cyclopropanes.[31]

Experimental Section[35]

Addition of Bromotrichloromethane to 1.—A solution of 1.0 g (4.9 mmol) of **1**[36] and 50 mg of benzoyl peroxide in 5.0 ml of bromotrichloromethane was held at reflux (105°) under nitrogen. Every hour *ca.* 40 mg of benzoyl peroxide was added to the mixture. The course of the reaction was followed by pmr spectroscopy. After 1 hr the reaction was about 20% complete and the pmr spectrum showed only **1** and **2** to be present. [If the solution is worked up at this point, careful chromatography (*vide infra*) yields first 0.7 g of recovered **1** followed by 0.3 g of **2**.] However, as the reaction proceeded the solution got progressively darker, and the pmr spectrum began to exhibit broadened high field multiplets. The reaction was stopped after 6 hr, and the solvent was removed by rotary evaporation. The resulting dark red oil was chromatographed over 60 g of Florisil packed in Skellysolve B. Elution with Skellysolve B first gave a dark red oil whose pmr and ir spectra, because of the nondescript peaks, were suggestive of a polymeric substance. This material was followed by a light brown oil which when crystallized from *n*-pentane gave 400 mg (20%) of **2**, mp 137–138°.

Anal. Calcd for $C_{17}H_{12}BrCl_3$: C, 50.72; H, 3.01. Found: C, 50.55; H, 3.06.

Although **2** was stable in refluxing bromotrichloromethane under nitrogen, the presence of benzoyl peroxide led to the decomposition of **2**.

Treatment of **1** with bromotrichloromethane under the influence of a high pressure uv light (Vycor filter) gives, as the major products, 4,6-dibromo-*cis*-dibenzobicyclo[3.3.0]-2,7-octadienes in the same ratio as has been observed in the ionic addition of bromine to **1**.[22]

Addition of Thiophenol to 1.—A solution of 2.0 g (9.8 mmol) of **1** in 10 ml of freshly distilled thiophenol was held at reflux under nitrogen for 18 hr. The course of the reaction was followed by tlc (silica gel). The excess thiophenol was removed by distillation at 25 mm and the resulting oil was chromatographed over 120 g of silica gel packed in Skellysolve B. Elution with 3% benzene in Skellysolve B gave 180 mg of diphenyl disulfide followed by 600 mg (30%) of **8**, mp 95–96° (lit.[37] mp 95°). Elution with 5% benzene in Skellysolve B gave the thio ethers **5**, **6**, and **7**. The first fractions were rich in **5** and the latter fractions were rich in **7**. Successive fractional crystallizations from *n*-pentane gave 0.25 g (8%) of *syn*-4-phenylthio-*cis*-dibenzobicyclo[3.3.0]-2,7-octadiene (**6**), mp 113–114°, 1.4 g (46%) of *anti*-4-phenylthio-*cis*-dibenzobicyclo[3.3.0]-2,7-octadiene (**5**), mp 73–74°, and 0.13 g (4%) of 5-phenylthio-*cis*-dibenzobicyclo[3.3.0]-2,7-octadiene (**7**), mp 118–119°.

The pmr spectrum of **5** in carbon tetrachloride shows two overlapping doublets (1 H each, C-1 and C-4 protons) from τ 5.4 to 5.7, a complex multiplet (3 H) from 6.2 to 7.6, and a complex multiplet (13 H) from 2.6 to 3.1.

Anal. Calcd for $C_{22}H_{18}S$: C, 84.03; H, 5.77. Found: C, 83.75; H, 5.91.

Oxidation of 300 mg (0.95 mmol) of **5** in 8 ml of dichloromethane by 500 mg of *m*-chloroperbenzoic acid gave 320 mg (97%) of the corresponding sulfone, mp 161–163°.

The pmr spectrum of the sulfone in chloroform-*d* shows two doublets (1 H each) at τ 5.37 (J_{45} = 1.6 Hz) and 5.77 (J_{15} = 7.6 Hz), a series of complex multiplets (3 H) from 6.0 to 7.6, and a complex multiplet (13 H) from 2.2 to 3.0.

Anal. Calcd for $C_{22}H_{18}O_2S$: C, 76.27; H, 5.24. Found: C, 76.07; H, 5.28.

The pmr spectrum of **6** in carbon tetrachloride shows two doublets (1 H each) at τ 5.08 (J_{45} = 7.0 Hz) and 5.55 (J_{15} = 7.4 Hz), a complex multiplet (1 H) from 6.1 to 6.6, a complex multiplet (2 H) from 6.8 to 7.1, and a complex multiplet (13 H) from 2.4 to 3.1.

Anal. Calcd for $C_{22}H_{18}S$: C, 84.03; H, 5.77. Found: C, 83.75; H, 5.87.

Oxidation of **6** under the same conditions as that described for **5** gave the sulfone of **6** (90%), mp 183–184°. Treatment of this sulfone with 0.5 *M* sodium ethoxide in ethanol at room temperature for 6 hr gave the sulfone of **5** in quantitative yield.

The pmr spectrum of the sulfone in chloroform-*d* shows two doublets (1 H each) at τ 4.83 (J_{45} = 5.8 Hz) and 5.53 (J_{15} = 6.8 Hz), a complex multiplet (3 H) from 6.2 to 7.2, and a complex multiplet (13 H) from 1.8 to 3.0.

(25) R. A. Gregg, D. M. Alderman, and F. R. Mayo, *J. Amer. Chem. Soc.*, **70**, 3740 (1948).

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(29) H. M. Frey and R. Walsh, *Chem. Rev.*, **69**, 103 (1969).

(30) See, for example, R. T. LaLonde and M. R. Tobias, *J. Amer. Chem. Soc.* **86**, 4068 (1964).

(31) Although cyclopropanes may be protonated more rapidly then analogous alkenes, olefins react far more readily with bromine than do cyclopropanes.[32] This is consistent with the Principal of Hard and Soft Acids and Bases (HSAB Principal).[33] Since olefins are certainly "softer" than cyclopropanes, the olefins should prefer to react with the softer electrophile, bromine. Radicals are believed to be quite "soft"[34] and hence should have an enhanced reactivity toward olefins compared with cyclopropanes.

(32) A. J. Gordon, *J. Chem. Educ.*, **44**, 461 (1967).

(33) R. G. Pearson, *ibid.*, **45**, 581, 643 (1968).

(34) R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, **89**, 1827 (1967).

(35) Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Proton magnetic resonance spectra were measured with a Varian A-60D nmr spectrometer with tetramethylsilane (τ 10.00) as the internal standard. *J* values reported are "observed" ones. Elemental analyses were performed by Dr. Franz J. Kasler, University of Maryland.

(36) E. Ciganek, *ibid.*, **88**, 2882 (1966).

(37) W. Baker, J. F. W. McOmie, S. O. Parfitt, and D. A. M. Watkins, *J. Chem. Soc.*, 4026 (1957).

Anal. Calcd for $C_{22}H_{18}O_2S$: C, 76.27; H, 5.24. Found: C, 75.99; H, 5.34.

The pmr spectrum of **7** in carbon tetrachloride shows a singlet (1 H) at τ 5.43, a pair of doublets (2 H each, J_{gem} = 16.4 Hz) at 6.62 and 6.83, and a complex multiplet (13 H) from 2.5 to 3.1.

Anal. Calcd for $C_{22}H_{18}S$: C, 84.03; H, 5.77. Found: C, 84.00; H, 5.97.

Oxidation of **7** under the same conditions as that described for **5** gave the sulfone of **7** (95%), mp 178–179°.

The pmr spectrum of the sulfone in chloroform-*d* shows a singlet (1 H) at τ 4.69, a pair of doublets (2 H each, J_{gem} = 17.6 Hz) at 6.10 and 6.78, and a complex multiplet from 2.0 to 3.0.

Anal. Calcd for $C_{22}H_{18}O_2S$: C, 76.27; H, 5.24. Found: C, 76.40; H, 5.29.

When **1** is treated with thiophenol at 150° for 30 hr, **5**, **6**, **7**, and **8** were isolated in high yield in the ratio of 7.5:1:0.5:1, respectively. The presence of oxygen, benzoyl peroxide, or benzoic acid had no observable effect on the rate or product distribution of the reaction. The reaction of **1** with thiophenol at 110° catalyzed by a trace of *p*-toluenesulfonic acid proceeded very rapidly to give 85% **5** and 15% **6**; no **7** or **8** was observed. Treatment of **1** (500 mg) with 10 ml of thiophenol in which 60 mg of potassium metal had been dissolved at 170° for 18 hr gave essentially identical results with that observed in the absence of potassium thiophenoxide. In all these cases, products **5**–**8** were stable to the conditions of the reactions. Attempts to photoinitiate the addition of thiophenol to **1** with either medium or low pressure mercury uv lamps failed to give any 1:1 adducts.

Treatment of thio ethers **5**–**7** with a 20-fold excess (by weight) of Raney nickel W-2[38] in refluxing ethanol for 14 hr gave an 80–85% yield of hydrocarbon **8** in each case.

Attempted Addition of *n*-Butanethiol to 1.—Treatment of **1** with *n*-butanethiol in the presence of either medium or low pressure mercury uv lamps did not result in any observable addition products. When **1** was treated in refluxing *n*-butanethiol with benzoyl peroxide, **1** was recovered unchanged after several days. Chromatography over silica gel did result in the isolation of *n*-butyl phenyl sulfide (eluted with 10% benzene in Skellysolve B) which proved to be identical (pmr and ir spectra) with an authentic sample.[39] This sulfide could be isolated from a solution of *n*-butanethiol treated with benzoyl peroxide in the absence of **1**.

Treatments of 1 with Fluorene and Dihydroanthracene.—A mixture of 0.50 g of **1** and 5.0 g of fluorene was sealed in a glass tube under nitrogen. The tube was heated at 195–200° in an oil bath for 2 days. The majority of the fluorene was removed by crystallization from methanol, and a pmr spectrum of the mother liquor showed only **1** and fluorene to be present. No **8** could be observed.

This same procedure was employed for 9,10-dihydroanthracene, and a pmr spectrum of the resulting mixture indicated that *ca.* 10% of **1** had been hydrogenated to **8**. This mixture was chromatographed over 60 g of silica gel packed in Skellysolve B. Elution with 3% benzene in Skellysolve B gave 950 mg of 9,10-dihydroanthracene, 45 mg of **8**, 400 mg of **1**, and 70 mg of 9,9′,10,10′-tetrahydro-9,10-bianthryl, mp 256–258° (lit.[40] mp 255°).

Registry No.—**1**, 2199-28-2; **2**, 23367-54-6; **5**, 23265-33-0; **5** sulfone, 23265-34-1; **6**, 23265-35-2; **6** sulfone, 23265-36-3; **7**, 23288-66-6; **7** sulfone, 23265-37-4.

Acknowledgment.—Financial support from the donors of the Petroleum Research Fund of the American Chemical Society is gratefully acknowledged.

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Conformational Studies of Perfluoro-2-halo-1,2-oxazetidines Using Nuclear Magnetic Resonance Spectroscopy[1]

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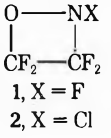
Received May 5, 1969

The high-resolution nmr spectra of perfluoro-2-fluoro-1,2-oxazetidine (**1**) and perfluoro-2-chloro-1,2-oxazetidine (**2**) were obtained over the temperature range 85 to −120°. The observed nonequivalence of geminal fluorines was attributed to restricted nitrogen inversion. The temperature dependence of the geminal fluorine–fluorine chemical-shift differences indicated equilibrating nonplanar conformers. The conformational free-energy differences for **1** and **2** were determined to be 900 and 1000 cal/mol, respectively.

The use of nmr spectroscopy to demonstrate the nonplanarity of cyclobutane rings has been reported by Lambert and Roberts.[2] These authors observed that the chemical-shift differences of geminal fluorines in certain substituted cyclobutanes showed temperature dependence. This was attributed to an equilibrium between the two possible puckered-ring conformations. We wish to present nmr evidence indicating similar nonplanarity in a perfluorooxazetidine ring system.

The room-temperature ^{19}F nmr spectra of perfluoro-2-fluoro-1,2-oxazetidine (**1**) and perfluoro-2-chloro-1,2-oxazetidine (**2**) showed AB quartets which were assigned to the CF_2O and CF_2N fluorines. The spectrum of **1** also contained a broad peak owing to the NF fluorine. The chemical shifts and geminal coupling constants are given in Table I. With the temperature varied from 85 to −120°, the same general pattern was obtained in the spectra of **1** and **2** with the geminal coupling constants remaining essentially unchanged. The volatility of the N-halooxazetidines precluded nmr studies above 85°. However, even at this temperature the quartet structures were clearly visible. The NF signal in the spectrum of **1** was detectably sharper at lower temperatures.[3]



1, X = F
2, X = Cl

The nonequivalence of the geminal fluorines in **1** and **2** results either from restricted oxazetidine ring inversion or from restricted nitrogen inversion. However, it seems very unlikely that the barrier to ring inversion would be sufficient to slow the ring-intercon-

(1) This investigation was performed under Contract No. N00019-67-c-0454 for the Naval Air Systems Command, Department of the Navy, Washington, D. C. 20360, with Mr. John Gurtowski as Project Officer.

(2) J. B. Lambert and J. D. Roberts, *J. Amer. Chem. Soc.*, **85**, 3710 (1963) **87**, 3884 (1965).

(3) Measurements of $W_{1/2}$ (signal width at half-height) indicate a change from 47 Hz at −120° to 108 Hz at 24° with further broadening to 135 Hz at 85°.

TABLE I
CHEMICAL SHIFTS AND GEMINAL COUPLING CONSTANTS FROM THE ^{19}F NMR SPECTRA OF 1 AND 2[a]

1

Assignment	24°	−73°	−115°
CF_2O	78.4, 80.1	77.7, 79.0	77.4, 78.5
J_{F-F}, Hz	89	89	90
CF_2N	105.0, 106.9	103.4, 107.0	102.7, 106.9
J_{F-F}, Hz	140	139	139
NF	−25.3	−25.6	−25.8

2

Assignment	24°	−73°	−115°
CF_2O	78.0, 81.6	77.4, 81.2	76.6, 80.6
J_{F-F}, Hz	89	90	90
CF_2N	95.5, 100.2	95.0, 99.1	94.4, 98.2
J_{F-F}, Hz	122	123	122

[a] Determined chemical shift of each fluorine in parts per million with $CFCl_3$ as internal standard.

version process at 85°. At this temperature a barrier of *ca.* 17 kcal/mol would be required.[4] The barrier to the ring inversion of cyclobutane has been estimated to be 0.47 kcal/mol.[5] Consideration of the effects of replacing hydrogens by fluorines and substitution of NF and O in the cyclobutane ring leads to the conclusion that the barrier to ring inversion of a perfluorooxazetidine ring should not be appreciably different.[6] Hence the observed nonequivalence must arise as a consequence of restricted nitrogen inversion.

Consistent with these results are the recent nmr studies of N-haloaziridines,[7,8] which demonstrate that nitrogen inversion is remarkably restricted in the N-chloro and N-bromo compounds. Although there apparently are no examples of similar behavior by an NF substituent,[9] equally effective retardation of nitrogen inversion by fluorine in small-ring compounds would not be unreasonable. Lee and Orrell[10] reported that nitrogen inversion in the related perfluoro-2-methyl-1,2-oxazetidine is essentially frozen at −74°. The higher barrier observed for **1** is thus consistent with this fact, since substitution of F for CF_3 would on steric and electrostatic grounds[11] lead to a higher barrier to nitrogen inversion.

The chemical-shift difference, δ,[12] for the geminal fluorines of **1** and **2** showed temperature dependence and was determined over the range 85 to −120°. These values of δ are given in Tables II and III. The fact that the δ values for the pairs of geminal fluorines in both compounds respond in different and opposite manners to change in temperature indicates that a direct temperature effect is not involved. Instead the change of δ with temperature suggests the presence of

(4) Assuming a coalescence temperature (T_c) of 85° and δ 100 Hz, ΔG^* = 17 kcal/mol is calculated using the expression $\Delta G^* = 4.57\ T_c\ (9.97 + \log T_c/\delta)$.

(5) H. E. Simmons and J. K. Williams, *J. Amer. Chem. Soc.*, **86**, 3222 (1964).

(6) (a) G. V. D. Tiers, *Proc. Chem. Soc.*, 389 (1960); (b) R. K. Harris and R. A. Spragg, *J. Chem. Soc.*, 864 (1968); (c) J. Lee and K. G. Orrell, *Trans. Faraday Soc.*, **63**, 16 (1967).

(7) S. J. Brois, *J. Amer. Chem. Soc.*, **90**, 506, 508 (1968).

(8) J. M. Lehn and J. Wagner, *Chem. Commun.*, 148 (1968).

(9) (a) Rapid inversion at nitrogen in perfluoro-N-fluoropiperidine was reported to be occurring even at −74°.[5c] (b) Restricted nitrogen inversion in an NF_2 group has been reported: F. A. Johnson, C. Haney, and T. E. Stevens, *J. Org. Chem.*, **32**, 466 (1967).

(10) J. Lee and K. G. Orrell, *Trans. Faraday Soc.*, **61**, 2342 (1965).

(11) F. A. L. Anet, R. D. Trepka, and D. J. Cram, *J. Amer. Chem. Soc.*, **89**, 357 (1967).

(12) $\delta = [(d_3 - d_1)^2 - J^2]^{1/2}$, where d_3 and d_1 are the chemical shifts of peaks 3 and 1 of an AB quartet.

TABLE II
FLUORINE–FLUORINE CHEMICAL-SHIFT DIFFERENCES FOR PERFLUORO-2-FLUORO-1,2-OXAZETIDINE (1)

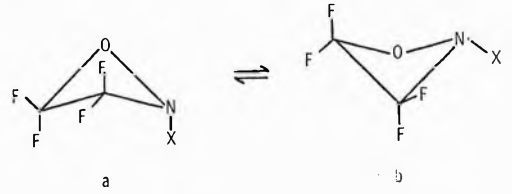
Temp, °C	δ_{CF_2N}, Hz	δ_{CF_2O}, Hz
85	68[a]	108
24	112	95
1	134	91
−20	153	84
−35	167	80
−55	184	74
−76	206	68
−85	215	66
−98	230	60[a]
−120	255	52[a]

[a] Center peaks of quartet not resolved. ($d_3 - d_1$) calculated from $(d_4 - d_1) - J$.

TABLE III
FLUORINE–FLUORINE CHEMICAL-SHIFT DIFFERENCES FOR PERFLUORO-2-CHLORO-1,2-OXAZETIDINE (2)

Temp, °C	δ_{CF_2N}, Hz	δ_{CF_2O}, Hz
75	277	194
24	262	202
−10	254	207
−37	247	211
−73	232	216
−91	226	219
−115	214	222

two conformers which are equilibrating at a rate such that only one AB pattern is observed for each set of geminal fluorines. This equilibrium involves the nonplanar conformations, a and b, and is represented as follows.



a b

1a, 1b, X = F
2a, 2b, X = Cl

As a result of the 1,3 fluorine–fluorine and 1,3 fluorine–chlorine interactions in the a conformers, it might be expected that the b conformers would be the more stable. The fraction of molecules, p, in this latter conformation is related to the conformational free-energy difference, ΔG, by the expression

$$p/(1 - p) = K = e^{-\Delta G/RT} \qquad (1)$$

This fraction, p, of molecules in conformer b is likewise related to δ, since the observed chemical-shift difference is simply the weighted average of the chemical-shift differences, δ_a and δ_b, of the individual conformers.

$$\delta = p\delta_b + (1 - p)\,\delta_a \text{ or } \delta = \delta_a + p(\delta_b - \delta_a) \qquad (2)$$

Values of p for those temperatures utilized in the nmr study were calculated using expression 1 with ΔG varied in units of 100 cal/mol from −1600 to −400 cal/mol. These values of p[13] were then plotted *vs.* the

(13) With ΔG = −900 cal/mol, p values at different temperatures are, at 85°, 0.780; 24°, 0.821; 1°, 0.839; −20°, 0.857; −35°, 0.870; −55°, 0.889; −76°, 0.909; −85°, 0.912; −98°, 0.930; −120°, 0.953. With ΔG = −1000 cal/mol, p values at different temperatures are, at 75°, 0.809; 24°, 0.845; −10°, 0.871; −37°, 0.894; −73°, 0.925; −91°, 0.941; −115°, 0.960.

corresponding values of δ to give a series of curves. This procedure was followed for both the CF_2N and CF_2O fluorines of **1** and **2**. In each case the best linear relationship between δ and p was obtained when $\Delta G = -900 \pm 100$ cal/mol (compound with NF) and $\Delta G = -1000 \pm 100$ cal/mol (compound with NCl).[14] From the slopes of the best straight lines, $\delta_b - \delta_a$ and subsequently values of δ_a and δ_b for all pairs of fluorines were determined. These values are given in Table IV. The relationship between p and δ is indicated in Figure 1.

TABLE IV
CONFORMATIONAL DATA

	δ_{1a}, Hz	δ_{1b}, Hz	δ_{2a}, Hz	δ_{2b}, Hz
CF_2N	−798	+311	+604	+202
CF_2O	+387	+35	+50	+229
ΔG, cal/mol	−900 ± 100		−1000 ± 100	

The determined conformational free-energy differences lend support to the initial assignment of greater stability to conformer b. Such destabilization of conformer a as a consequence of the 1,3-halogen interactions is not unreasonable[15] with the lesser destabilization in **1** consistent with the smaller size of the fluorine.

The chemical shifts of the geminal fluorines of **1** and **2** obtained from spectra at several temperatures are given in Table I. It may be concluded that both fluorines of the CF_2O of **1** and **2** are less shielded in conformer b, since all signals move downfield as the temperature is lowered and the proportion of the more stable conformer increases. The upfield fluorine of the CF_2O group of **1** appears to undergo the greater change in chemical shift, while the opposite is the case with the related fluorines of **2**. The chemical shift of the upfield fluorine of the CF_2N group of **1** is essentially unchanged throughout the temperature range, indicating nearly the same value in both conformers. Relative to this stationary fluorine, the other CF_2N fluorine is less shielded in conformer **1b** and more shielded in conformer **1a**. The negative value of δ_a for these fluorines reflects this reversal in the relative signal positions. Both the CF_2N fluorines of **2** appear to be less shielded in **2b** than in **2a** with the upfield fluorine undergoing the greater change in chemical shift.

High-resolution spectra of the CF_2O and CF_2N fluorines of **1** and **2** were obtained. The outer members of the AB quartet observed for the CF_2O fluorines of **1** showed an eight-peak pattern, indicating that these fluorines are coupled not only with the CF_2N fluorines, but also with NF. One of the CF_2N fluorines of **1** in its spectrum at 24° shows apparent coupling with all vicinal fluorines (eight-peak patterns) whereas the upfield members of this quartet are very broad, unresolved peaks. However, at low temperature (−100°), each member of the CF_2N quartet is clearly resolved into eight peaks. The spectrum of the N-chloro compound **2** similarly reveals that both of the CF_2O and one of the CF_2N fluorines undergo coupling with the adjacent fluorines and are well resolved peaks (doublet of doublets). In this case, the downfield

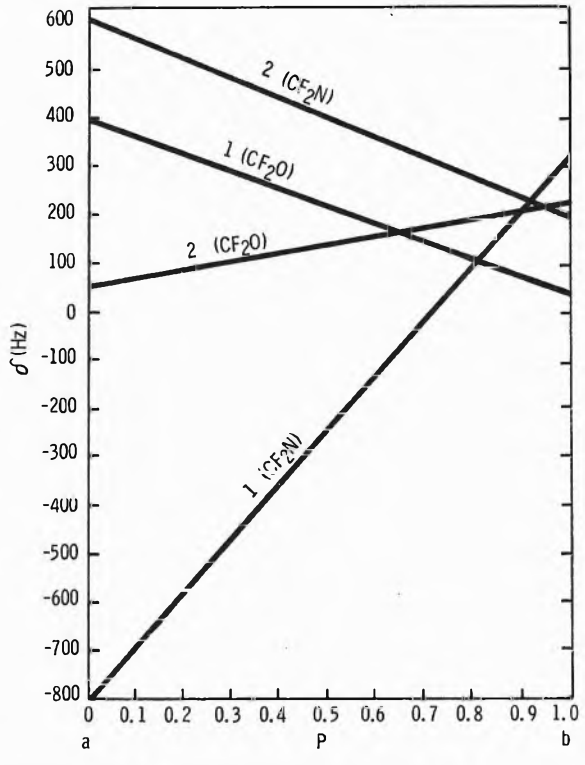


Figure 1.—Chemical-shift difference *vs.* conformer population.

members of the CF_2N quartet are those which are broad and essentially structureless. These members are likewise resolved in −100° spectra (doublet of doublets). Neither the complex ABMXY pattern of **1** nor the ABXY pattern of **2** were analyzed; thus the vicinal coupling constants are not given.

The assignment of nmr peaks to the CF_2N fluorines in **1** can be made if one assumes that a significant change in the nuclear shielding will be experienced by the fluorine *trans* and axial to the free electron pair of nitrogen. This assumption is based on the observation that the chemical shift of a proton located on a carbon bonded to nitrogen depends on its orientation relative to the unshared electrons of nitrogen, the *trans*-axial relationship giving rise to a pronounced upfield shift. The equatorial proton *cis* to the electron pair is essentially unaffected.[16] Since the CF_2N fluorine *cis* to NF would become axial and coplanar with the unbonded nitrogen electrons in conformer **1b**, one might expect that the chemical shift of this fluorine would be significantly different in conformer **1b** than in **1a**. Only one fluorine of the CF_2N group undergoes any detectable change in chemical shift in going from conformer **1a** to **1b**, that being the fluorine which appears as the resolved downfield portion of the AB quartet. This half is thus assigned to the fluorine *cis* to NF, while the broad upfield absorptions are attributed to the *trans* fluorine. Although the downfield shift of the *cis* fluorine in **1b** is contrary to the results referenced above for a similarly substituted hydrogen, the absence of change in chemical shift observed for the upfield fluorine makes the alternative assignment much less attractive.

The apparent relationship between configuration and peak broadening is the basis for the assignment of the

(14) It is assumed in this treatment that ΔG is constant over the temperature range studied; hence $\Delta S = 0$.

(15) Lambert and Roberts[2] determined $\Delta G = -750$ cal/mol as the energy difference for conformers of 1,1-difluoro-2,2,3-trichlorocyclobutane.

(16) H. P. Hamlow, S. Okuda, and N. Nakagawa, *Tetrahedron Lett.*, 2553 (1964); J. B. Lambert, R. G. Keske, R. E. Carhart, and A. P. Jovanovich, *J. Amer. Chem. Soc.*, **89**, 3761 (1967).

unresolved peaks in the spectrum of the CF_2N fluorines of **2** to the fluorine *trans* to NCl. The downfield shift of the *cis* CF_2N fluorine on going from **2a** to **2b** is consistent with that observed for the related fluorine in **1**. Lee and Orrell[10] have made the same assignment to the CF_2N fluorines of perfluoro-2-methyl-1,2-oxazetidine (spectrum obtained at −74°). The fluorine showing coupling with the CF_3 group (upfield half of AB quartet) was assigned *cis* to NCF_3, while the downfield fluorine was observed as a broad, structureless absorption.

The assignment of nmr peaks to the CF_2O fluorines is somewhat more difficult. However, it may be argued that the fluorine of this group, which is *cis* to the N-halo group, will experience a greater environmental change and consequently a more pronounced variation in chemical shift as a result of the 1,3-diaxial interaction in conformer a. On this basis, then, the *cis* CF_2O fluorine is assigned to the upfield half of the AB pattern in the spectrum of **1** and to the lower field half in the spectrum of **2**.

A small chemical-shift change was detected for the NF of **1** when the sample was cooled from 24 to −120°. The downfield shift amounted to *ca.* 0.5 ppm (ϕ^* −25.8 ppm at −120°). The broadness of the signal made the exact measurements of peak position difficult. Since the fraction of conformer **1b** would increase by 0.13 over this temperature range, the change in the NF chemical-shift in going from **1a** to **1b** would represent *ca.* 217 Hz.

Experimental Section

The ^{19}F nmr spectra were obtained with a Varian Model V-4302B spectrometer operating at 56.4 MHz. The spectra were calibrated by the sideband modulation technique using a Hewlett-Packard wide-range oscillator. Chemical shifts and coupling constants represent the average of at least eight measurements. Errors of ±0.1 ppm and ±1 Hz, respectively, were estimated.

For both low- and high-temperature studies, the variable-temperature accessory supplied by Varian was used. Temperature measurements were made both before and after recording spectra by means of a copper–constantan thermocouple immersed in a tube filled with a Kel-F oil. The temperature measurements are believed to be accurate to ±1°.

The chemical-shift differences (Tables II and III) obtained from nmr spectra of $CFCl_3$ solutions of **1** and **2** were essentially unchanged with the weight per cent of **1** and **2** varied from 25 to 50. However, the chemical-shift values were affected significantly by traces of acetone.

Perfluoro-2-fluoro-1,2-oxazetidine (**1**) and **perfluoro-2-chloro-1,2-oxazetidine** (**2**) were prepared by fluorination and chlorination, respectively, of perfluoro-1,2-oxazetidine as described previously.[17] Both compounds are low-boiling materials, with boiling points below −30°.

Registry No.—**1**, 21720-81-0; **2**, 21720-80-9.

Acknowledgments.—The authors wish to thank Dr. P. D. Readio for valuable discussions and Dr. J. I. Musher of Yeshiva University for his helpful suggestions. We also appreciate the able assistance of Mr. J. Bienvenue in the preparation of the samples.

(17) R. A. Falk and J. D. Readio, *J. Org. Chem.*, **34**, 4088 (1969).

Polyfluoroaryl β-Dicarbonyl Compounds[1]

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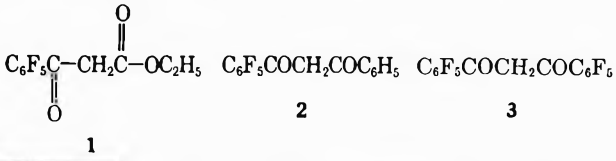
Received July 22, 1969

Ethyl pentafluorobenzoylacetate (**1**) is prepared by oxidation of ethyl 3-hydroxy-3-pentafluorophenylpropionate with Jones reagent, or, better, by reaction of pentafluorobenzoyl chloride (**4**) with diethyl malonate in the presence of magnesium ethoxide. Compound **1** exhibits 54% enolic character as the neat liquid, whereas ethyl benzoylacetate possesses 22% enol. The unsymmetrical 1,3 diketone pentafluorodibenzoylmethane (**2**) is prepared by reaction of the morpholine enamine of acetophenone with (**4**) or from pentafluoroacetophenone and methyl benzoate in the presence of sodium hydride. The symmetrical 1,3 diketone bis(pentafluorobenzoyl)-methane (**3**) has been obtained by three methods, the preferred route being the reaction of **4** with vinyl acetate.

As part of studies aimed at evaluating the effect of pentafluorophenyl substitution on the properties and chemical behavior of neighboring functional groups in organic molecules, we have examined several polyfluoroaryl β-dicarbonyl compounds. In this paper, we report the preparation and some properties of ethyl pentafluorobenzoylacetate (**1**) and the 1,3 diketones pentafluorodibenzoylmethane (**2**) and bis(pentafluorobenzoyl)methane (**3**).



1 **2** **3**

(1) Presented, in part, at the Southeastern Regional Meeting of the American Chemical Society, Louisville, Ky., Oct 1966, and at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1968.

(2) To whom inquiries should be sent.

(3) Abstracted, in part, from the M.S. thesis of V. D. B., Jan 1966, and the Ph.D. thesis of F. N. M., Jan 1967.

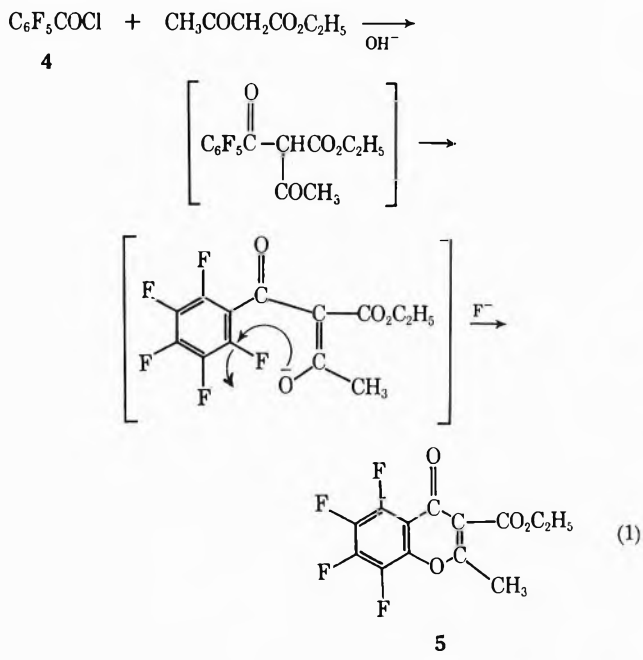
Ethyl Pentafluorobenzoylacetate (**1**).—In our initial approach to compound **1**, pentafluorobenzoyl chloride (**4**) was treated with ethyl acetoacetate in alkaline medium, according to an established procedure for the preparation of ethyl benzoylacetate.[4] Instead of the desired β-keto ester, the sole product isolated was a substance whose elemental composition and infrared and proton magnetic resonance spectra were consistent with compound **5**, a substituted chromone (eq 1).

Compound **5** is formed by intramolecular displacement of *ortho* fluorine by the intermediate enolate anion. Such nucleophilic substitution cannot occur on a non-halogenated aromatic ring, and the reaction proceeds by an alternate course, *i.e.*, cleavage of the acetyl group to give the β-keto ester.

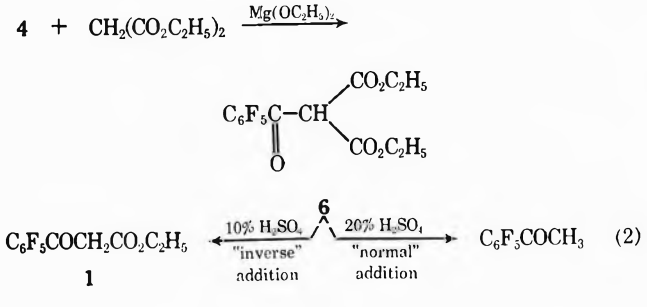
Shortly after completion of this work, our attention was drawn to similar observations by Soviet workers,[5]

(4) J. M. Straley and A. C. Adams, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 415.

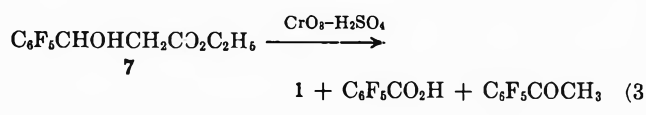
(5) N. N. Vorozhtsov, Jr., V. A. Barkhash, A. T. Prudchenko, and T. I. Khomenko, *Zh. Obshch. Khim.*, **35**, 1501 (1965).

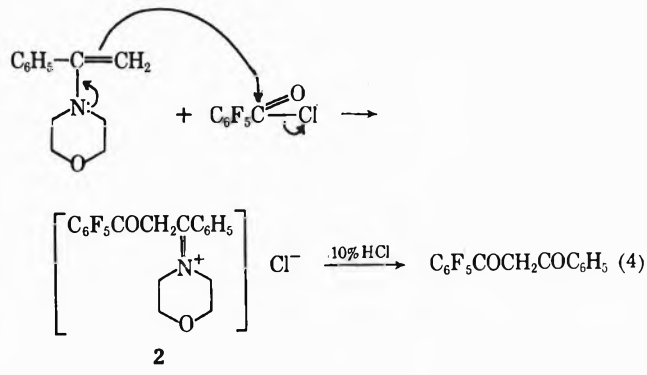


who in subsequent papers[6] described two methods for the preparation of **1**: (a) reaction of the acid chloride **4** with diethyl malonate in the presence of magnesium ethoxide, and (b) condensation of ethyl pentafluorobenzoate with ethyl acetate, catalyzed by diisopropylaminomagnesium bromide. We have examined method a in some detail and confirm the previous observations. However, we noted that the partial hydrolysis of the intermediate diester **6** is extremely sensitive to the concentration and mode of addition of mineral acid. Thus, when **6** is slowly added to 10% H_2SO_4 (inverse addition) and the product is removed by continuous steam distillation, a 48% yield of **1** is obtained. In contrast, normal addition of 20% H_2SO_4 led to complete hydrolysis and decarboxylation to form pentafluoroacetophenone, also in 48% yield (eq 2).



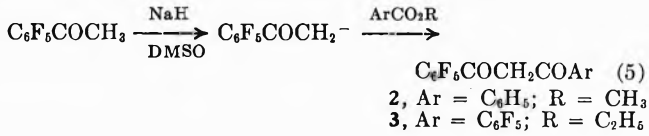
We also prepared compound **1** by a third method, oxidation of ethyl 3-hydroxy-3-pentafluorophenylpropionate (**7**), obtained in 91% yield by the Reformatsky reaction of pentafluorobenzaldehyde with ethyl bromoacetate. Attempts to oxidize **7** to **1** using $KMnO_4$, MnO_2, CrO_3–pyridine, or dicyclohexylcarbodiimide in dimethyl sulfoxide were all unsuccessful. However, oxidation with Jones reagent proceeded readily, but without selectivity, to give **1** in only 17% yield after a difficult separation from pentafluorobenzoic acid and pentafluoroacetophenone (eq 3).





Pentafluorodibenzoylmethane (**2**).—This new unsymmetrical 1,3 diketone was obtained in 25% yield by reaction of the morpholine enamine of acetophenone with the acid chloride **4** (eq 4). A better route to **2**

is the reaction of pentafluoroacetophenone with methyl benzoate in the presence of sodium hydride (eq 5),

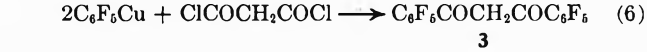


2, Ar = C_6H_5; R = CH_3
3, Ar = C_6F_5; R = C_2H_5

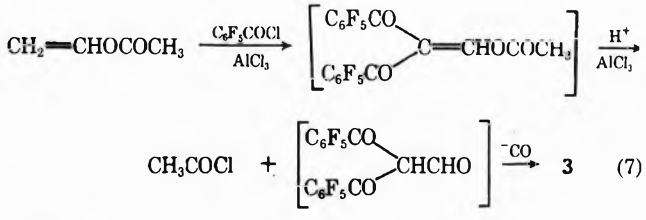
a method described recently by Anselme.[7] The yield of diketone was 60%.

Bis(pentafluorobenzoyl)methane (**3**).—This new symmetrical 1,3 diketone could not be obtained by the enamine route, because all attempts to prepare enamines of pentafluoroacetophenone failed. Instead, there was evidence of nucleophilic attack on the fluorinated ring.

However, three methods of preparation of compound **3** were developed: (a) reaction of $C_6F_5COCH_3$ with ethyl pentafluorobenzoate (eq 5) gave a 60% yield; (b) reaction of pentafluorophenylcopper with malonyl dichloride (eq 6) proceeded in a manner analogous to



the preparation of other polyhalo diketones, as described recently by Gilman and coworkers,[8] and yields in this reaction varied from run to run with a maximum of only 30%; (c) reaction of vinyl acetate with **4** in tetrachloroethane solvent in the presence of anhydrous aluminum chloride gave the desired diketone in 34% yield (eq 7) together with a 20% yield of a by-product,



$C_6F_5COCH_2COCH_3$ (**8**). Compound **8** probably arises from reaction of vinyl acetate with a mixture of **4** and

(6) A. T. Prudchenko, V. A. Barkhash, and N. N. Vorozhtsov, Jr., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1798 (1965); see also N. N. Vorozhtsov, Jr., V. A. Barkhash, A. T. Prudchenko, and G. S. Shchegoleva, *Zh. Obshch. Khim.*, **35**, 1501 (1965).

(7) J. P. Anselme, *J. Org. Chem.*, **32**, 3716 (1967).

(8) S. S. Dua, A. E. Jukes, and H. Gilman, *J. Organometal. Chem.*, **12**, 24 (1968); *J. Org. Chem.*, submitted for publication.

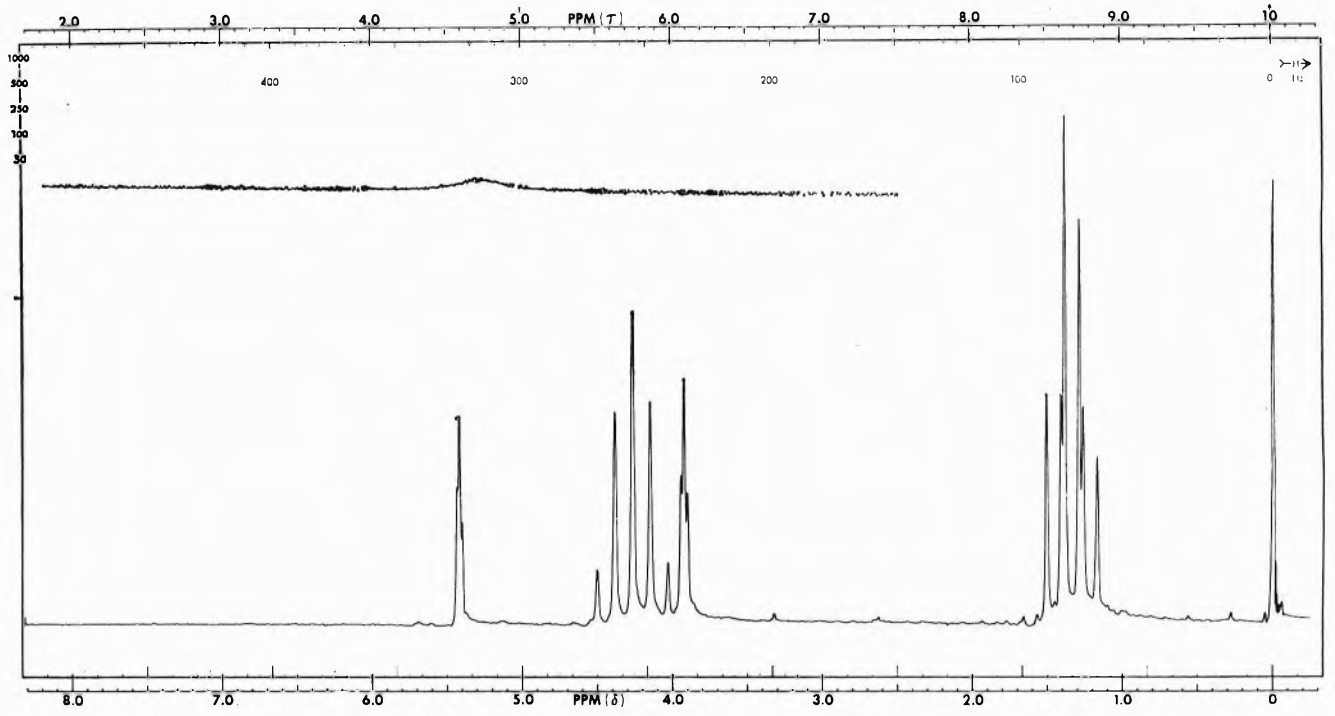
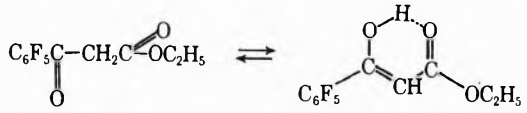


Figure 1.—Proton magnetic resonance spectrum of ethyl pentafluorobenzoylacetate (1) at 60 MHz. Chemical shifts from internal TMS at 37° follow: keto CH_3, 77 Hz (J = 7 Hz); enol CH_3, 82 Hz (J = 7 Hz); keto CH_2, 235 Hz (J = 1.3 Hz); keto + CH_2 (Et group), 255 Hz (J = 7 Hz); enol CH, 325 Hz (J = 1Hz); enol OH, 693 Hz.

acetyl chloride (formed either from vinyl acetate and $AlCl_3$ or as a by-product of the main reaction). Similar behavior with other aroyl chlorides has been observed.[9] Although the yield of **3** by this latter method is not high, the ready availability of the starting materials makes this the preferred route.

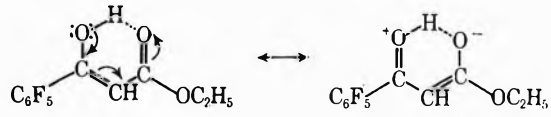
Spectral Properties of the 1,3-Dicarbonyl Compounds and the Keto/Enol Ratio of Ethyl Pentafluorobenzoylacetate.—The infrared spectrum of ethyl pentafluorobenzoyl acetate reveals the presence of the intramolecularly hydrogen-bonded enolic structure (**1b**), characterized by strong absorption at 1656 cm^{-1} (neat liquid), ascribed to "conjugate chelation" of the ester carbonyl group.[10] The presence of a substantial concentration of the keto form (**1a**) is indicated by a band of medium intensity at 1748 cm^{-1}, associated with a "free" ester carbonyl moiety.



1a **1b**

In order to establish the position of keto–enol equilibrium, we examined the proton magnetic resonance spectrum of compound **1** (Figure 1). The percentage of enol was determined by comparing the integrated intensity of the vinylic hydrogen in **1b** with that of the keto methylene group or of the methyl groups of **1a** and **1b** combined. Compound **1** possesses 54 ± 1% enol as the neat liquid at room temperature and K_e = 1.17. In contrast, the hydrogen analog, ethyl benzoylacetate, exhibits only 22% enolic character[11] under the same conditions, and K_e = 0.28.

The internally hydrogen-bonded enolic form is stabilized more in **1b** than in ethyl benzoylacetate because of two factors associated with the increased electron-attracting ability of the C_6F_5 over the C_6H_5 group: (a) enhanced acidity of the enol, leading to a stronger hydrogen bond, and (b) greater resonance stabilization by encouraging charge separation.



We have shown earlier[12] the remarkable influence of neighboring fluorine atoms in altering the keto/enol ratios in β-keto esters. Ethyl 4,4,4-trifluoroacetoacetate exhibits 89% enolic character, whereas ethyl acetoacetate possesses about 8% enol (neat liquids).

The 1,3 diketones **2**, **3**, and **8** exist essentially completely in the monoenolic form, as determined by titration with sodium methoxide[13] and by examination of their pmr spectra. However, the infrared spectra of **2** and **3** merit comment. Dibenzoylmethane, which exists completely in the monoenol form, fails to exhibit normal conjugated carbonyl absorption. Instead, a broad, more intense band in the range 1639–1538 cm^{-1} is observed.[14] This shift is ascribed to "conjugate

(9) A. Sieglitz and O. Horn, *Chem. Ber.*, **84**, 607 (1951).

(10) L. J. Bellamy, "The Infrared-red Spectra of Complex Molecules." 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1958, p 184.

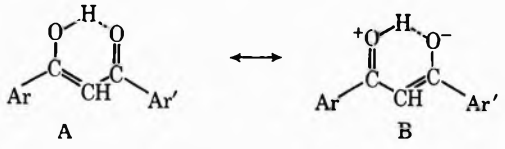
(11) J. L. Burdett and M. T. Rogers, *J. Amer. Chem. Soc.*, **86**, 2105 (1964). Their results were confirmed by us.

(12) R. Filler and S. M. Naqvi, *J. Org. Chem.*, **26**, 2571 (1961); see also ref 11.

(13) J. S. Fritz, "Acid-Base Titrations in Non-Aqueous Solvents," G. F. Smith Chemical Co., Columbus, Ohio, 1952, pp 28, 31.

(14) R. S. Rasmussen, D. D. Tunnicliff, and R. R. Brattain, *J. Amer. Chem. Soc.*, **71**, 1068 (1949).

chelation," a resonance effect involving structures A and B.

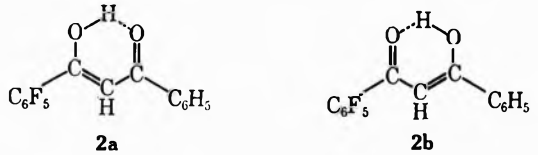


A B

Ar = Ar′ = C_6H_5
Ar = Ar′ = C_6F_5

However, compound **3**, in which both phenyl groups are replaced by C_6F_5, shows a near-normal carbonyl vibration (1677 cm^{-1}), close to that observed in the structurally similar fluorinated benzalacetophenone,[15] $C_6F_5CH{=}CH(C{=}O)C_6F_5$ (1689 cm^{-1}). The strong electron attraction of the pentafluorophenyl group reduces "conjugate chelation" by increasing the double-bond character of the carbonyl group, thus enhancing the contribution of structure A and destabilizing structure B. The spectrum of the unsymmetrical diketone **2** appears to have features common to both dibenzoylmethane and **3**.

The question of the direction of enolization in compound **2** has occupied us for some time. There are three possibilities, **2a**, **2b**, or a rapidly equilibrating mixture of the two forms.



2a **2b**

The infrared data are somewhat ambiguous and do not permit a decision between **2a** or **2b**. The ultraviolet spectra [dibenzoylmethane (λ_{max}^{EtOH} 342 nm), **3** (340), **2** (333)][16] do not provide useful information, even when compared with data for the corresponding benzalacetophenones,[15] to make a clear choice.

The proton magnetic resonance spectra of the diketones in carbon tetrachloride reveals a sharp triplet at 386 Hz (J = 1.5 Hz) for the vinylic proton in **2**, an unresolved multiplet at 386 Hz in **3**, and a singlet at 405 Hz for =CH in dibenzoylmethane. These data suggest a similar environment for this proton in **2** and **3**, =CH-(C=O)C_6F_5.

The sharp vinylic resonance in **2** indicates that the compound probably exists in a single form, unless equilibration occurs more rapidly than the nmr time scale. Finally, comparison with the coupling constants in the model compounds, $C_6F_5COCH_3$ and $C_6F_5C(OCH_3){=}CH_2$ lead us to the *tentative* conclusion that **2b** is the correct structure for the monoenol. This conclusion is based on the following arguments: (1) the coupling constant of the vinylic proton in **2** is similar to that for the methyl protons in $C_6F_5COCH_3$ (J = 1.7 Hz), suggesting that =CH and CH_3 have a similar relationship to the C_6F_5 group, namely, that both are bonded to a carbonyl group, and (2) the vinylic protons in $C_6F_5C(OCH_3){=}CH_2$ are not appreciably coupled (J < 1.0 Hz) to the ring fluorine atoms, in support of the conclusion that in **2** there is no carbon–carbon double bond in conjugation with the fluorinated ring.

(15) The chemistry of fluorinated benzalacetophenones will be the subject of a forthcoming paper.

(16) These intense absorptions are attributed to n → π* transitions in the enols: G. S. Hammond, W. G. Borduin, and G. A. Guter, *J. Amer. Chem. Soc.*, **81**, 4682 (1959).

Experimental Section[17]

Pentafluorobenzoic Acid.—Pentafluorobromobenzene (39.5 g), dissolved in 100 ml of anhydrous ether was added to 100 ml of *n*-butyllithium in hexane solution and the mixture was cooled to −78° and kept under a nitrogen atmosphere. After addition was complete, the solution was kept at this temperature for 1 hr. Carbon dioxide, dried by passing through H_2SO_4, was passed through the solution at −78° for 20 min and then for an additional 1 hr while the solution was allowed to warm to room temperature. Then 200 ml of 6 *N* HCl was added with vigorous stirring and the organic phase was separated. The aqueous phase was extracted with three 40-ml aliquots of ether and the combined organic extracts were washed with water and dried over $MgSO_4$. The solvent was stripped off to give a white solid, mp 100–102°, after recrystallization from hexane–benzene (10:1), yield 32 g (93%).

Pentafluorobenzoyl Chloride (4).—Pentafluorobenzoic acid (21.0 g) was mixed with 14 g of thionyl chloride and the mixture was refluxed for 16 hr. Excess reagent was drawn off and the residue was fractionated *in vacuo*. The acid chloride was collected as a slightly yellow oil, bp 35–38° (1.2 mm), yield 18.8 g (81%).

Reaction of Ethyl Acetoacetate with Pentafluorobenzoyl Chloride.—Water (13.3 ml), 6.7 ml of petroleum ether (bp 65–70°), and 5.2 g (0.04 mol) of freshly distilled ethyl acetoacetate were placed in a 100-ml, three-necked, round-bottomed flask, equipped with an efficient stirrer and two dropping funnels. The mixture was cooled to 5° and 1.6 ml of 33% sodium hydroxide solution was added. As the temperature was maintained below 10° and the pH near 11, the mixture was stirred vigorously while 10 g (0.043 mol) of pentafluorobenzoyl chloride and 7.0 ml of 33% sodium hydroxide solution were added dropwise simultaneously from the two funnels. The addition was complete after 1.5 hr and a yellow-white solid formed. The mixture was allowed to warm to room temperature over a 1-hr period. The precipitate was filtered off and washed with petroleum ether. After air drying, the solid weighed 11 g, mp 113–114°.

This white material (5 g) was dissolved in 30 ml of water, and 1.0 g of ammonium chloride was added with stirring. After a few minutes of stirring at room temperature, a white solid began to precipitate. After 45 min, the precipitate was filtered and dried *in vacuo* over Drierite, mp 114–115°. A 1.0-g sample of this compound was heated under reflux with 50 ml of absolute ethanol for 1 hr. The solution was evaporated to dryness, leaving a tacky, yellow solid, which was recrystallized several times by dissolving in ethanol and precipitating with water. After drying, 0.56 g of the chromone **5**, mp 89.8–90.1°, was obtained as white plates: ir (CCl_4) 1678 (s) and 1730 cm^{-1} (s); pmr δ 4.31 (q, CH_2), 2.47 (s, CH_3), and 1.36 (t, CH_3 of C_2H_5 group).

Anal. Calcd for $C_{13}H_8F_4O_4$: C, 51.31; H, 2.63. Found: C, 51.75; H, 2.93.

Ethyl Benzoylacetate.—Ethyl benzoylacetate was prepared according to the procedure described in *Organic Syntheses*.[4] The product distilled at 144–147° (2 mm), yield 23 g (40%).

Ethyl 3-Hydroxy-3-pentafluorophenylpropionate.—Zinc dust (3.5 g, 0.058 g-atom) was placed in a flask under a nitrogen atmosphere, and 13 g (0.066 mol) of pentafluorobenzaldehyde and 9.7 g (0.058 mol) of ethyl bromoacetate were mixed and dissolved in a mixture of 2.5 ml of anhydrous ether and 10 ml of dry benzene. This mixture (3 ml) was added to the zinc and the flask was heated until reaction started. The remaining solution was added dropwise at such a rate as to maintain reflux. After addition was complete, the reaction mixture was refluxed for an additional 2 hr and left at room temperature overnight. The mixture was hydrolyzed with 25 ml of 10% (v/v) H_2SO_4, the aqueous phase was extracted with three 20-ml portions of ether, and the combined extracts were washed with water, sodium carbonate solution, and twice with water and then dried over $MgSO_4$. The solvents were stripped off and the slightly yellow residual oil crystallized completely upon cooling and scratching to give 15.2 g (91%) of crude product. White crystals, mp 46–

(17) All melting points and boiling points are uncorrected.

48°, were obtained after sublimation, ir (CCl_4) 1718 (s) and 3480 cm^{-1} (br).

Anal. Calcd for $C_{11}H_9F_5O_3$: C, 46.48; H, 3.19. Found: C, 46.75; H, 3.53.

Ethyl 3-Keto-3-pentafluorophenylpropionate (1).—Ethyl 3-hydroxy-3-pentafluorophenylpropionate (7.0 g) was dissolved in 200 ml of acetone and treated with 20 ml of Jones reagent (13.4 g of CrO_3, 11.5 ml of concentrated H_2SO_4/50 ml of solution), the temperature not being allowed to exceed 26°. The solution was kept at 24–26° for 1.5 hr and then the excess reagent was destroyed by adding isopropyl alcohol. The resulting dark green mixture was poured into 1500 ml of ice-cooled water and extracted with five 150-ml portions of ether. The ether extracts were washed with water until colorless and then dried over $MgSO_4$. The solvent was stripped off and the residue was fractionated *in vacuo*. The fraction boiling at 85–105° (1 mm) was refractionated and yielded the desired product, a colorless oil, bp 89–93° (0.9 mm), $n^{23}D$ 1.4594 (lit.[6] nD 1.4604). The yield was 1.2 g (17%).

When treated at room temperature for 4 hr or at temperatures exceeding 30° for a shorter time with Jones reagent, the hydroxy ester gave as the main product pentafluorobenzoic acid (as determined by melting point and mixture melting point determination with an authentic sample). Oxidation below 12° gave, for varying times from 10 min to 2 hr, only unreacted starting material. Oxidation at 15–20° for 1 hr gave a mixture of product and starting material. Oxidation above 20° gave as a by-product varying amounts of pentafluorobenzoic acid. No combination of time and temperature could be found which gave the keto ester as the only oxidation product. The keto ester was always accompanied by an unidentified by-product, a yellow oil, boiling slightly higher than the keto ester, bp 105–110° (1 mm), $n^{24}D$ 1.4540, and an ir spectrum very similar to that of 1, except for a pronounced OH absorption band. The separation of those two compounds required the product to be refractionated at least two times.

Ethyl 3-Keto-3-pentafluorophenylpropionate (1).[6]—Magnesium (1.7 g, 0.069 g-atom) was covered with 8.9 ml (0.067 mol) of absolute ethanol, a 3-ml portion of 10.7 g (0.067 mol) of freshly distilled diethyl malonate and 0.2 ml of carbon tetrachloride was added, and the reaction mixture was heated until reaction started. The remaining diethyl malonate was added dropwise, and, after slight cooling, 16 ml of anhydrous ether was added and the mixture was refluxed for 3 hr, by which time all of the magnesium had reacted. The solvent was distilled off, 20 ml of dry benzene were added and distilled to remove any excess ethanol, and the remaining syrupy liquid was dissolved in 20 ml of dry ether. Pentafluorobenzoyl chloride (16.0 g, 0.069 mol) dissolved in 10 ml of anhydrous ether was added dropwise and the mixture was heated under reflux for 15 min, cooled, and hydrolyzed by adding 15 ml of water and 8 ml of 20% sulfuric acid. The aqueous phase was extracted with three 15-ml portions of ether and the combined organic phases were washed with water, a dilute solution of sodium bicarbonate, and water, and dried over $MgSO_4$. The solvent was stripped off to leave a dark yellow, liquid residue. Sulfuric acid (10%, 100 ml) was carefully heated to boiling in a three-necked flask equipped with a dropping funnel and a distillation condenser. The crude diethyl pentafluorobenzoyl malonate was added to the boiling acid in small portions during 3 hr. Simultaneously, water was added to maintain the acid volume, while steam distillate of the product was collected. Caution had to be taken that reactant and product did not accumulate in the reaction vessel, or else hydrolysis and decarboxylation would proceed to the stage of pentafluoroacetophenone. The steam distillate was saturated with ammonium chloride and the oil was extracted with ether; the extracts were washed with water and dried over $MgSO_4$. The solvent was stripped off and the residue was fractionated *in vacuo:* bp 90–93° (1.2 mm); $n^{23}D$ 1.4590; yield 9.2 g (48%); ir (neat) 3565 (vw), 1748 (s), 1715 (m), 1656 (vs), and 1635 cm^{-1} (m); pmr, see Figure 1. Derivatives follow: copper chelate, light green crystals, mp 179–181°; 2,4-dinitrophenylhydrazone (from ethanol–water), mp 117–118° (lit.[6] mp 118°), formed by allowing reactants to stand at room temperature for 3 days. If reactants were heated under reflux for 2 hr, the 2,4-dinitrophenylhydrazone of pentafluoroacetophenone (hydrolysis and decarboxylation), mp 155–157°, was isolated.

When the preparative procedure was modified so that the crude diethyl pentafluorobenzoyl malonate was mixed with 200 ml of 20% sulfuric acid and the product was steam distilled, the sole substance isolated was pentafluoroacetophenone, bp 43–45° (1.2 mm), $n^{25}D$ 1.4323, yield 48.2%.

Bis(pentafluorobenzoyl)methane (3). Anselme's Method.[7]—To a 100-ml, three-necked, round-bottomed flask, equipped with a magnetic stirrer, a condenser to which was attached a drying tube and an addition funnel, attached to a dry nitrogen supply, and a thermometer, was added 1 g of a suspension of sodium hydride (60% in mineral oil). The flask was cooled in an ice bath and 15 ml of dimethyl sulfoxide was added. The cooling bath was removed and the mixture was stirred for 30 min. The temperature was then lowered to 15° and 6.0 g of ethyl pentafluorobenzoate was added while the temperature was kept at 15°. The temperature was allowed to drop to 5° and 3.2 g of pentafluoroacetophenone was added during 30 min. The temperature was then raised to 35° and the mixture was stirred for 24 hr. The dark reaction mixture was poured in a thin stream into 50 g of crushed ice containing 1 ml of 85% phosphoric acid, with stirring. The organic layer was extracted with ether and the ether layer was washed free of sulfur compounds with bromine water. After repeated washings with water, the ether layer was dried and distilled to give a red oil. Chromatography over alumina and elution with benzene and methanol gave 3 (3.5 g, 60%): mp 119–120°; copper chelate, green-blue crystals; mp 192°; uv λ_{max}^{EtOH} 340 nm; ir (KBr) 1675 (s) and 1630 cm^{-1} (w); pmr (CCl_4, 60 MHz, internal TMS) 386 Hz.

Anal. Calcd for $C_{15}H_2F_{10}O_2$: C, 44.55; H, 0.49. Found: C, 44.49; H, 0.51.

Bis(pentafluorobenzoyl)methane (3). Vinyl Acetate Method.—Anhydrous aluminum chloride (5.3 g) was heated with pentafluorobenzoyl chloride (9.22 g) in 20 ml of tetrachloroethane at 45° until the addition compound of $AlCl_3$ and the acid chloride was formed. Vinyl acetate (3.44 g) was added dropwise at 25° during 30 min. The mixture was heated at 35° for 24 hr and decomposed with ice-cold, dilute hydrochloric acid. The mixture was steam distilled to remove the solvent, the residue was extracted with ether, the ether extract was dried over Na_2SO_4, and the ether was evaporated. On distillation at 80° (1 mm), 2 g (20%) of acetyl pentafluorobenzoylmethane (8) was obtained: ν (CCl_4) 1640 (s) and 1595 cm^{-1} (br s; nmr δ 2.18 (s, CH_3) and 5.90 (5, J = 1.5 Hz vinyl CH). The residue was eluted over alumina with benzene and methanol to give 5.5 g (34%) of 3, mp 119°.

Bis(pentafluorobenzoyl)methane (3). Pentafluorophenylcopper Method.—Magnesium (1.25 g) was placed in a dry, three-necked flask under nitrogen, 3 ml of dry ether and 1 ml of bromopentafluorobenzene were added, and the flask was heated until reaction started. The remainder of 12.3 g (0.05 mol) of bromopentafluorobenzene, dissolved in 250 ml of dry ether, was added dropwise. The reaction mixture was refluxed gently for 20 min after addition was complete. Then 5.6 g (0.056 mol) of cuprous chloride was added in small portions during 20 min and the mixture was stirred at room temperature for 2.5 hr. Freshly distilled malonyl dichloride (3.7 g, 0.026 mol) dissolved in 20 ml of dry ether was added dropwise and the reaction mixture was left overnight at room temperature. The mixture was hydrolyzed with 300 ml of ice-cooled 5 *N* HCl, the aqueous phase was extracted three times with ether, and the combined organic phase was washed with water, dilute sodium bicarbonate solution, and water and dried over $MgSO_4$. After evaporation of the solvent, a residual yellow oil was obtained, which partly crystallized upon cooling. The product crystallized from 15 ml of ethanol and was further purified by sublimation at 60° (2 mm) to give 2.54 g (31%) of bis(pentafluorobenzoyl)methane, mp 116–118°. There was no melting point depression when this material was admixed with the samples prepared by the other two methods.

2,3,4,5,6-Pentafluoroacetophenone.—In a 250-ml, three-necked, round-bottomed flask fitted with an efficient stirrer, a reflux condenser, and a dropping funnel with a nitrogen inlet tube were put 3.0 g (0.12 g-atom) of magnesium turnings and 30 ml of anhydrous ether (dried over sodium). Bromopentafluorobenzene (30 g, 0.12 mol) in 45 ml of dry ether was added during a 60-min period. After addition was complete, the mixture was stirred at room temperature for 1 hr. The flask was cooled in ice, the dropping funnel was removed, and 11.7 g (0.064 mol) of anhydrous cadmium chloride (dried at 100°) was added over a 5-min period. The funnel was replaced, the ice bath was removed, and the mixture was heated under reflux for 75 min. At this point the Gilman test for the presence of Grignard reagent was negative. The flask and condenser were arranged for

distillation and ether was distilled off as stirring was continued until the residue became very viscous. Anhydrous, thiophene-free benzene (45 ml) was added, and 15 ml of liquid were removed by distillation. An additional 45 ml of benzene was added and the reflux condenser was replaced. The mixture was refluxed with vigorous stirring for a few minutes and cooled to 5°, and a solution of 8.3 g (0.11 mol) of freshly distilled acetyl chloride in 25 ml of dry benzene was added during 2–3 min. After addition, the mixture was stirred at room temperature for 18 hr. It was then poured into 150 g of crushed ice containing 75 ml of 25% (v/v) sulfuric acid, and the resulting two-phase mixture was stirred for 5 min. The dark brown benzene layer was separated, and the water layer was extracted with two 30-ml portions of benzene. The combined benzene layers were washed successively with 45 ml of saturated sodium chloride solution, 45 ml of saturated sodium bicarbonate solution, 45 ml of water, and 25 ml of saturated sodium chloride solution. The benzene layer was dried over anhydrous sodium sulfate and the benzene was removed on a flash evaporator at room temperature. The dark residue was distilled *in vacuo* to give 14.0 g (56%) of 2,3,4,5,6-pentafluoroacetophenone: bp 65–66° (5 mm); pmr δ 2.67 (5, CH_3); 2,4-dinitrophenylhydrazone mp 156–157°.

Dibenzoylmethane.—Dibenzoylmethane, mp 77–78°, was prepared according to the procedure described by Sieglitz and Horn.[8]

Pentafluorodibenzoylmethane (2). Enamine Method.—A mixture of 174 g (2.0 mol) of morpholine, 120 g (1.0 mol) of acetophenone, and 8.6 g (0.05 mol) of *p*-toluenesulfonic acid in 250 ml of toluene was heated under reflux for 72 hr. The water which formed was collected in a Dean–Stark trap and removed from the system. After completion of the reaction, the toluene was removed *in vacuo* and the residue was vacuum distilled to give the enamine in low yield. A large amount of viscous tar remained in the distillation flask.

A mixture of 3.22 g (0.014 mol) of pentafluorobenzoyl chloride and 5.3 g (0.028 mol) of α-(4-morpholino)styrene in 100 ml of dry dioxane was stirred overnight in a dry nitrogen atmosphere, at room temperature. The reaction mixture was filtered and the residue was washed with ether. The organic layers were combined, mixed with 75 ml of 10% hydrochloric acid, and heated under reflux for 4 hr. The aqueous solution was then diluted with water to a volume of *ca.* 1 l. and the ether layer was separated and combined with three 100-ml extracts of the aqueous layer. The ethereal solution was dried over Na_2SO_4 and evaporated *in vacuo* to give a red oil which later solidified. Two recrystallizations of the oil from methanol gave 1.1 g (25%) of colorless needles: mp 118°; uv λ_{max}^{EtOH} 333 nm (log ϵ 4.28) and 246 (3.82); ir (CCl_4) 1645 (s), 1598 (br s), and 1568 cm^{-1} (br s); pmr (CCl_4) 386 Hz (t, J = 1.5 Hz, vinyl CH).

Anal. Calcd for $C_{15}H_7F_5O_2$: C, 57.34; H, 2.25. Found: C, 57.23; H, 2.35.

Pentafluorodibenzoylmethane (2). Anselme's Method.[7]—This diketone, mp 118°, was prepared in 60% yield from pentafluoroacetophenone and methyl benzoate, according to the procedure described above for bis(pentafluorobenzoyl)methane.

Enol Contents of 1,3 Diketones.—The percentage of enol in the following 1,3 diketones was determined by titration with standard sodium methoxide solution, according to a known procedure.[13] The results follow: $C_6H_5COCH_2COC_6H_5$, 100%; $C_6F_5COCH_2COC_6H_5$ (**2**), 93%; $C_6F_5COCH_2COCH_3$ (**8**), 100%; $C_6F_5COCH_2COC_6F_5$ (**3**), 98.8%.

Registry No.—**1**, 3516-87-8; **2**, 23074-28-4; **3**, 23074-29-5; **4**, 2251-50-5; **5**, 4487-61-0; pentafluorobenzoic acid, 602-94-8; ethyl 3-hydroxy-3-pentafluorophenylpropionate, 23115-90-4; 2,4-dinitrophenylhydrazone of pentafluoroacetophenone, 858-82-2; 2,3,4,5,6-pentafluoroacetophenone, 652-29-9.

Acknowledgment.—This research was supported by Grant GM-12146 from the National Institutes of Health.

Liquid Fluorocarbon from Hexafluoropropene by an Electrical Discharge Process[1a]

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Received July 25, 1969

A mixture of liquid fluorocarbons derived from C_3F_6 was prepared by an electrical discharge process. The gas-phase discharge was initiated at 150–800 Torr in concentric quartz tube reactors at 15–60° using field strengths of 9–13 kV/mm and alternating current at 1.4 or 10 kc/sec. The liquid discharge product contained substantial quantities of linear and branched fluoro alkanes as well as unsaturated (olefinic) fractions. No small-ring components were found. Carbon numbers of the products were shown to be random rather then multiplets of the monomer units. Base-catalyzed reaction of the liquid fluorocarbon with alcohol gave three fractions: (1) unsaturated ethers, (2) nonreactive fluoro alkanes, and (3) small amounts of perfluoroalkyl carboxylic acids. One of the sources of the carboxylic acids could be the stable free radicals shown by epr measurement (10^{21}–10^{17} spins/cc) to be present in the discharge products. A radical mechanism was suggested in which C_3F_6 was fragmented by the discharge process into reactive radicals which combined with each other and with neutral molecules to form higher molecular weight fractions. The fact that many linear alkanes were found indicated that difluorocarbene ($:CF_2$) was involved in the chain-extension process. A significant amount of F radical was also postulated to explain the formation of alkanes. Perfluorodienes were suggested as reaction intermediates for the presence of many identified olefinic groups. Halogenation of the discharge product proceeded readily with elemental fluorine, but not with chlorine or bromine trifluoride.

Reports in the literature concerning electrical discharge of gaseous fluorocarbons[2–5] have described only the discharge at low pressure. The present investigation was made at higher pressures and the electrical conditions were milder than those of previous workers. The products obtained with hexafluoropropene were predominantly liquids. Instrumental and chemical analyses indicated that the liquid product (herein called liquid fluorocarbon) contained perfluoro alkanes as well as unsaturated fractions.[2]

Results and Discussion

Hexafluoropropene was converted into a mixture of gaseous (3–10%) and liquid fluorocarbons in quantita-

(1) (a) Presented in part at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968. (b) To whom inquires should be addressed: 102 Maclean Circle, Princeton, N. J. 08540.

(2) (a) P. B. Weisz, *J. Phys. Chem.*, **59**, 464 (1955); (b) P. B. Weisz, *et al.*, U. S. Patent 2,676,145 (1954).

(3) J. Goodman, *J. Polym. Sci.*, **44**, 551 (1960).

(4) A. Bradley and J. P. Hammes, *J. Electrochem. Soc.*, **110**, No. 1, 15 (1963).

(5) Y. Kometani, A. Katsushima, T. Fukui, and K. Nakamura, Japanese Patent 10,989 (1965).

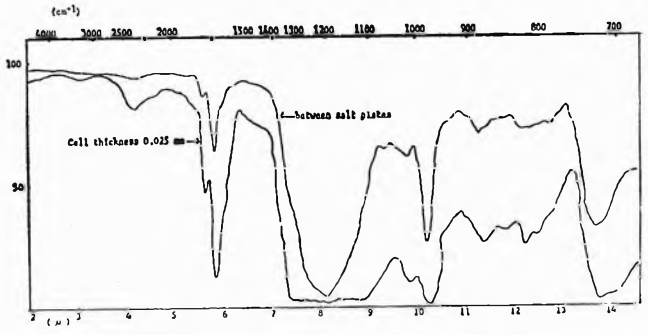

Figure 1.—Infrared spectrum of the liquid fluorocarbon from hexafluoropropene by the electrical discharge process.

tive yield[6] by passing the monomer through an electrical discharge cell. The discharge was initiated across gaseous gaps of 1.5–2.0 mm at monomer pressures of 150–800 Torr, total applied voltages of 12–24 kV (rms), and AC currents at 1.4–10 kc/sec.[6] Within these diversified reaction conditions, the crude products showed the same general infrared spectrum (Figure 1). Molecular weight distribution of the products, however, varied, as shown by the fractional distillation results (Table I). The major components of the gaseous fraction identified by instrumental analyses were $F(CF_2)_nF$ (n = 1, 2, 3, 4, 5), $(CF_3)_3CF$, $CF_3CF{=}CF_2$, and CO_2. In addition, the following components were sought, but were not observed by any of the analytical methods: $CF_2{=}CF_2$, c-C_3F_6, $CF_2{=}CFCF{=}CF_2$, CF_3CF_2-$CF{=}CF_2$, c-C_4F_8,[7] $(CF_3)_2C{=}CF_2$, CF_3OF, CF_3-CFO, CO, F_2,[7] SiF_4,[7] and COF_2.[7]

TABLE I

PHYSICAL PROPERTIES OF LIQUID FLUOROCARBON PREPARED AT TWO DIFFERENT FREQUENCIES (1.4 AND 10 kc/sec)

Bp, °C	Wt %	η at 20° cSt	$n^{25}D$	ρ at 22°
A. Frequency, 1.4 kc/sec; Energy Input/mol of Reactant (kcal/mol), 1320				
→100	10	0.56	<1.3	1.6888
100–150	34	1.01	<1.3	1.7820
150–200	30	3.96	1.3132	1.8730
>200	17	35.5	1.3262	1.9119
Gaseous products	9	...	...	...
B. Frequency, 10 kc/sec; Energy Input/mol of Reactant (kcal/mol), 3010				
→100	6	0.60	<1.3	1.5926
100–150	17	1.05	<1.3	1.6903
150–200	38	2.77	1.3069	1.8557
>200	31	55.4	1.3254	1.9186
Gaseous products	8	...	...	...

The low-boiling liquids were further fractionated by gas chromatography. Many linear and branched alkanes were separated and identified (Table II). There were also many unsaturated fluorocarbons present in this fraction, as shown by the infrared spectrum. Small amounts of perfluorohexene and perfluoroheptene were identified by mass and infrared spectroscopy. The fact that most of the larger peaks in the gaseous and low-boiling fractions were identified as saturated fluorocarbons showed that these components were much less reactive toward further discharge reactions than were the olefinic components.

(6) S. W. Osborn, E. Broderick, E. L. Kutch, M. Kawabata, and J. C. Fraser, presented at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 1968, Abstracts, p Fluo. 1 (to be published).

(7) Present in the electrical discharge product of tetrafluoroethylene: E. S. Lo, unpublished data.

TABLE II

MAJOR COMPONENTS IDENTIFIED[a] FROM THE LOW-BOILING LIQUID FLUOROCARBON[b]

Structures	%[c]
n-C_5F_{12}	6.19
i-C_5F_{12}	2.05
n-C_6F_{14}	9.31
i-C_6F_{14}	24.30
$(CF_3)_2CFCF(CF_3)_2$	17.75
$(CF_3)_2CF(CF_2)_3CF_3$	6.92
$(i$-$C_3F_7)_2CF_2$	12.20
Other C_7F_{16} isomers	8.61
Unidentified (many peaks)	12.67

[a] By mass infrared, and ^{19}F nmr spectroscopy. [b] This fraction (57%) was collected at 35–150° from the fractional distillation of a liquid fluorocarbon having a viscosity of 1.8 cSt at 20°. [c] Area measurement by gas chromatographic analysis.

No carbon deposit was found in either the discharge cell or the liquid fluorocarbon. The yield of the liquid fluorocarbon was quantitative; however, it varied with the electrical power input to the system within constant-temperature or constant-pressure limits. Viscosity of the product was more effected by temperature than by applied voltage (Table III).

TABLE III

EFFECT OF DISCHARGE CONDITION ON YIELD AND VISCOSITY OF PRODUCT

Temp of electrode, °C		Monomer pressure, mm	Operating voltage, kV (rms)	Power,[a] W	Energy input per mol of C_3F_6 charged, kcal/mol	Yield,[b] g	η at 20°, cSt
Inner	Outer						
18	11	260	18.0	499	1182	193	2.05
21	11	260	16.9	353	870	185	1.99
20	11	260	15.8	252	784	164	1.87
19	10	260	14.5	238	835	130	1.71
52	36	260	18.0	481	1303	156	4.01
52	36	260	15.9	363	1257	132	3.67
52	37	260	15.0	264	992	121	3.46
53	37	260	14.5	247	1030	109	3.17
27	13	150	18.0	418	1616	118	2.89
27	13	150	16.5	378	1616	107	2.86
28	13	150	15.0	302	1403	98	2.72
28	13	150	14.0	265	1297	93	2.25
52	37	150	18.0	378	2534	68	8.27
52	37	150	16.5	319	2107	69	7.74
52	37	150	15.0	258	1645	72	5.65
52	37	150	14.0	227	1567	66	4.9

[a] The frequency of all the experiments was set at 1.4 kc/sec. [b] The time for all the experiments was 3.5 hr. The yield is quantitative; *i.e.*, the amount of C_3F_6 consumed was the same as the gram yield of each experiment.

The C_6 and C_9 fractions of the liquid fluorocarbon were compared with the dimers and trimers of C_3F_6 prepared in dimethylaniline and methanol.[8] None of the isomers prepared by that method was found in the liquid fluorocarbon of the present process.

Base-catalyzed reaction of the liquid fluorocarbon with alcohol showed the presence of three types of structures: perfluoro alkanes, perfluoro olefins, and a

(8) W. J. Brehm, *et al.*, U. S. Patent 2,918,501 (1959).

small third fraction. The olefins were isolated as unsaturated ethers.[9,10] The third fraction was identified as carboxylic acids. The carboxylic acids can also be obtained by treating the liquid fluorocarbon with aqueous alkali. Since the discharge product showed no OH absorption in its infrared spectrum, the carboxylic acids must result from the hydrolysis of some precursors in the discharge product. Epr study[11] of the liquid fluorocarbon indicated the presence of stable fluorocarbon radicals. The electron spin densities range from 10^{21} to 10^{17} spins/cc. High spin densities have also been observed in the radio-frequency discharge with benzene.[12] These radicals were known to chemisorb oxygen readily.[12,13] Mass spectroscopy of an air-exposed liquid fluorocarbon sample indicated the presence of SiF_4, CO_2, and oxygen-containing components such as $C_4F_7O^+$, $C_2F_3O^+$, and $C_2F_2O^+$. Hydrolysis of these radicals would be expected to produce carboxylic acids.

Another precursor of these carboxylic acids may be oxygen-containing fragments present in the discharge product. The source of oxygen is not clear, but it could be the Pyrex discharge cell, since the cell was slightly etched after the discharge reaction.

About 98% of the unsaturation shown by infrared spectrum could be effectively removed by elemental fluorination. Prolonged fluorination, even at higher temperature, did not saturate the liquid fluorocarbon further. Infrared analyses during the fluorination process indicated the presence of a small new peak at 5.3 μ (–FC=O), which appeared at the beginning of fluorination and remained at the same intensity until the end of the process. This acyl fluoride peak could result from oxygen, chemisorbed by the stable fluorocarbon radicals.

Halogenation of the liquid fluorocarbon was sluggish. Both vapor-phase chlorination[14] and bromine trifluoride addition reactions succeeded only partially in reducing the unsaturation present in the liquid fluorocarbon.

Mechanism of Reaction.—Both ionic[2,15] and free-radical[12,16,17] mechanism have been proposed for the reactions involved in electrical discharge processes. The reaction path of the discharge process is not only influenced by applied electrical fields, but also by the temperature of the gas plasma, which is often much higher[18] than the wall temperature of the reactor. The present study is made at much higher monomer pressures than those used by previous workers.[2–5] The interaction of electrons and molecular assembly, therefore, is much greater than that encountered in low-pressure discharges. In the present systems, it is possible to consider reaction paths otherwise unavailable in normal thermal or regular free-radical systems.

The dissociation of C_3F_6 to excited free radicals and the combination of these radicals with each other and with C_3F_6 (Scheme I) could account for a number of

SCHEME I

SUGGESTED MECHANISM OF REACTION FOR THE ELECTRICAL DISCHARGE PROCESS

A. Initial Reactions

$$CF_3CF{=}CF_2 \longrightarrow \cdot CF_3 + \cdot CF{=}CF_2$$
$$CF_3CF{=}CF_2 \longrightarrow CF_3\dot{C}{=}CF_2 + \cdot F$$
$$\cdot CF_3 \longrightarrow :CF_2 + \cdot F$$

B. Radical Reactions

$$\cdot CF_3 + n(\cdot CF_2) + \cdot F \text{ (or } \cdot CF_3) \longrightarrow CF_3(CF_2)_nF^{a,b}$$
$$\cdot F + CF_2{=}CFCF_3 \longrightarrow (CF_3)_2\dot{C}F \xrightarrow{\cdot CF_3} (CF_3)_3CF^a$$
$$2(CF_3)_2\dot{C}F \longrightarrow (CF_3)_2CFCF(CF_3)_2{}^{a,c}$$
$$\downarrow :CF_2$$
$$(i\text{-}C_3F_7)_2CF_2{}^a$$
$$(CF_3)_2\dot{C}F + n(:CF_2) + \cdot F \text{ (or } \cdot CF_3) \longrightarrow (CF_3)_2CF(CF_2)_nF^d$$
$$2\cdot CF{=}CF_2 \longrightarrow CF_2{=}CFCF{=}CF_2$$
$$\cdot CF{=}CF_2 + CF_3\dot{C}{=}CF_2 \longrightarrow CF_2{=}CFC(CF_3){=}CF_2$$

C. Polymerization

$$\cdot F \text{ (or } \cdot CF_3) + \text{"dienes"} + n(:CF_2) + mCF_3CF{=}CF_2 \longrightarrow \text{liquid fluorocarbon polymers (containing terminal and internal } -C{=}C-)$$

[a] Identified; see text. [b] Alkanes from methane to hexane were individually identified. [c] Dresdner, *et al.*, described the formation of $(CF_3)_2CFCF(CF_3)_2$ by radicals coupling: R. D. Dresdner, F. N. Tlumac, and J. A. Young, *J. Amer. Chem. Soc.*, **82**, 5831 (1960). [d] Isopentane, isohexane, and isoheptane were isolated and identified.

components identified. The fact that many linear alkanes were present suggested the presence of difluorocarbene ($:CF_2$). The large number of branched alkanes found also indicated the presence of the isopropyl radicals, which could easily be formed from the fluorine radicals and the C_3F_6 molecules. The larger amounts of branched alkanes (Table II) further indicated the abundance of the isopropyl radicals and thus of the fluorine radicals in the discharge system.

Dienes have not been identified among the gaseous and low-boiling fractions of the discharge products; however, their presence as intermediates in the discharge system is considered possible. The following groups were identified by ^{19}F nmr in the liquid fluorocarbon: $CF_3\dot{C}=$, $(CF_3)_2C=$, $CF_3CF=$, $CF_2=CF-$, $-CF=C(CF_3)-$, $-CF=CF-$, CF_3CF_2-, $(CF_3)_2CF-$, and $CF_3\dot{C}F-$. Many of these olefinic groups could result from 1,2 or 1,4 radical addition to the appropriate diene. Perfluorobutadiene is "polymerized" readily to a viscous liquid under similar discharge conditions.[19] The absence of 1,3-dienes among the identified components is probably due to their much greater reactivity in the discharge system.

Alkanes are not necessarily the ultimate product of the present discharge process. Perfluoropropane[19] gives a small amount of liquid fluorocarbon after several hours of discharge under the same electrical conditions

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used to synthesize the liquid fluorocarbon. This experiment, as well as previous work,[2,4] indicates that alkanes are much more stable than olefins under discharge conditions. Nevertheless if alkanes remain in the discharge zone, further dissociation of carbon–carbon and carbon–fluorine bonds are likely to occur.

Some of the groups identified in the liquid fluorocarbon may also be explained by an ionic mechanism, especially the branched unsaturated olefinic groups. However, none of the products is unequivocally the product of an ionic mechanism, as indicated by the absence of the dimers and trimers of C_3F_6 prepared by the ionic method.[8] There is a possibility that both the ionic and the radical mechanisms could exist in an electrical discharge process and that one could be made to predominate over the other by changing monomer pressure, temperature, and electrical conditions. The present study, however, seems to indicate that higher monomer pressures favor the radical mechanism.

Experimental Section

The Electrical Discharge Cell.—The electrical discharge cell used was similar to a Siemens ozonizer and has been described in the literature.[2,6] Typical reactions were carried out as follows. The glassware was dried and assembled, then evacuated and refilled two times with N_2 and then with C_3F_6. Hexafluoropropene was led into the evacuated assembly at the desired pressure. High-voltage electrical power was applied to the reactor. Within minutes, oil droplets streamed down the reactor wall were collected in the receiver. The yield was quantitative; *i.e.*, the loss of monomer weight from the tank was the same as the weight of the product.

To collect the dissolved gaseous components, a small, evacuated trap kept closed during the discharge process was placed between the pump and the discharge cell. At the end of the reaction, the C_3F_6 supply valve was closed. The trap cooled in liquid N_2 was opened to the system. Gaseous components were collected for analyses before the system was opened to air.

Spectra.—Proton and ^{19}F nmr data were obtained with Varian DP-60 high-resolution nmr spectrometer. Gas chromatographic data were obtained with a Nester–Faust preparatory gas chromatograph. The analytical columns (0.25 in. × 24 ft) were packed with silicone stationary phases, either SF96 on Chromosorb P or UCW98 on Chromosorb G. Infrared spectra were run on a Beckman IR-2 spectrophotometer. Mass spectrograms were obtained using a Bendix time-of-flight mass spectrometer.

Materials.—Perfluoropropene (Thiokol Chemical Corp.) and trifluoroethanol (Pennsalt Chemical Corp.) were of 99+% purity. Elemental fluorine and bromine trifluoride were from Matheson Scientific, Inc., and were used without further purification.

Reaction of Liquid Fluorocarbon with Trifluoroethanol.—Liquid fluorocarbon (80 g) was dropped slowly into a solution of CF_3CH_2OH (160 g) and KOH (10 g) at 50°. The reaction was slightly exothermic. After 5 hr at 50°, the solution was distilled. The distillate contained two immiscible, colorless liquids: the top layer (CF_3CH_2OH) and the lower layer (36 g, fraction a). The residue also contained two liquid layers and solid inorganic salts. The salts were identified as KF and K_2CO_3. The yellow lower layer (44 g, fraction b) was the alcohol reaction product. The brown, alcoholic upper layer was poured into 5% sulfuric acid and a small amount of pale yellow liquid (3 g, fraction c) was precipitated.

Fraction a.—The major components in this fraction were saturated perfluorocarbons. Proton nmr gave no signal, indicating the absence of CH groups. The infrared spectrum showed no absorption at 2750–3500 and 1450–2000 cm^{-1}, indicating the absence of both CH and C=C, respectively. ^{19}F nmr, however, indicated the presence of a small amount of unsaturation owing to $(CF_3)_2C=$ and $CF_3C=$ groups. This discrepancy is common in the analyses of fluoro olefins, especially olefins having internal trans unsaturation.[8] The density of fraction a at 20° was 1.855. Ninety-five per cent of the liquid boiled at 93–108° and 5% boiled above 180°.

Fraction b.—The major components in this fraction were the ethers of fluoro olefins.[9,10] Typical CH absorption at 2850–2950 cm^{-1} and strong C=C absorption at 1650 cm^{-1} were observed in the ir. Some of these unsaturated ethers were the result of multiple substitution by alkoxide groups.

Fraction c.—A minor component (2–5%) was also obtained by reacting the liquid fluorocarbon with 8% aqueous KOH solution. Its neutralization equivalent varied from 350 to 800. A broad absorption at 2750–3500 cm^{-1} (hydroxy) and a sharp absorption at 1725 cm^{-1} (carbonyl) indicated a carboxylic acid structure. The surface tension of an aqueous solution (0.025%) of the potassium salt of fraction c was 24.4 dynes/cm^2.

Fluorination of Liquid Fluorocarbon with F_2.—Fluorination with elemental F_2 was done in a barricaded cell with a protective window and remotely controlled valves.[20] For room-temperature fluorination, a dried glass reactor equipped with a condenser was used. For high-temperature fluorination, a stainless steel or monel cylinder heated by a remotely controlled thermal tape was used instead. A bubbler with Kel-F oil was attached to the exit side of the condenser to measure the gas flow. Occasional accumulation of F_2 in the system often resulted in flame or even explosion.

Liquid fluorocarbon (200 g) was placed in a 500-cc flask. Nitrogen was passed through the system for 30 min, then F_2 was added slowly to the N_2 stream. There was usually a noticeable exotherm which could be controlled by the F_2 flow rate. After fluorination with N_2–F_2 (1:1) for 2 hr, the amount of F_2 in the gas mixture was increased slowly by gradually turning off the N_2. The exotherm still had to be watched closely to prevent flaming or explosion. Fluorination took about 20 hr, and the system was then purged with nitrogen for 1 hr before being opened to air. The yield was 190.5 g. About 98% of the unsaturation in the infrared spectrum had been removed; however, a small amount of unsaturation persisted. Also a new peak at 5.3 μ appeared at the beginning of the fluorination period and remained at the same intensity until the end of the process.

Fluorination at higher temperature (120–180°) in a stainless steel cylinder shortened the time required for saturation of double bonds, but also resulted in some carbon–carbon bond cleavage. It was more difficult to control the exothermic reaction at higher temperature. Often carbonaceous materials were carried into the Kel-F bubbler. For fluorination of the liquid fluorocarbon, high temperatures did not offer appreciable advantage.

Vapor-Phase Chlorination.[14]—Liquid fluorocarbon (150 g) was placed in a flask connected to a gas inlet and a hot tube packed with 0.25 in. Berl Saddles. The temperature of the hot tube was automatically controlled at 250°. Chlorine gas was bubbled through the liquid fluorocarbon maintained at 100°. The product was collected in a cooled receiver at the other end of the heated tube and weighed 93 g. It contained 14% Cl. The infrared spectrum indicated that a substantial amount of unsaturation still remained.

Reaction of Liquid Fluorocarbon with BrF_3 in Br_2.—The liquid fluorocarbon (300 g) was dropped into a solution containing BrF_3 (38 g) and Br_2 (77 g) during 45 min. The reaction was mildly exothermic. After 1 hr, the temperature dropped from 45 to 25°. The brown solution was washed with 10% $NaHSO_3$ and water and dried over $MgSO_4$. The yield was 291 g. The resulting fluorocarbon liquid contained 6.6% Br. The infrared spectrum indicated reduction of the unsaturation peak at 5.8 μ, but a new peak at 5.35 μ was introduced.

Registry No.—Hexafluoropropene, 116-15-4.

Acknowledgments.—The authors are indebted to Dr. J. D. Readio for the instrumental analyses, Mr. E. Kutch for the synthesis of the liquid fluorocarbon, and Mr. J. Magazzu for laboratory assistance.

(20) Fluorine was handled according to the procedures described in the Matheson Gas Data Book, 4th ed, p 237, 1966.

A Nonlinear Hammett Plot. Substituent Effects in the Substitution and Elimination–Rearrangement Reactions of 1,1-Diaryl-2-bromoethenes with Potassium *t*-Butoxide in an Aprotic Solvent[1]

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Received June 17, 1969

A series of 1,1-diaryl-2-bromoethenes was synthesized and allowed to react with potassium *t*-butoxide in anhydrous diglyme at 0°. The substitution products were isolated by solvent extraction and column chromatography and identified by nuclear magnetic resonance spectrometry and elemental analysis. The elimination–rearrangement products were identified by ultraviolet spectrophotometry. The rate constants for the rearrangements step were calculated by the time-ratio method. An increase in electron-withdrawing character of the substituent caused the elimination–rearrangement reaction to proceed slower and the substitution reaction to proceed faster. None of the compounds tested underwent both reactions. The Hammett reaction constant, ρ, was found to be -1.3 for elimination–rearrangement and $+9$ for substitution. This produces a nonlinear Hammett plot which is concave. An unusually large solvent effect was noted when anhydrous *t*-butyl alcohol was added to the anhydrous diglyme. This is tentatively explained in terms of a cage of *t*-butyl alcohol molecules solvating the attacking *t*-butoxide anion, thus altering its character.

A change in the mechanism of a reaction owing to a change in the substituents on the substrate is known to affect the linearity of a Hammett plot, producing a curve which is concave.[4–6] Subtle changes in mechanism do not affect the sign of the Hammett reaction constant, ρ. Abupt changes in mechanism change the sign of ρ, yielding a minimum in the curve.[5] This last generalization was based on the mechanistic change from acyl oxygen fission to alkyl oxygen fission in the solvolysis of substituted ethyl benzoates by 99.9% sulfuric acid as the substituent increases in electron-withdrawing character.[7] Since both reactions are addition–elimination reactions, we thought that it would be desirable to have two completely different mechanisms operative to test this generalization.

The reaction of 1,1-diaryl-2-haloethenes ($Ar_2C{=}CHX$) with alkali-metal alkoxides (M^+, OR^-) leads to two entirely different products.[8–10] Rearrangement (reaction 1) proceeds by a preequilibrium proton ab-

$$Ar_2C{=}CHBr + {}^-O\text{-}t\text{-}Bu \underset{k_r}{\overset{k_f}{\rightleftharpoons}} Ar_2C{=}CBr^- + HO\text{-}t\text{-}Bu \quad (1a)$$

$$Ar_2C{=}CBr^- \xrightarrow{k_1} ArC{\equiv}CAr + Br^- \quad (1b)$$

straction producing a configurationally stable anion, followed by rearrangement of the aryl group *trans* to the bromine atom with simultaneous elimination of bromide, to produce diarylacetylene.[11,12]

Substitution (reaction 2) proceeds by addition of the alkoxide anion to the number 2 carbon followed by

$$(Ar)_2C{=}CHX + OR^- \rightleftharpoons (Ar)_2C^-{-}CH(X)OR \quad (2a)$$

$$(Ar)_2C^-{-}CH(X)OR \longrightarrow (Ar)_2C{=}CHOR + X^- \quad (2b)$$

elimination of bromide to produce a diaryl alkyl vinyl ether.[13–18]

An examination of available data concerning substituent effects on the elimination–rearrangement[15,17–19] and our work on the substitution reactions indicates that a minimum could be obtained in the Hammett plot. The effect of substituents on the elimination–rearrangement reaction and the substitution reaction are described and the combined substituent effects are examined in terms of their effect on the Hammett plot.

Experimental Section

Syntheses. A. 1,1-Diaryl-2-bromoethenes.—These were prepared from the aryl bromides and ethyl acetate using previously described procedure.[20,21] The synthetic procedures and methods of characterization are shown in Table I.

B. 2,2-Bis(*p*-trifluoromethylphenyl)vinyl *t*-Butyl Ether.—A large excess (*ca.* 3 g) of potassium *t*-butoxide was dissolved in dry diglyme (see below) in the drybox, filtered, stoppered with a serum rubber cap, and brought into the room. *Ca.* 1 g of bis-(*p*-trifluoromethylphenyl)-2-bromoethene was dissolved in dry diglyme and injected into the potassium *t*-butoxide solution at ambient temperature. The reaction was followed roughly by taking samples with a syringe, quenching with 95% ethyl alcohol, and examining the ultraviolet spectrum. The reaction appeared to be over after 30 sec but was allowed to continue for several days.

The reaction mixture was diluted with water and extracted with carbon tetrachloride until no fluorescence was found in the CCl_4 wash. The combined CCl_4 portions were washed with water, dried over $CaSO_4$, and evaporated. Three crystallizations from pentane of the orange-red crystals obtained yielded slightly yellowish rods, mp 103.5–105°.

Proton nuclear magnetic resonance spectroscopy (Varian A-60) in carbon tetrachloride showed three sharp peaks with the expected relative areas: aliphatic, 1.49 ppm; vinyl, 6.8 ppm; aromatic, 7.35–7.51 ppm; relative areas, 9:1:8. The ultraviolet spectrum (Beckman DB) in 95% ethyl alcohol showed an absorption maximum at 297 mμ and a shoulder at 234 mμ.

(1) Taken in part from the Ph.D. dissertations of T. Thippeswamy, 1963, and D. F. Bender, 1967, University of Cincinnati, Cincinnati, Ohio.

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(3) Lowenstein-Twitchell Fellow, 1961–1962; Laws Fellow, 1962–1963.

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TABLE I

SYNTHESIS AND CHARACTERIZATION OF SYMMETRICALLY SUBSTITUTED 1,1-DIARYL-2-BROMOETHENES

Substituent	Registry no.	Ref to synthetic procedure	Characterization[a]
H	13249-58-6	*b*	Recrystn from pentane, mp 42° (lit. mp 49–50°,[c,d] 41–49° [e])
p-CH_3	7208-11-9	*f*	Recrystn from pentane and then methanol, mp 55–57° (lit. mp 55–56°,[g] 53–54° [h–j])
p-OCH_3	2132-64-1	*b*	Recrystn from ethanol and then pentane, mp 80–82° (lit.[k] mp 85°)
p-F	23349-10-2	*b, l*	Bp 138–145° (5 mm). *Anal.*[m] Calcd: C, 57.00; H, 3.07; Br, 27.07; F, 12.86. Found: C, 57.65; H, 3.09; Br, 26.51; F, 12.75
m-CH_3	23349-11-3	*f*	Bp 145–151° (2 mm) [lit.[n] bp 186–191° (10 mm)]
p-Cl	23349-12-4	*l, o*	Recrystd from ether and then pentane, mp 71–72° (lit. mp 71–73°,[g] 72° [p])
m-F	23349-13-5	*b, l*	Bp 120–125° (3 mm). *Anal.*[m] Calcd: C, 57.00; H, 3.07; Br, 27.07; F, 12.86. Found: C, 57.11; H, 3.68; Br, 27.08; F, 12.13
p-CF_3	23349-14-6	*f*	Bp 116–121° (2.5 mm). *Anal.*[m] Calcd: C, 48.63; H, 2.30; F, 28.85; Br, 20.22. Found: C, 49.01; H, 2.41; F, 27.94; Br, 20.64
m-CF_3	23349-15-7	*b*	Bp 120–125° (3 mm). *Anal.*[m] Calcd: C, 48.63; H, 2.30; F, 28.85; Br, 20.22. Found: C, 49.09; H, 2.35; F, 28.61; Br, 19.95

[a] Recrystallizations were carried out several times. [b] Reference 20. [c] E. Hepp, *Chem. Ber.*, **7**, 1410 (1874). [d] G. Wittig and R. Kethner, *ibid.*, **69**, 2078 (1936). [e] P. Lipp, *ibid.*, **56**, 567 (1923). [f] Reference 21. [g] D. Y. Curtin and E. W. Flynn, *J. Amer. Chem. Soc.*, **81**, 4714 (1959). [h] F. Bergmann, S. Israelashvili, and D. Gottlieb, *J. Chem. Soc.*, 2522 (1952). [i] O. Fischer and L. Castner, *J. Prakt. Chem.*, **282**, 280 (1910). [j] R. Anschütz and A. Hilbert, *Chem. Ber.*, **57**, 1697 (1924). [k] E. E. Harris and G. B. Frankforter, *J. Amer. Chem. Soc.*, **48**, 3144 (1926). [l] Bromination–dehydrobromination carried out in CS_2. [m] Analysis performed by Mikroanalytisches Laboratorium, Stablistrasse 25, Brugg, Switzerland. [n] G. H. Coleman, W. H. Holst, and R. D. Maxwell, *J. Amer. Chem. Soc.*, **58**, 2310 (1936). [o] Prepared from reaction of 4,4′-dichlorobenzophenone with methylmagnesium iodide, dehydrated to 1,1-bis(*p*-chlorophenyl)ethenes by refluxing in 20% H_2SO_4. [p] W. Tadros, A. B. Sakla, and Y. Akhcokh, *J. Chem. Soc.*, 2701 (1956).

Anal.[22] Calcd: C, 61.85; H, 4.67; F, 29.35. Found: C 61.69; H, 4.80; F, 29.61.

C. 1,1-Bis-(*m*-trifluoromethylphenyl)vinyl *t*-Butyl Ether.—This compound was prepared as above except that the crude product was chromatographed on a neutral aluminum oxide column with pentane. An impure liquid was obtained which absorbed at 271 mμ. Its nuclear magnetic resonance spectrum showed sharp peaks at 1.25, 6.65, and 7.27–7.48 ppm with approximate area ratios of 9:1:8 in addition to smaller aliphatic and aromatic peaks owing to impurities. The presence of impurities which could not be separated cast a shadow on the significance of elemental analyses and of molar absorptivity determination for the kinetic determinations. The molar absorptivity was therefore calculated from the infinity kinetic readings, as described below.

Bis-(*m*-fluorophenyl)acetylene.—Reaction conditions like those for the *p*-trifluoromethyl isomer were employed. The crude product was chromatographed on silica gel with pentane. Evaporation of the first 200-ml fraction gave white crystals which melted at 55.5–58°. The nuclear magnetic resonance spectrum showed only highly split aromatic protons. The ultraviolet spectrum was characteristic of a diarylacetylene with maxima at 299, 290, 271, and 263 mμ.

Reagents. A. Diglyme (diethylene glycol dimethyl ether, Ansul ether 141) was twice refluxed over sodium and distilled under nitrogen into dried, 500-ml, round-bottomed flasks in *ca.* 300-ml aliquots. The flasks were immediately stoppered with serum rubber caps which were then fastened with copper wire and transferred into a dry box containing an argon atmosphere.

B. *t*-Butyl alcohol was distilled into a 100-ml, round-bottomed flask which was immediately stoppered with a serum rubber cap. Potassium *t*-butoxide was added *ca.* 10 min before use and the flask was restoppered and swirled to ensure dryness. In later experiments the *t*-butyl alcohol was distilled from a solution of potassium *t*-butoxide in *t*-butyl alcohol to ensure dryness of the solvent and eliminate the possibility of the presence of hydroxide ions; no difference in the reproducibility of previous kinetic constants was obtained.

C. Preparation of Potassium *t*-Butoxide Solution.—Scoops of solid potassium *t*-butoxide (M.S.A. Research Corp., Evans City, Pa.) on a spatula, depending upon the base concentration range desired, were placed in a 250-ml, round-bottomed flask, and *ca.* 150 ml of diglyme was added. The glass-stoppered flask was swirled and then allowed to sit for *ca.* 10 min. The solution was then filtered under vacuum through glass wool and filter paper, transferred to another 250-ml, round-bottomed flask, and stoppered with a serum rubber cap for transfer into the room. Some nitrogen was introduced through a 20-gauge needle to produce a positive pressure in the base flask and thereby allow withdrawal of the necessary volume of base. The solution was then incubated at 0° for 30 min, and 5-ml portions were withdrawn with a syringe and placed in 25-ml volumetric flasks containing water for determination of the base concentration.

D. Standardization of Potassium *t*-Butoxide Solution.—The base solution was titrated conductometrically with standard hydrochloric acid.

E. Preparation of 1,1-Diaryl-2-bromoethene Solution.—A 100-ml stock solution (10^{-3} *M*) of each bromodiarylethene was prepared with diglyme. (Rigorously maintained anhydrous conditions were used throughout.) Exactly 20 ml of a solution was prepared by diluting *ca.* 2 ml of stock solution to 28 ml. The 20-ml solution was thermostated in the reaction flask for 30 min. The zero time absorbance was obtained by diluting 5 ml of the remaining 8 ml with 5 ml of diglyme followed by a 1:10 dilution with 95% alcohol.

Kinetics. A. Kinetic Procedure and Aliquot Sampling.—Exactly 20 ml of thermostated base solution was added to the bromoethene solution (see above). *Ca.* 1-ml aliquots were withdrawn and diluted to 10 ml with 95% alcohol. Absorbances were determined at two wavelengths on a Beckman DU spectrophotometer. (Since the *ratio* of absorption measurements was used, extremely accurate aliquots were not needed.) The final absorbances were constant for at least 24 hr (a successive reaction has been shown to occur under other conditions[23]). *t*-Butyl alcohol (5%) was added to the stock base solution to prevent rearrangement in the case of the *m*-fluorophenyl derivative and to study the solvent effect on other derivatives.

B. Kinetic Procedure with Alcohol Present.—It was necessary to have *t*-butyl alcohol present to prevent rearrangement in

(22) Analysis performed by Galbraith, Laboratories, Knoxville, Tenn.

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TABLE II

KINETIC DATA FOR THE REACTION OF SYMMETRICALLY SUBSTITUTED 1,1-DIARYL-2-BROMOETHENES WITH POTASSIUM *t*-BUTOXIDE–DIGLYME

A. Substitution in Diglyme

Substituent	Substituent constant	$c_i \times 10^4$ [a]	[B], M [b]	$k_{exp}' \times 10^3$ [c]	$k_S \times 10^2$ [d]	Avg $k_S \times 10^2$	Std devn
p-Trifluoromethyl	0.551	2.02	0.055	9.5	15.9		
		3.09	0.057	7.4	12.7	13.8	1.1
		3.70	0.057	7.9	13.8		
		4.51	0.055	8.5	12.7		
m-Trifluoromethyl	0.415	3.13	0.154	4.3	2.8		
		3.13	0.154	4.3	2.8	2.9	0.1
		3.22	0.125	3.9	3.1		
		3.60	0.064	1.8	2.8		

B. Rearrangement in Diglyme

Substituent	Substituent constant	$c_i \times 10^4$	[B], M	$k_{exp} \times 10^3$ [e]	$k_R \times 10^2$ [f]	Avg $k_R \times 10^2$	Std devn
m-Fluoro	0.337	3.34	0.179	1.2	0.69		
		3.78	0.092	0.42	0.42	0.62	0.13
		4.80	0.179	1.3	0.74		

[a] c_i is the initial concentration of 1,1-diaryl-2-bromoethene in moles per liter. [b] [B], M is the potassium *t*-butoxide concentration. [c] k_{exp}' is the pseudo-first-order rate constant for the substitution reaction. [d] k_S is the second-order rate constant for substitution. [e] k_{exp} is the pseudo-first-order rate constant for the rearrangement reaction. [f] k_R is the second-order rate constant for rearrangement.

TABLE III

KINETIC DATA FOR THE REACTION OF SYMMETRICALLY SUBSTITUTED 1,1-DIARYL-2-BROMOETHENES WITH POTASSIUM *t*-BUTOXIDE IN 3% *t*-BUTYL ALCOHOL–DIGLYME

Substituent	Substituent constant	$c_i \times 10^4$ [a]	[B], M [a]	$k_{exp}' \times 10^3$ [a]	$k_S \times 10^2$ [a]	Avg $k_S \times 10^2$	Std devn
m-Fluoro	0.337	3.51	0.119	0.042	0.035		
		3.54	0.129	0.051	0.040	0.039	0.002
		3.65	0.081	0.033	0.041		
m-Trifluoromethyl	0.415	3.50	0.113	0.69	0.63		
		3.72	0.202	2.6	1.32	0.77	0.36
		4.28	0.113	0.40	0.37		

[a] See footnotes to Table II.

the case of the *m*-fluorophenyl derivative and to study the solvent effect of the alcohol with the other derivatives in order to correct the *m*-fluorophenyl value. For this purpose the distilled and stoppered *t*-butyl alcohol was further dried by adding some potassium *t*-butoxide. Since this procedure probably produced some hydroxide ions, later kinetic runs were carried out using *t*-butyl alcohol which had been distilled from a potassium *t*-butoxide–*t*-butyl alcohol solution. However, no change in the reproducibility of the results resulted. Enough of this solution to make a 5% *t*-butyl alcohol–diglyme base solution was transferred by syringe to the base solution in diglyme before the aliquot of base was withdrawn for titration.

C. Kinetic Calculations. Substitution Reaction.—The raw data obtained consisted of time readings and absorbance readings at two wavelengths, one at the absorption maximum of the starting material, which decreases with a decrease of starting material, and the other at the absorption maximum of the product, which increases with an increase of product. The wavelengths were so close together that there was some overlap; therefore, simultaneous equations were needed to find relative concentration data. There were not two separate maxima, but rather one continuously shifting maximum, so that readings were taken on the sides of this maximum, thereby contributing to scatter among the points. A discussion of this phenomenon can be found in the literature.[24]

D. Kinetic Calculations. Elimination–Rearrangement Reaction.—The appearance of the diarylacetylene was followed spectrophotometrically at the longest wavelength band (unsubstituted, 297 mμ; *p*-methyl, 303.5 mμ; *p*-methoxy, 311.5 mμ; *p*-fluoro, 295 mμ; *m*-methyl, 300.8 mμ; and *p*-chloro, 307 mμ). The kinetic calculations were based upon the time-ratio method,[25] with certain assumptions explained in the next section.

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(25) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1966, p 170 ff.

Results and Discussion

Solvent Choice.—In order to reduce the importance of the preequilibrium step (reaction 1a) in the rearrangement and to ensure that the identity of the base was known, an aprotic solvent was desired. This solvent also had to be able to dissolve the base, potassium *t*-butoxide. Investigations showed that anhydrous "diglyme" had the necessary properties.

Kinetics. Substitution Reaction.—Tables II and III contain the concentrations used and the kinetic results obtained. An examination of the data indicates that the reaction is probably overall second order, first order in 1,1-diaryl-2-bromoethene and probably first order in base in agreement with previously reported results.[13] The rate constants for *p*-CF_3 and *m*-CF_3 were obtained in anhydrous diglyme at 0°; however, for *m*-F, rearrangement occurred under these conditions. A "corrected" rate constant[26] for substitution when *m*-F was used is given.

The positive-sloped line in Figure 1 is the Hammett plot using the second-order rate constants for the sub-

(26) The preequilibrium of the rearrangement reaction was suppressed by the addition of *t*-butyl alcohol, which lead to a surprisingly large solvent effect. The correction

$$k_S(m - F) = k_S'(m - F)[k_S(m - CF_3)/k_S'(m - CF_3)]$$

was used, where k_S is the second-order rate constant for the reaction in anhydrous diglyme and k_S' is the second-order rate constant for the reaction in anhydrous diglyme containing 3% anhydrous *t*-butyl alcohol. Hydrogen bonding between the alcohol and the anion is suggested as being responsible for altering the attacking power of the anion.

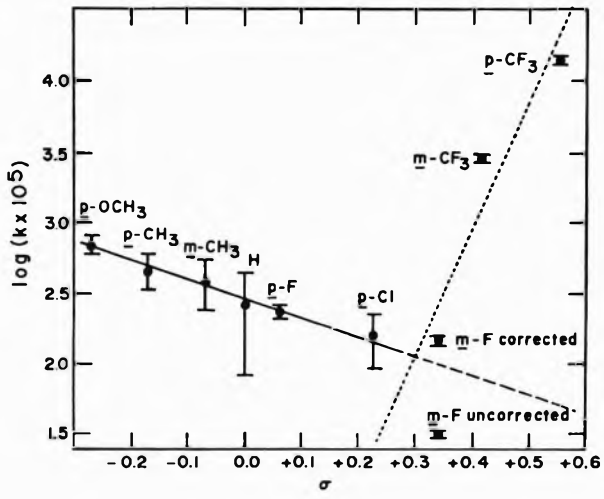

Figure 1.—Hammett plot for the elimination-rearrangement and substitution reactions of 1,1-diaryl-2-bromoethenes with potassium *t*-butoxide in dry diglyme at 0°; k is $(k_S + k_1)/(k_S^0 + k_1^0)$, as explained in the discussion.

stitution reaction of the three compounds, including the corrected and uncorrected value for the *m*-fluoro substituent. The Hammett reaction constant (ρ) is +9. A positive value was expected because electron-withdrawing groups in the *meta* or *para* position would be expected to stabilize the intermediate anion by dispersing the negative charge. The magnitude of the ρ value is interpreted as evidence that an anionic intermediate forms in the rate-determining step from a neutral substrate molecule, making the reaction sensitive to electron-withdrawing groups. Large ρ values have been obtained for aromatic nucleophilic substitution,[27,28] although of the order of +5. Even larger, though negative, values of ρ have been reported for aromatic electrophilic substitution,[29] of the order of −11. The electrophilic protonation of *para*-substituted 1,1-diarylethenes to form 1,1-diarylethyl cations yields a Hammett reaction constant value of +8 when K is plotted *vs.* σ^+. This is equilibrium data and is therefore interpreted as a measure of the stability of the cation.[30] The acid hydration of styrene, which yields a Hammett reaction constant of −4, is also an equilibrium reaction.[31] If the corrected value for the *m*-fluoro derivative were ignored, the ρ value would be in the +5 or +6 range; however, only two points would be available to obtain this value. Beltrame[23,32] has used the additive σ values in the Hammett plot for this reaction, thereby producing a ρ value which is regarded as a lower limit. Doing so would give a ρ value of *ca.* +4.5 in this case. Beltrame also points out that steric hindrance would prevent coplanarity of the aromatic moieties and the ethylenic plane for strong resonance contribution. We feel that the total effect of both moieties would be closer to the σ than to 2σ because of this steric hindrance. Therefore, the "true" value of the reaction constant, if it could be assessed, would be closer to +9 than to +4.5 with +9 itself being the upper limit.

Kinetics. Elimination–Rearrangement Reaction.—In the only previously reported example of a concave, nonlinear Hammett plot, the solvolysis of substituted ethyl benzoates, the rate-determining step involves the *breaking* of nonidentical carbon–oxygen bonds.[7] In the reaction of 1,1-diaryl-2-halogenoethenes with strong base, the rate-determining step involves the *formation* of a carbon–carbon bond *vs.* a carbon–oxygen bond while the same carbon–bromine bond breaks.[33] In this case the shape of the nonlinear Hammett plot depends upon which bond is established. In order to get the kinetic constant for the step in which the formation of the carbon–carbon bond is rate determining (eq 1b) and not have any contribution from the preequilibrium (eq 1a), we applied the time-ratio method[25] to the kinetic data obtained.

A plot of log(concentration) *vs.* time presents a typical, consecutive reaction curve. The assumption was made that the initial slope represents that time before k_r of the preequilibrium (eq 1a) becomes significant. According to this interpretation it is possible to consider the reaction as two consecutive first-order reactions and thus separate k_f of the preequilibrium (eq 1a) from k_1, the rate constant for the rearrangement step (eq 1b). However, since the initial slope changed significantly after *ca.* 30% of the starting material was consumed, and the time-ratio method involves data obtained after 15, 35, and 70% of the starting material is consumed, it was necessary to extrapolate the initial slope line. The validity of extending this line is another assumption. Since most plots of concentration *vs.* time are somewhat curved, there is error inherent in the assumption as well.

A study of the order of the reaction showed that, with a 15-fold excess of base, the reaction was pseudo-first-order. The second-order rate constant for 1,1-diphenyl-2-bromoethene at 0° held constant at 0.01 l. mol^{-1} sec^{-1} while concentrations of the enthene of 1×10^{-4}, 5×10^{-4}, and 7.5×10^{-4} mol/l. were used at constant base concentration, and while concentrations of potassium *t*-butoxide of 0.63×10^{-2}, 1.25×10^{-2}, and 3.1×10^{-2} mol/l. were used with a constant concentration of 1,1-diphenyl-2-bromoethene. The order in potassium *t*-butoxide has been reported[32] as $^3/_2$ when *t*-butyl alcohol was the solvent, rather than one, as we found with anhydrous diglyme as the solvent.

The results given in Table IV and plotted as the negative-sloped line in Figure 1 against Hammett substituent constants show a ρ of −1.3. The slope and general magnitude obtained under these conditions agree in general with the results of others,[15,17-19] as expected when one examines the electronic demands of the rate-determining step. Considerations of the nature of these electronic demands in relation to the sign of ρ have already been presented.[15,17-19]

Nonlinear Hammett Plot.—The Hammett plot for the overall reaction over a wide range of substituents can be drawn using the data shown in Tables II–IV. Figure 1 shows that a concave curve with a minimum value exists. The uncorrected point shown in the figure does not belong on the curve but was obtained

(27) J. F. Bunnett and R. F. Snipes, *J. Amer. Chem. Soc.*, **77**, 5422 (1955).
(28) A. M. Porto, L. Altieri, A. J. Castro, and J. A. Brieux, *J. Chem. Soc., B*, 963 (1966).
(29) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **79**, 1913 (1957).
(30) N. C. Deno, P. T. Groves, and G. Saines, *ibid.*, **81**, 5790 (1959).
(31) J. Durand, M. Davidson, M. Hellin, and F. Coussemant, *Bull. Soc. Chim. Fr.*, 152 (1966).
(32) P. Beltrame, D. Pitea, and M. Simonetta, *J. Chem. Soc., B*, 1108 (1967).
(33) J. G. Pritchard and A. A. Bothner-By, *J. Phys. Chem.*, **64**, 1271 (1960).

TABLE IV

KINETIC DATA FOR THE REACTION OF SYMMETRICALLY SUBSTITUTED 1,1-DIARYL-2-BROMOETHENES WITH POTASSIUM *t*-BUTOXIDE–DIGLYME[a]

Substituent	Substituent constant	[B], M[b]	$k_{exp} \times 10^3$[c]	$k_1 \times 10^3$[d]	Avg $k_1 \times 10^3$
p-Methoxy	−0.268	0.0175	9.4	8.0	
		0.0135	7.8	8.0	7.1
		0.0149	8.2	5.3	
p-Methyl	−0.170	0.0243	1.3	6.0	
		0.0197	7.5	3.1	4.6
		0.0169	6.7	3.4	
		0.0259	1.1	5.9	
m-Methyl	−0.069	0.0083	2.6	1.5	
		0.0198	5.6	5.4	3.9
		0.0165	5.0	4.8	
None	0.000	0.0310	6.6	1.6	
		0.0125	2.5	1.7	2.6
		0.0495	1.0	4.5	
p-fluoro	+0.062	0.0265	5.5	2.0	
		0.0264	4.7	2.4	2.4
p-Chloro	+0.227	0.0227	2.7	1.2	
		0.0170	2.0	1.0	1.6
		0.0255	2.1	2.6	

[a] c_i, the initial concentration of 1,1-diaryl-2-bromoethene, was 1×10^{-3} mol/l. [b] [B], M is the potassium *t*-butoxide concentration. [c] k_{exp} is the pseudo-first-order rate constant for the elimination–rearrangement reaction. [d] k_1 is the second-order rate constant for the rearrangement step of the elimination–rearrangement reaction by the time-ratio method.

as explained above and was included to illustrate where it appears in relation to the overall graph. Figure 1 is a plot of log k *vs.* σ; however, it mathematically represents a plot of log $[(k_S + k_1)/(k_S^0 + k_1^0)]$ *vs.* σ.[6] Since either k_S or k_1 is zero and k_S^0 is always zero, the two slopes of the curve represents data obtained in two slightly different ways, the time-ratio method for k_1 and simple kinetic calculations[34] for k_S, unified by the equation shown above. The substituent constant, σ, was used rather than additive σ values as Beltrame[23,32] used, for the reasons pointed out above.

By-Products of Substitution Reaction.—Chromatographic separation of the extracted material from the preparative-scale substitution reaction yielded other material having various ultraviolet absorption maxima. These by-products were present in very small amounts, and were not isolated and characterized. They could not be detected by ultraviolet spectrophotometry in the kinetic runs, nor in the preparative-scale runs until after chromatographic separation, owing to concentration effects. It was not known if these resulted from the room-temperature reaction or from subsequent reactions on the chromatographic columns. Their minute concentrations were considered to have no significant effect on the kinetics.

Color Changes.—A series of interesting color changes occurred in the preparative-scale reactions. When the clear solution of 1,1-bis-(*p*-trifluoromethylphenyl)-2-bromoethenes was added to the clear solution of potassium *t*-butoxide at ambient temperature, an immediate orange color was observed. The color rapidly became green, then so dark that it appeared to be black with a green tinge at higher concentrations. The same occurred for the bis-*m*-trifluoromethylphenyl derivative. When the bis-*m*-fluoro derivative was used to synthesize bis-(*m*-fluorophenyl)acetylene, the color change was from an immediate, short-lived orange color to red, then back to a more stable orange. These results lead to the speculation that the intermediate anion in the substitution reaction is green in anhydrous diglyme, and the intermediate anion in the rearrangement reaction is orange in anhydrous diglyme. If this proves correct, an interesting and useful "handle" may be available to determine the kinetic constants of the various steps of each reaction.

(34) A. A. Frost and R. G. Pearson, *J. Phys. Chem.*, **64**, 10 (1960).

Conclusion

The reaction of symmetrically substituted 1,1-diaryl-2-bromoethenes with potassium *t*-butoxide in anhydrous diglyme produces two different products as a function of substituents on the aromatic ring.

The overall Hammett plot obtained is nonlinear and concave with a minimum at a σ of *ca.* +0.3. This provides another example of the type of nonlinear Hammett plot expected when an abrupt change in mechanism occurs as a result of a change in the substituents on an aromatic ring in the substrate molecule.

The Hammett plot of the substitution reaction is interpreted to indicate that a carbanion intermediate forms in the rate-determining step.

The large solvent effect on the substitution reaction when *t*-butyl alcohol is present has been tentatively explained in terms of a cage of hydrogen-bonded *t*-butyl alcohol molecules around the anion which alters the character of the anion. It was assumed, for the present, that this alteration can be linearly corrected.

The fact that substitution occurs at all in aprotic solvent rules out the *necessity* of proton addition to the intermediate anion followed by elimination of HX. Previously this had been considered a *possibility* in a *t*-butyl alcohol system.[13] The suggested[13] mechanism shown in eq 2a and 2b is most likely occurring under aprotic conditions. This is probably true for the reaction in the presence of *t*-butyl alcohol as well, since the simplest, most consistent paths that are available will usually be followed despite minor changes in a reaction system.

Registry No.—*t*-Butoxide anion, 16331-65-0; bis-(*m*-fluorophenyl)acetylene, 23349-16-8; 2,2-bis(*p*-trifluoromethylphenyl)vinyl *t*-butyl ether, 23349-17-9.

Acknowledgment.—We wish to thank Professor Hans H. Jaffe for his helpful suggestions concerning the preparation of the manuscript.

Hydrogen Atom Abstraction from Substituted Diphenylmethanes by Bromine Atoms

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Received August 4, 1969

The relative reactivities of a variety of *ortho*-, *meta*-, and *para*-substituted diphenylmethanes with N-bromosuccinimide in refluxing carbon tetrachloride have been determined by competition experiments. The reactivities of diphenylmethanes bearing nucleophilic *ortho* substituents, *e.g.*, $COOC_6H_5$, NO_2, $COSC_6H_5$, $OCSC_6H_5$, and C_6H_5, are somewhat less than those of their *para* isomers, and the rate ratios for reaction of these isomeric pairs with bromine atoms are not significantly different from those of pairs in which the substituents are incapable of *ortho* participation. Possible reasons for the failure of the nucleophilic groups to function as intramolecular catalysts when located adjacent to the reaction center are discussed. On the basis of a consideration of the magnitude of the ρ value observed for bromine atom abstraction of benzylic hydrogen from *meta*- and *para*-substituted diphenylmethanes, it is suggested that the effectiveness of *ortho* substituents as participants in radical processes relates to the degree of polarization at the transition state.

This report is one of a series dealing with the influence of substrate substituents on the rate of abstraction of benzylic hydrogen by bromine atoms generated from N-bromosuccinimide.[1] The current investigation has been concerned with the influence of ring substituents on the rate of conversion of diphenylmethanes into benzhydryl bromides. The research was stimulated in part by the observation[2-5] that certain nucleophilic *ortho* substituents ($COOC_6H_5$ and NO_2) function effectively as intramolecular catalysts in solvolysis reactions of benzhydryl halides. It has seemed of interest to determine whether or not these and other potentially nucleophilic *ortho* substituents may also participate in reactions proceeding by way of benzhydryl radical (as contrasted to benzhydryl cation) type intermediates.[6] Accordingly, a number of pairs of *ortho* and *para* isomers of appropriately substituted diphenylmethanes have been included among the substrates used in the present study. The relative rates of reaction of the various substrates with N-bromosuccinimide in carbon tetrachloride have been determined by means of competition experiments. In correlating the experimental results the relative reactivities of certain *meta*- and *para*-substituted diphenylmethanes have been treated by the Hammett equation as a means of assessing the extent of polarization at the transition state of the reactions in question.

Experimental Section

Analytical Procedures.—Melting points and boiling points are uncorrected. Visible spectra were recorded on a Beckman DB instrument and infrared spectra were taken with a Perkin-Elmer Model 237B instrument. Nuclear magnetic resonance spectra were obtained using a Varian Associates Model A-60A instrument. Nmr proton chemical shifts are reported in parts per million (δ) downfield from TMS. Microanalyses were performed by Mr. V. Tashinian and Associates, Berkeley, Calif.

Materials.—Commercial samples of toluene (Eastman Organic Chemicals), ethylbenzene, anisole (Matheson Coleman and Bell), benzyl chloride (Mallinckrodt), diphenylmethane (Aldrich Chemical Co., Inc.), and N-bromosuccinimide (Arapahoe Chemicals, Inc.) were used without further purification. J. T. Baker reagent grade carbon tetrachloride was used as the reaction medium in the competition experiments.

o- and *p*-methoxydiphenylmethane were prepared in 85% yield by the reaction of *o*- and *p*-benzylphenol (Columbia Organic Chemicals), respectively, with a slight excess of dimethyl sulfate in aqueous sodium hydroxide. The usual product recovery procedures were employed[7] to obtain *o*-methoxydiphenylmethane, bp 104–105° (0.4 mm) [lit.[8] b 159–160° (12 mm)], $n^{23}D$ 1.5800, and *p*-methoxydiphenylmethane, bp 123–123.5° (1 mm) [lit.[9] bp 133–135° (4 mm)].

o-Phenylbenzophenone was prepared from 2-bromobiphenyl (K & K Laboratories) by the procedure of Bradsher.[10]

o- and *p*-benzylbiphenyl[11,12] were obtained through the Wolff–Kishner reduction of *o*- and *p*-phenylbenzophenone (*para* isomer from Eastman Organic Chemicals), respectively.

The *o*- and *p*-benzoyloxydiphenylmethane were synthesized from the corresponding *o*- and *p*-benzylphenol and benzoyl chloride as described previously.[2]

To prepare *o*-thionbenzoyloxydiphenylmethane, 6.3 g of thiobenzoyl chloride[13] was added dropwise to a solution of 7.4 g of *o*-benzylphenol in 30 ml of pyridine as the mixture was stirred. The reaction mixture was warmed on a steam bath for *ca.* 2 hr and then stirred at room temperature for an additional 12 hr. The reaction was carried out under a nitrogen atmosphere. The mixture was separated into two layers by the addition of ether and water. The ether phase was washed successively with dilute hydrochloric acid and sodium hydroxide solutions and dried over anhydrous magnesium sulfate. The ether solvent was then removed, and the residual oil was purified by alumina column chromatography. A yellow band was removed from the column by use of a 3:1 *n*-pentane–anhydrous ether mixture. On evaporation of the solvent from the eluent, an orange-yellow oil was obtained which solidified upon standing at room temperature. Recrystallization of this material from mixed hexanes yielded 4.8 g (39%) of *o*-thionbenzoyloxydiphenylmethane as yellow crystals: mp 86–88°; visible max (C_2H_5OH) 435 mμ (ϵ 116); ir (Nujol) 1270 cm^{-1} (ester C=S); nmr (CCl_4) δ 3.85 (s, 2, CH_2), 7.25(br, 12, aromatic), and 8.20 ppm (m, 2, *ortho* to C=S).

Anal. Calcd for $C_{20}H_{16}OS$: C, 78.90; H, 5.31; S, 10.53. Found: C, 78.64; H, 5.45; S, 10.44.

p-Thionbenzoyloxydiphenylmethane was prepared from 4.9 g of *p*-benzylphenol and 4.3 g of thiobenzoyl chloride by much the same procedure described for the synthesis of the *ortho* isomer.

(1) Two recent publications are (a) S. S. Friedrich, E. C. Friedrich, L. J. Andrews, and R. M. Keefer, *J. Org. Chem.*, **34**, 900 (1969); (b) I. Horman, S. S. Friedrich, R. M. Keefer, and L. J. Andrews, *ibid.*, **34**, 905 (1969).

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(3) A. D. Mease, M. J. Strauss, I. Horman, L. J. Andrews, and R. M. Keefer, *ibid.*, **90**, 1797 (1968).

(4) M. J. Strauss, L. J. Andrews, and R. M. Keefer, *ibid.*, **90**, 3473 (1968).

(5) M. J. Strauss, I. Horman, L. J. Andrews, and R. M. Keefer, *J. Org. Chem.*, **33**, 2194 (1968).

(6) The influences of neighboring groups on the rates of polar displacement processes have been subject to extensive investigation, but relatively few examples have been reported of homolytic processes which are accelerated through participation by a group adjacent to the reaction center. Notable in this connection are the decompositions of certain perbenzoates as investigated by J. C. Martin and his associates; see T. H. Fisher and J. C. Martin, *J. Amer. Chem. Soc.*, **88**, 3382 (1966), and preceding papers.

(7) A. I. Vogel, "Practical Organic Chemistry," Longmans, Green and Co., London, 1956, p 669.

(8) F. Kremers, F. Roth, and E. Tietze, *Justus Liebigs Ann. Chem.*, **442**, 239 (1925).

(9) R. C. Huston, *J. Amer. Chem. Soc.*, **46**, 2775 (1924).

(10) C. K. Bradsher, *ibid.*, **66**, 45 (1944).

(11) J. P. Freeman, *ibid.*, **80**, 1926 (1958).

(12) N. G. Rule and W. J. Hickinbottom, *J. Chem. Soc.*, 2509 (1959).

(13) H. Staudinger and J. Siegwart, *Helv. Chim. Acta*, **3**, 824 (1920).

Purification was accomplished by alumina column chromatography. Recrystallization of the crude product from *n*-hexane yielded 3.0 g (37%) of *p*-thionbenzoyloxydiphenylmethane as yellow needles: mp 67–69.5°; visible max (C_2H_5OH) 435 mμ (ε 118); ir (Nujol) 1270 cm^{-1} (ester C=S); nmr (CCl_4) δ 4.00 (s, 2, CH_2), 7.25 (br, 12, aromatic), and 8.35 ppm (m, 2, *ortho* to C=S).

Anal. Calcd for $C_{20}H_{16}OS$: C, 78.90; H, 5.31; S, 10.53. Found: C, 78.74; H, 5.43; S, 10.35.

o-Bromobenzophenone was obtained from *o*-bromobenzoyl chloride by a procedure described previously.[14]

o- and *p*-bromodiphenylmethane[15,16] were prepared by reduction of *o*- and *p*-bromobenzophenone (*para* isomer from Aldrich Chemical Co., Inc.) in a mixture of 47% hydriodic acid and red phosphorus as described elsewhere.[15]

The preparation of *o*- and *p*-benzylbenzoic acid and *o*- and *p*-carbophenoxydiphenylmethane has been described previously.[2]

To prepare *o*-thiolcarbophenoxydiphenylmethane, 8.4 g of thionyl chloride was added slowly to a solution of 13.4 g of *o*-benzylbenzoic acid[2] in 35 ml of dry pyridine. When the reaction mixture had cooled to room temperature, 7.9 g of thiophenol was added and the mixture was heated on a steam bath for 2.5 hr. Approximately 150 ml each of ether and water were added, and the ether layer was washed successively with dilute hydrochloric acid, 3 *N* sodium hydroxide, and water. The ether solution was dried ($MgSO_4$) and concentrated. The residual oil crystallized upon standing at room temperature. Recrystallization of the crude product from 110 ml of mixed hexanes provided 13.7 g (71.5%) of *o*-thiolcarbophenoxydiphenylmethane as white crystals: mp 63–64°; ir (Nujol) 1680 cm^{-1} (ester C=O); nmr (CCl_4) δ 4.19 (s, 2, CH_2), 7.29 (m, 13, aromatic), and 7.84 ppm (m, 1, *ortho* to C=O).

Anal. Calcd for $C_{20}H_{16}OS$: C, 78.90; H, 5.31; S, 10.53. Found: C, 79.17; H, 5.24; S, 10.56.

p-Thiolcarbophenoxydiphenylmethane was prepared in 65% yield from 10.8 g of *p*-benzylbenzoic acid,[2] 7.00 g of thionyl chloride, and 6.5 g of thiophenol in 40 ml of pyridine by much the same procedure described for the synthesis of the *ortho* isomer. Recrystallization of the crude product from *n*-hexane gave 10 g of white crystals: mp 84–84.5°; ir (Nujol) 1660 cm^{-1} (ester C=O); nmr (CCl_4) δ 3.97 (s, 2, CH_2), 7.24 (br, 12, aromatic), and 7.90 ppm (m, 2, *ortho* to C=O).

Anal. Calcd for $C_{20}H_{16}OS$: C, 78.90; H, 5.31; S, 10.53. Found: C, 78.79; H, 5.21; S, 10.71.

o-Nitrodiphenylmethane was prepared from *o*-nitrobenzyl bromide according to the procedure described previously,[3] bp 130–131° (0.4 mm) [lit.[3] bp 156–157° (1.3 mm)], $n^{23}D$ 1.5966.

p-Nitrodiphenylmethane[17] was synthesized by the reaction of *p*-nitrobenzyl bromide[18] with benzene in the presence of aluminum chloride.

p-Methyldiphenylmethane was prepared in 91% yield by the Wolff–Kishner reduction of *p*-methylbenzophenone (Eastman Organic Chemicals), bp 96–97° (0.9 mm) [lit.[19] bp 144° (16 mm)].

m-Methoxybenzophenone was prepared by the reaction of *m*-methoxybenzoyl chloride with benzene in the presence of anhydrous aluminum chloride, bp 142–143° (0.2 mm), mp 37–38° [lit.[20] bp 342–343° (730 mm), mp 37°].

m-Methoxydiphenylmethane[21] was obtained in low yield (19.5%) by the Wolff–Kishner reduction of *m*-methoxybenzophenone.

p-Fluorodiphenylmethane[22] and *p*-chlorodiphenylmethane[23] were prepared in *ca.* 90% yield by reduction of *p*-fluorobenzophenone (Aldrich Chemical Co., Inc.) and *p*-chlorobenzophenone (Matheson Coleman and Bell), respectively, in a mixture of red phosphorus and 47% hydriodic acid. The procedure was similar to that employed by Bradsher[15] in the synthesis of *o*-bromodiphenylmethane.

p-Carbomethoxydiphenylmethane was prepared in 91.5% yield by the sulfuric acid catalyzed reaction of *p*-benzylbenzoic acid[2] and methanol: bp 149–150° (1 mm); $n^{23}D$ 1.5746; nmr (CCl_4) δ 3.87 (s, 3, CH_3), 4.01 (s, 2, CH_2), 7.21 (br, 7, aromatic), and 7.90 ppm (m, 2, *ortho* to C=O).

Anal. Calcd for $C_{15}H_{14}O_2$: C, 79.61; H, 6.25. Found: C, 79.55; H, 6.39.

p-Cyanobenzyl bromide[24] was obtained through the light-induced reaction of equimolar quantities of N-bromosuccinimide and *p*-cyanotoluene (Eastman Organic Chemicals) in carbon tetrachloride solution. From the product of reaction of *p*-cyanobenzyl bromide and anhydrous aluminum chloride in dry benzene, *p*-cyanodiphenylmethane[25] was obtained. Alternatively, this material was isolated in 76% yield from the crude products obtained by refluxing a mixture of *p*-benzylbenzamide,[25] thionyl chloride, and dry benzene.

m-Nitrobenzyl bromide[18] was prepared through the light-induced reaction of equimolar quantities of *m*-nitrotoluene (Eastman Organic Chemicals) and N-bromosuccinimide. From products of the Friedel–Crafts reaction of 30 g of *m*-nitrobenzyl bromide and 18.5 g of anhydrous aluminum chloride in 300 ml of benzene, 18.2 g (61.5% yield) of *m*-nitrodiphenylmethane was isolated as a yellow liquid: bp 143–144° (0.5 mm); $n^{23}D$ 1.5980; nmr (CCl_4) δ 4.02 (s, 2, CH_2), 7.25 (br, 7, aromatic), and 8.95 ppm (br, 2, *ortho* to NO_2).

Anal. Calcd for $C_{13}H_{11}NO_2$: C, 73.21; H, 5.21; N, 6.57. Found: C, 73.28; H, 5.18; N, 6.79.

Competition Experiments.—The particular pair of compounds used in an individual competition reaction were chosen such that they were relatively similar in their rates of reaction with N-bromosuccinimide (NBS) and their nmr proton absorption positions were well separated. For each determination the two competing compounds were weighed into a 50-ml flask containing a weighed quantity of NBS. This mixture was diluted to *ca.* 20–25 ml with carbon tetrachloride, treated with 0.1 g of benzoyl peroxide, stirred vigorously, and heated under reflux (measured pot temperature 77°) until the brominating agent had disappeared completely from the bottom of the flask (15–30 min).

After the reactions were complete, the cooled mixtures were treated with weighed samples of an appropriate internal standard and the amounts of the unreacted starting materials and their bromides in the liquid portion of the product mixture were determined using a Varian Associates Model A-60A instrument as described elsewhere.[1a] The relative reactivities, k_A/k_B, of the competing pairs of compounds were calculated using the usual[26] integrated rate equation $k_A/k_B = \log (A_0/A_f)/\log (B_0/B_f)$, where A_0 and B_0 are the initial and A_f and B_f are the final quantities of the compounds competing for the brominating agent.

The results of the analyses of the various reaction mixtures are summarized in Table I. The quantities of the substituted diphenylmethane bromination products, ABr and BBr, were usually determined directly from the appropriate integrated proton peak areas. In some instances, and always when the bromide products did not have any benzylic or other nonaromatic protons, ABr and BBr were calculated as $(A_0 - A_f)$ and $(B_0 - B_f)$, respectively. In such cases, and also in those cases in which A_f or B_f were calculated as the difference between the amounts of starting materials and the products, the numerical values are reported in parentheses.

In most of the experiments summarized in Table I, the agreement between the amounts of bromide products formed, the amounts of competing substrates consumed, and the quantity of NBS initially present in the reaction mixture is very good. Notable among the exceptions are the results of experiments with diphenylmethanes bearing *o*-$COSC_6H_5$ and *o*-$OCSC_6H_5$ substituents.

Results

In Table II the relative reactivities of various isomeric pairs of *ortho*- and *para*-substituted diphenylmethanes with N-bromosuccinimide are compared. Included in this tabulation are *k*(*ortho*)/*k*(*para*) values for several systems in which the substituents are

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TABLE I

COMPETITIVE BROMINATIONS OF SOME SUBSTITUTED DIPHENYLMETHANES WITH N-BROMOSUCCINIMIDE (CCl_4, 77°)

$C_6H_5CH_2C_6H_4X$ (A), X	B	Registry no.	A_0, mmol	A_f, mmol	B_0, mmol	B_f, mmol	ABr, mmol	BBr, mmol	NBS,[a] mmol	k_A/k_B	$k_A/k_{toluene}$ (per H)
o-$COOC_6H_5$	(A), X = *o*-$OCOC_6H_5$	A, 23450-10-4 B, 23450-11-5	8.02	4.46	8.02	4.08	(3.56)	(3.94)	7.78	0.865	5.54[b]
o-$COOC_6H_5$	A, X = Br		6.11	2.02	5.89	2.28	(4.09)	3.56	7.64	1.17	5.40[b]
o-$COOC_6H_5$	A, X = *p*-$COOC_6H_5$	B, 23450-12-6	5.01	2.37	4.49	1.56	(2.64)	2.85	5.65	0.710	5.56[b]
p-$COOC_6H_5$	$C_6H_5CH_3$	B, 108-88-3	7.74	3.78	25.18	(21.96)	(3.96)	3.22	7.41	5.18	7.77[c]
p-$COOC_6H_5$	$C_6H_5CH_3$		8.20	4.78	32.59	(29.32)	(3.42)	3.27	6.87	5.09	7.64[c]
p-$COOC_6H_5$	$C_6H_5CH_2CH_3$[d]	B, 100-41-4	6.05	3.71	4.25	0.926	2.32	3.31	5.90	0.320	8.06[c]
o-NO_2[e]	$C_6H_5CH_3$	A, 5840-40-4	6.00	2.53	6.28	2.73	(3.47)	(3.53)	7.20	1.04	1.56[f]
o-NO_2[e]	$C_6H_5CH_3$		4.94	2.34	5.77	2.82	(2.60)	(2.95)	5.70	1.04	1.56[f]
p-NO_2	$C_6H_5CH_3$	A, 1817-77-2	7.25	2.38	6.48	4.34	4.53	(2.14)	7.36	2.78	4.17[f]
p-NO_2	$C_6H_5CH_3$		7.11	2.46	5.70	3.79	4.55	1.82	6.70	2.61	3.92[f]
o-$OCOC_6H_5$	$C_6H_5CH_3$		7.08	4.46	25.19	(22.68)	(2.62)	2.51	5.10	4.35	6.53[c]
o-$OCOC_6H_5$	$C_6H_5CH_3$		7.89	5.16	33.79	(30.51)	(2.73)	3.28	6.08	4.18	6.27[c]
p-$OCOC_6H_5$	$C_6H_5CH_3$	A, 23450-15-9	7.02	3.65	24.41	(22.89)	(3.37)	1.52	5.00	10.1	15.2[c]
p-$OCOC_6H_5$	$C_6H_5CH_3$		7.35	3.60	31.59	(29.43)	(3.75)	2.16	6.12	10.3	15.5[c]
p-$OCOC_6H_5$	$C_6H_5CH_3$		8.89	5.00	28.43	(26.89)	(3.89)	1.54	5.57	10.4	15.6[c]
p-$OCOC_6H_5$	$C_6H_5CH_2CH_3$[d]		5.97	2.91	6.21	2.05	3.08	(4.16)	7.24	0.646	16.3[c]
o-OCH_3	$C_6H_5CH_2CH_3$[d]	A, 883-90-9	4.80	2.13	4.41	1.91	(2.67)	(2.50)	5.80	0.970	24.4[c]
o-OCH_3	$C_6H_5CH_2CH_3$[d]		4.44	2.07	5.19	2.21	(2.37)	3.02	6.02	0.897	22.6[c]
o-OCH_3	$C_6H_5CH_2CH_3$[d]		3.84	1.77	4.71	1.93	(2.07)	2.70	5.40	0.866	21.8[c]
p-OCH_3	$C_6H_5CH_2CH_3$[d]	A, 834-14-0	8.19	4.03	6.79	4.23	4.14	(2.56)	7.55	1.50	37.8[c]
p-OCH_3	$C_6H_5CH_2CH_3$[d]		7.95	2.92	6.10	3.34	4.84	(2.76)	8.22	1.66	41.9[c]
p-OCH_3	$C_6H_5CH_2CH_3$[d]		7.26	2.90	5.21	3.04	4.34	2.18	6.79	1.70	42.9[c]
o-Br	$C_6H_5CH_3$	A, 23450-18-2	8.04	5.11	22.39	(19.37)	(2.93)	3.02	5.74	3.13	4.70[c]
o-Br	$C_6H_5CH_3$		15.72	8.31	30.05	(24.39)	(7.41)	5.66	13.10	3.01	4.52[c]
p-Br	$C_6H_5CH_3$	A, 2116-36-1	9.03	4.68	33.18	(30.51)	(4.35)	2.67	7.05	7.92	11.9[c]
p-Br	$C_6H_5CH_3$		9.06	4.93	42.90	(39.96)	(4.13)	2.94	7.22	8.28	12.4[c]
p-Br	$C_6H_5CH_2CH_3$[d]		6.85	3.97	5.53	1.91	2.84	3.65	6.56	0.512	12.9[c]
o-$COSC_6H_5$	$C_6H_5CH_3$	A, 23450-20-6	5.29	3.56	5.14	(3.93)	(1.73)	1.21	7.69	1.48	2.22[g]
o-$COSC_6H_5$	$C_6H_5CH_3$		4.45	2.46	5.70	(4.23)	(1.99)	1.47	7.74	1.98	2.97[g]
o-$COSC_6H_5$	$C_6H_5CH_3$		6.11	4.09	5.85	4.43	(2.02)	(1.42)	7.67	1.45	2.18[g]
o-$COSC_6H_5$	$C_6H_5CH_2CH_3$[d]		7.92	7.45	5.76	3.38	(0.47)	(2.38)	4.72	0.116	2.04[c]
p-$COSC_6H_5$	$C_6H_5CH_3$	A, 23450-21-7	7.30	4.32	34.41	(30.76)	(2.98)	3.65	6.60	4.60	6.90[c]
p-$COSC_6H_5$	$C_6H_5CH_3$		6.95	3.51	21.68	(18.81)	(3.44)	2.87	6.40	4.79	7.19[c]
p-$COSC_6H_5$	$C_6H_5CH_2CH_3$[d]		6.35	4.60	5.16	1.74	1.82	3.44	5.36	0.296	7.45[c]
o-$OCSC_6H_5$	$C_6H_5CH_2CH_3$[d]	A, 23450-22-8	3.42	2.43	3.56	1.48	(0.99)	2.02	4.84	0.388	9.78[c]
o-$OCSC_6H_5$	$C_6H_5CH_2CH_3$[d]		4.04	2.90	4.35	1.74	(1.14)	2.26	5.18	0.362	9.11[c]
p-$OCSC_6H_5$	$C_6H_5CH_3$	A, 23450-23-9	4.56	2.20	20.10	(18.50)	(2.36)	1.60	4.16	8.80	13.2[c]
p-$OCSC_6H_5$	$C_6H_5CH_2CH_3$[d]		4.65	3.03	3.34	1.53	1.64	1.79	3.93	0.546	13.8[c]
o-C_6H_5	$C_6H_5CH_3$	A, 606-97-3	6.90	2.75	29.60	(26.86)	(4.15)	2.74	6.90	9.40	14.1[c]
o-C_6H_5	$C_6H_5CH_3$		6.54	2.74	21.50	(19.55)	(3.80)	1.95	5.81	9.21	13.8[c]
o-C_6H_5	$C_6H_5CH_2CH_3$[d]		5.12	2.20	3.92	(0.97)	2.93	2.92	5.95	0.605	15.2[c]
p-C_6H_5	$C_6H_5CH_3$	A, 613-42-3	7.31	2.70	28.20	(26.71)	(4.62)	1.49	6.32	18.0	27.0[c]
p-C_6H_5	$C_6H_5CH_3$		7.24	2.72	32.65	(30.76)	(4.52)	1.89	6.63	16.3	24.5[c]
p-C_6H_5	$C_6H_5CH_2CH_3$[d]		7.31	3.04	6.34	2.65	4.24	3.78	8.16	1.01	25.4[c]
p-CH_3	$C_6H_5CH_2CH_3$[d]	A, 620-83-7	8.14	4.42	7.16	4.15	3.59[h]	(3.01)	7.44	1.11	28.0[c]
p-CH_3	$C_6H_5CH_2CH_3$[d]		6.86	3.11	5.82	2.88	3.70[h]	2.99	7.39	1.12	28.2[c]
m-OCH_3	$C_6H_5CH_2CH_3$[d]	A, 23450-27-3	5.74	2.40	5.76	1.60	3.36	4.13	7.91	0.679	17.1[c]
m-OCH_3	$C_6H_5CH_2CH_3$[d]		5.80	3.41	6.30	2.94	2.44	3.32	5.95	0.699	17.6[c]
p-F	$C_6H_5CH_2CH_3$[d]	A, 587-79-1	6.06	2.63	5.95	1.62	3.40	4.38	8.04	0.642	16.2[c]
p-F	$C_6H_5CH_2CH_3$[d]		7.32	4.90	6.60	3.46	2.45	3.19	5.79	0.621	15.7[c]
p-Cl	$C_6H_5CH_2CH_3$[d]	A, 831-81-2	9.26	5.36	7.21	2.48	3.81	(4.73)	8.96	0.514	12.9[c]
p-Cl	$C_6H_5CH_2CH_3$[d]		8.00	4.61	7.40	2.63	3.33	4.74	8.25	0.532	13.4[c]
p-$COOCH_3$	$C_6H_5CH_2CH_3$[d]	A, 23450-30-8	6.89	4.50	4.85	1.31	2.29	3.43	5.97	0.324	8.17[c]
p-$COOCH_3$	$C_6H_5CH_2CH_3$[d]		7.04	5.03	4.31	1.54	2.10	(2.77)	4.99	0.326	8.21[c]
p-CN	$C_6H_5CH_3$	A, 23450-31-9	7.02	2.18	5.35	3.71	4.79	1.60	6.62	3.30	4.95[f]
p-CN	$C_6H_5CH_3$		7.71	2.24	5.15	3.57	5.49	(1.58)	7.41	3.38	5.07[f]
m-NO_2	$C_6H_5CH_3$	A, 5840-41-5	7.30	2.41	6.24	3.94	4.93	(2.30)	7.55	2.41	3.62[f]
m-NO_2	$C_6H_5CH_3$		7.35	2.41	5.66	3.61	4.90	(2.05)	7.30	2.47	3.71[f]

[a] Initial N-bromosuccinimide. [b] Internal standard is ethylbenzene. [c] Internal standard is benzyl chloride. [d] $k_{ethylbenzene}/k_{toluene}$ per hydrogen is 25.2 (see ref 1a). [e] The competition reaction was conducted under irradiation with a 750-W projection lamp. [f] Internal standard is anisole. [g] Internal standard is diphenylmethane. [h] ABr is the quantity of *p*-methylbenzhydryl bromide produced. A small amount (0.48 mmol) of $C_6H_5CH_2C_6H_4CH_2Br$ is also formed as a result of some bromination at the *p*-CH_3 substituent.

functionally incapable of serving as internal nucleophiles when located *ortho* to the reaction center. In this category are the diphenylmethanes with substituents such as Br, $OCOC_6H_5$,[27] and OCH_3, for which $k(ortho)/k(para)$ values vary from 0.37 to 0.56. That is, when participation cannot occur the *ortho* isomer is somewhat less reactive than the *para*. This is presumed to be a reflection of steric hindrance by the *ortho* substituent to the approach of a bromine atom in the abstraction of a hydrogen atom at the reaction center. Values of $k(ortho)/k(para)$ somewhat less than unity are also observed in those cases in which the substituents are NO_2, $COOC_6H_5$, C_6H_5, $OCSC_6H_5$, and $COSC_6H_5$. The observation that in these cases the *ortho* isomers are not substantially more reactive than the *para* is taken as evidence that nucleophilic groups located *ortho* to the methylene group of a diphenylmethane do not, in fact, facilitate hydrogen abstraction.

A possible explanation for the lack of *o*-$COOC_6H_5$ involvement in this process is based on a consideration of the capacity of the carbonyl oxygen of that substituent to release electrons to the reaction center at the transition state. For purposes of simplification, it is assumed that an organic radical (I) is fully developed at this phase of the reaction and that the two rings of that radical lie perpendicular to each other;

(27) Although this substituent is potentially nucleophilic in character, it does not so function in the solvolysis of *o*-benzoyloxybenzhydryl bromide.[2]

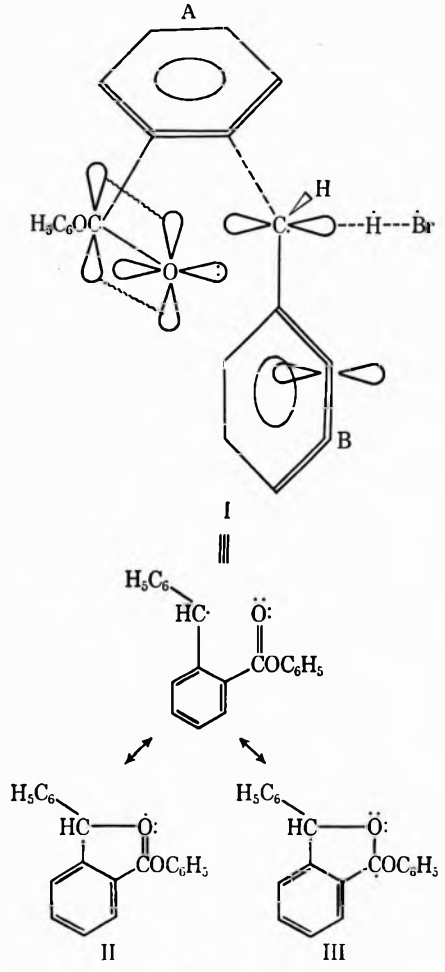
TABLE II

RATES RELATIVE TO TOLUENE FOR THE REACTIONS OF SUBSTITUTED DIPHENYLMETHANES WITH N-BROMOSUCCINIMIDE

$C_6H_5CH_2C_6H_4X$, X	$kX/k_{toluene}$ (per H), CCl_4, 77°	$k(ortho)/k(para)$	$C_6H_5CH_2C_6H_4X$, X	$kX/k_{toluene}$ (per H), CCl_4, 77°	$k(ortho)/k(para)$
o-OCH_3	22.9	0.56	*o*-Br	4.61	0.37
p-OCH_3	40.9		*p*-Br	12.4	
o-C_6H_5	14.4	0.56	*o*-$COOC_6H_5$	5.50	0.70
p-C_6H_5	25.6		*p*-$COOC_6H_5$	7.82	
o-$OCOC_6H_5$	6.40	0.41	*o*-$COSC_6H_5$	2.35	0.33
p-$OCOC_6H_5$	15.7		*p*-$COSC_6H_5$	7.18	
o-$OCSC_6H_5$	9.45	0.70	*o*-NO_2	1.56	0.39
p-$OCSC_6H_5$	13.9		*p*-NO_2	4.05	
p-CH_3	28.1		*p*-Cl	13.2	
H	17.6[a]		*p*-$COOCH_3$	8.19	
m-OCH_3	17.4		*p*-CN	5.01	
p-F	16.0		*m*-NO_2	3.67	

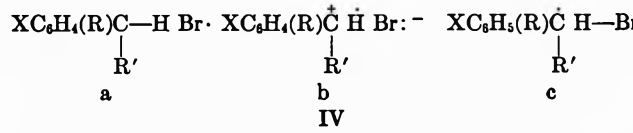
[a] Reference 1a.

the reasons for the latter assumption are much the same as those presented in the earlier discussion of *o*-carbophenoxy participation in the formation of a diphenylmethyl cation.[2] It is highly unlikely that the nonbonding electrons of carbonyl oxygen are involved in stabilization of the radical. This would lead to an energetically unfavorable electronic arrangement (II), since oxygen does not have low-energy d orbitals to provide for accommodation of nine electrons in its valence shell. Participation by ether oxygen of the carbophenoxy group can be ruled out on the same grounds. For effective involvement of the π electrons of the carbonyl group (III), the π orbital must be rotated through an angle of *ca.* 90° (so that it overlaps the partially filled orbital at the reaction center). This also may be energetically unlikely, since it is accomplished with the sacrifice of conjugation of the carbonyl group with ring A. Much the same argument can be advanced in accounting for the lack of evidence for acceleration by the ring substituent in the radical bromination of *o*-nitrodiphenylmethane.



The thionbenzoyloxydiphenylmethanes ($C_6H_5CH_2C_6H_4OCSC_6H_5$) and thiolcarbophenoxydiphenylmethanes ($C_6H_5CH_2C_6H_4COSC_6H_5$) have been included in this study on the premise that, unlike oxygen, sulfur can readily expand its valence shell to accomodate more than eight electrons and that the reactions of the *ortho* isomers might, therefore, be subject to intramolecular catalysis. Although the outcome is negative in both instances, it should be noted that neighboring-group participation in which the sulfur of the *o*-phenylthio group is involved has been reported to occur in the free-radical decomposition of *t*-butyl *o*-(phenylthio)-perbenzoate.[6]

Application of the Hammett ρ–σ Correlation.—The structure at the transition state (IV) for bromine atom abstraction of benzylic hydrogen is considered to receive contribution from a, b, and c.[28] In situations in which b makes a significant contribution to structure,



separation of a hydrogen atom at the reaction center must have proceeded to a considerable degree.[29] Under such circumstances ρ values obtained in a Hammett correlation of relative substrate reactivities with substituent constants (σ or σ^+) for groups X should be substantially negative. The ρ value of -1.38 reported for the reactions of ring-substituted toluenes[26]

(28) See ref 1a for a discussion and pertinent references.

(29) G. A. Russell and R. C. Williamson, Jr., *J. Amer. Chem. Soc.*, **86**, 2357 (1964).

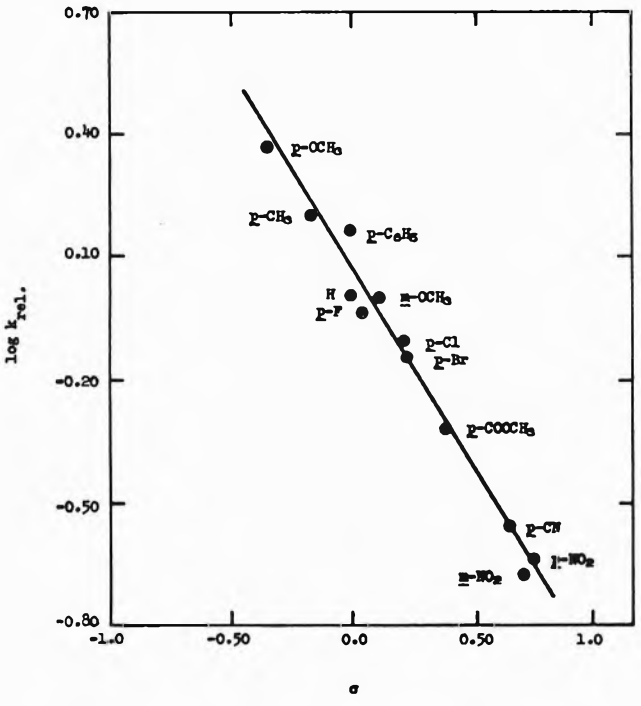


Figure 1.—Logarithms of rates, relative to that for diphenylmethane, for the reactions of $C_6H_5CH_2C_6H_4X$ with N-bromosuccinimide (CCl_4, 77°) *vs.* σ values for the substituents X.

with bromine atoms has been explained in these terms.[29] Presumably there is relatively little C–H rupture at the transition state for benzylic bromination of the more reactive cumenes[30] ($k_{C_6H_5CH(CH_3)_2}/k_{C_6H_5CH_3}$ = 57.5)[1a] and the highly reactive benzyl methyl ethers[31] ($k_{C_6H_5CH_2OCH_3}/k_{C_6H_5CH_3}$ = 159).[1a] For these processes the ρ values are small (−0.38 and −0.35, respectively). Ethylbenzenes ($k_{C_6H_5CH_2CH_3}/k_{C_6H_5CH_3}$ = 25.2)[1a] and allylbenzenes ($k_{C_6H_5CH_2CH=CH_2}/k_{C_6H_5CH_3}$ = 26.2)[32] which are of intermeidate reactivity exhibit ρ values of intermediate magnitude (−0.69[33] and −0.76,[32] respectively).[34]

(30) G. J. Gleicher, *J. Org. Chem.*, **33**, 332 (1968).
(31) R. L. Huang and K. H. Lee, *J. Chem. Soc.*, 5963 (1964).
(32) M. M. Martin and G. J. Gleicher, *J. Org. Chem.*, **28**, 3266 (1963).
(33) R. L. Huang and K. H. Lee, *J. Chem. Soc., C*, 935 (1966).

A plot of average values (Table II) of log $k_{C_6H_5CH_2C_6H_4X}/k_{diphenylmethane}$ (log k_{rel}) *vs.* σ is presented in Figure 1.[35] In this case the observed ρ value is −0.97 (correlation coefficient r = 0.990 and standard deviation s = 0.044). The corresponding plot when σ^+ values are used has a slope (ρ) of −0.72 (r = 0.973 and s = 0.054). This ρ value (−0.97) for the reaction of diphenylmethanes lies between those for the reactions of substituted toluenes and ethylbenzenes with bromine atoms. Correspondingly, diphenylmethane lies between toluene and ethylbenzene in reactivity ($k_{C_6H_5CH_2C_6H_5}/k_{C_6H_5CH_3}$ = 17.6).[1a]

For benzhydryl chloride alcoholysis, in which the degree of polarization at the transition state is unquestionably high, ρ is of the order of −4 (as based on correlation with σ^+).[36] Compared with benzhydryl halide solvolysis, the reaction of substituted diphenylmethanes toward bromine atoms is accompanied by a relatively low degree of polarization during activation. Conceivably extensive polarization is an essential feature of processes in which nucleophilic *ortho* substituents have a noticeably favorable effect on reactivity. In this connection it should be recalled that there is strong evidence that at the transition state for the *o*-phenylthio-assisted thermal decomposition of *t*-butyl (*o*-phenylthio)perbenzoate significantly polar structural character has developed.[37]

Registry No.—N-Bromosuccinimide, 128-08-5.

Acknowledgment.—The authors are indebted to the National Science Foundation for a grant in support of this research.

(34) For earlier discussion of the relationships between the relative reactivities of various benzyl systems, their Hammett reaction constants, and the degree of bond breaking at the transition state in processes involving bromine atoms, see ref 30 and 33.
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Charge-Transfer Interaction between Tetracyanoethylene and Pyridines[1]

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Received August 14, 1969

The absorption peak at 400 nm sometimes attributed to charge-transfer complexes between tetracyanoethylene (TCNE) and pyridines is in fact caused by the pentacyanopropenide ion. Broad bands which are formed in the region of 340–350 nm when TCNE reacts with pyridine, 4-picoline, 3,4-lutidine, and 3,5-lutidine are now attributed to charge transfer. The bands become distorted and overshadowed in time by absorption owing to formation of the pentacyanopropenide ion and also of the TCNE anion radical. Charge transfer between TCNE and 2-picoline and TCNE and 2,6-lutidine could not be detected. The indications are that charge transfer is of the n–π type.

Tetracyanoethylene (TCNE) forms charge-transfer complexes with aromatic π donors, and this type of interaction has been extensively studied.[3–5] Comparatively little work, however, has been reported on TCNE complexes with n-electron donors. In many of the systems using n-electron donors that have been studied, the presence of the TCNE anion radical has been detected by electron spin resonance and optical spectroscopy. In most of these instances, radical formation was attributed to dissociation of the charge-transfer complex with complete one-electron transfer.[6,7] Very few workers, however, have shown conclusive evidence for the presence of the corresponding cation radical, necessarily formed by this dissociation. In studies of complexes between TCNE and heteroatomic donors by spectrophotometric methods, most workers report reactions which make complex detection difficult.

Pyridine, which may conceivably act either as an n- or π-electron donor, was first treated with TCNE by Merrifield and Phillips[8] in 1958. The optical spectrum obtained by these workers showed a doublet at 400 and 421.5 nm which was attributed to the formation of a complex. A Benesi–Hildebrand-type plot of absorbance data for these maxima gave an equilibrium constant of 12.0 for the complex.

Also in 1958, Middleton and coworkers[9] published their results on the reaction of TCNE with aqueous pyridine. They observed the formation of pyridinium 1,1,2,3,3-pentacyanopropenide in 81% yield. The reaction was not unique to pyridine, and basic hydrolysis of TCNE produced similar salts with several bases studied. Hydrolysis in neutral or acidic solution, however, produced only tricyanoethenol, which was isolated as the tetramethylammonium salt.

The optical spectrum of the pentacyanopropenide ion in water showed a doublet at 393 and 412 nm.[9] The tricyanoethenolate ion exhibited a single band at 297 nm.[10]

Nepras and Zahradnik[11] studied the reaction of TCNE with pyridine and a series of nitrogen heteroaromatic donors. These authors stated that the TCNE–pyridine systems yielded a yellow color, erroneously attributed by Merrifield and Phillips to the charge-transfer complex, but Nepras and Zahradnik did not identify the species responsible for the color. The reaction with pyridine was so rapid that no complex could be detected.

In an esr investigation, Pen'kovskii[12] detected the presence of the TCNE anion radical when TCNE was dissolved in pyridine. Pen'kovskii attributed this radical-anion formation to one-electron transfer from pyridine to TCNE.

Farcasiu and Nicolau[13] have carried out a spectrophotometric study of the molecular complexes formed from TCNE and substituted pyridines in chloroform. Their donor series included pyridine, 2-picoline, 3-picoline, 4-picoline, 2,6-lutidine, and 2,4,6-collidine. The λ_{max} for each complex was chosen as the 400-nm peak of a doublet, and equilibrium constants were calculated from absorbances at this wavelength.

Middleton observed that the pentacyanopropenide ion is formed in the reaction of TCNE with aqueous pyridine, and that this ion absorbs at 393 and 412 nm.[9] Therefore, it is probable that the reported complexes of TCNE with pyridine and its derivatives[8,13] were only observations of the formation of the pentacyanopropenide ion.

The present paper describes what we consider to be charge-transfer bands between TCNE and pyridine and TCNE and some methylpyridines.

In an attempt to determine the scource of the TCNE anion radical which is present in these systems, the reduction of TCNE was also investigated.

Water reacts with the TCNE anion radical to form the tricyanoethenolate ion[14] and with TCNE, in the presence of a base, to form the pentacyanopropenide ion.[9] The TCNE anion radical also reacts with oxygen to produce both pentacyanopropenide and tricyanoethenolate ions.[14] To minimize the interference of these reaction products with complex formation, the

(1) (a) Taken from the M.S. Thesis of R. D. Goodin, Texas Technological College, June 1969; (b) presented at the 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969; (c) we thank the Directorate of Chemical Sciences, AFOSR, for partial support under Grant AF-AFOSR-69-1635.

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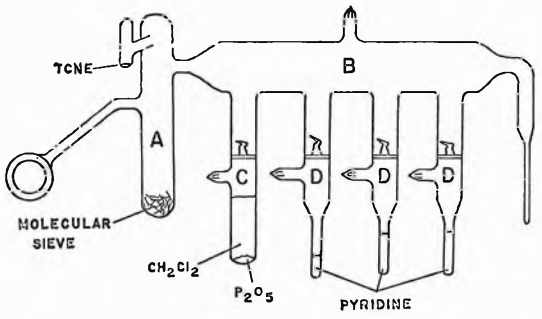

Figure 1.—Apparatus for the detection of charge transfer between TCNE and pyridine donors.

reactions were carried out in a sealed vacuum system under anhydrous conditions.

Experimental Section

Materials.—TCNE (Aldrich Chemical Co.) was crystallized from 1,2-dichloroethane[15] and sublimed under vacuum at 90°. The product was stable for months in a stoppered vial. Pyridine (Matheson, analyzed reagent grade) and the methylpyridines (Aldrich) were refluxed over calcium hydride for several hours, fractionally distilled from the hydride, and stored over fresh calcium hydride until used. Methylene chloride was refluxed over phosphorus pentoxide, distilled from the pentoxide, and stored in a septum-capped flask, from which it was withdrawn by syringe as needed.

Pyridinium 1,1,2,3,3-pentacyanopropenide and tetramethylammonium tricyanoethenolate were prepared by Middleton's procedures.[9] These salts were used for characterizing the anions spectroscopically.

Potassium Tetracyanoethylenide.[16]—Potassium cyanide was crystallized from water–ethanol to remove carbonate and dried in a pistol at 95° for 2 hr before use. Acetonitrile was Distillation Products anhydrous, septum-capped grade. A vacuum-line apparatus was constructed consisting of three chambers, one of which was separated from the other two by a sintered-glass disk. Potassium cyanide (2.65 g), some Linde 3A Molecular Sieve, and 50 ml of acetonitrile were placed in the first chamber. TCNE (5.1 g) was placed in the second chamber. The apparatus was connected to the high vacuum line and the acetonitrile was degassed by freeze–thaw cycles. The apparatus was sealed under vacuum with a torch. The suspension of potassium cyanide in acetonitrile was cooled to −5° and poured onto the TCNE. The solution bubbled violently and became very dark. After it had been stirred magnetically for 2 hr the solution was filtered through the sinter into the third chamber. A bronze solid precipitated overnight. The covering liquid was poured back through the sinter into the second chamber. The solid in the third chamber was washed several times by distilling fresh solvent from, and pouring it back into, the second chamber. Finally, the second chamber was frozen in liquid nitrogen, thus drying the solid in the third chamber. The third chamber was opened and the solid product was bottled under dry helium. The visible and infrared spectra agreed well with those in the literature.[12]

Charge-Transfer Spectroscopy.—The reactants were manipulated under vacuum in the apparatus shown in Figure 1. The solvent reservoir (C), containing a known amount of solvent, was degassed on the vacuum line and attached to the cell chamber (A) above the break seal. The assembly of calibrated pyridine reservoirs (D) were filled by vacuum distillation from a supply of pyridine kept on the vacuum line over calcium hydride. The side tube attached to A contained a known amount of TCNE. After all components were attached, the apparatus was pumped down, sealed by torch, and removed from the vacuum line. The system was manipulated so as to empty the TCNE into A. Solvent was distilled from C into A *via* the break seal. The absorption spectrum of the TCNE solution was recorded, showing no absorbance above 305 nm. The solution was poured back into A and frozen. Pyridine was distilled into A from one of the reservoirs D. The spectrum was recorded as soon as the mixture thawed and came to room temperature. The solution was immediately poured back into A and refrozen, and the second stored increment of pyridine was distilled into A. This procedure was repeated several times. The same technique was used for the picolines and lutidines.

A Benesi–Hildebrand plot was made when a well-defined charge-transfer band was observed and when there was little distortion of the early spectrum by reaction-product formation. In two cases (2-picoline and 2,6-lutidine) a well-defined band was not observed. In three cases (4-picoline, 3,4-lutidine, and 3,5-lutidine) only two spectroscopic points could be used because of the accumulation of reaction products by the time of the addition of a third increment of the donor. For this reason the equilibrium constants calculated remain questionable (Table I).

TABLE I
SUMMARY OF DATA FOR COMPLEXES WITH TCNE

Donor	λ_{max}, nm	Equilibrium constant, l./mol	Extinction coefficient, l./mol cm
Pyridine	342	1.3	2680
4-Picoline	347	1.8	2860
2-Picoline	~340[a]	*b*	*b*
3,5-Lutidine	355	1.8	3120
3,4-Lutidine	353	1.6	3250
2,6-Lutidine	*c*	...	...

[a] Band was very poorly defined. [b] No attempt was made to determine these values. [c] No charge-transfer band could be detected.

Results and Discussion

Initially, reactions were carried out with a 10-mm path-length cell requiring small concentrations of pyridine and TCNE. At these concentrations, the optical spectra showed only the doublet at 399 and 418 nm characteristic of the pentacyanopropenide ion and a band at 300 nm attributable to the tricyanoethenolate ion. We assume that we were unable to remove the small amount of water necessary for the formation of these ions at the concentrations in question.

A cell with a path length of 0.1 mm permitted the use of concentrations of reactants far higher than that expected of unremoved water, and this enabled the observation of what we consider to be the charge-transfer bands without interference by reaction products. Increments of donor did have to be added rapidly, however, since absorbances owing to reaction products began to distort the charge-transfer bands after *ca.* 30 min. In most cases, the spectrum taken after the third addition of donor showed significant absorbance owing to reaction-product formation and a decrease in the intensity of the charge-transfer band.

No charge-transfer band was detected with 2,6-lutidine as donor, and only weak absorbance with no well-defined maximum could be observed in the 2-picoline–TCNE system. The other four donors, pyridine, 4-picoline, 3,4-lutidine, and 3,5-lutidine, gave broad bands at 340–355 nm. These bands increased in intensity as the donor concentration was increased. The intensity of the bands decreased with time and increasing reaction-product formation. For this reason, spectra taken after addition of the third increment of donor showed lower intensities for the charge-transfer band than were expected. In some cases the intensity of the band after the third increment was lower than that after the second increment.

Benesi–Hildebrand plots were made on absorbance data obtained from these complexes whenever a well-

(15) We thank Dr. O. W. Webster for advising the use of this solvent in place of chlorobenzene.

(16) We are indebted to Dr. O. W. Webster for helpful and generous discussions on the preparation of this salt. Attempts to prepare the salt by the literature method[14] failed.

defined charge-transfer band was observed and whenever there was little distortion of the spectrum owing to reaction-product formation. Only absorbance data from the first two increments of donor could be used because significant amounts of reaction product had accumulated by the time the third addition of donor was made. Considering these limitations, the equilibrium constants obtained are questionable. Results for the complexes are given in Table I.

Although valid comparisons cannot be made from the equilibrium constants, some qualitative differences are evident from the optical spectra. There certainly appears to be some hindrance to complex formation by methyl substitution in the positions adjacent to the nitrogen atom, and the effect is more pronounced with disubstitution than with monosubstitution. Also, if the assumption is made that all of the complexes have approximately equal extinction coefficients, the amount of complexation may be estimated from the intensity of the charge-transfer band after the initial addition of donor, since the concentrations of reactants were the same for each system. The initial spectrum was used, since only small amounts of reaction products had distorted the spectrum and consumed TCNE at this point. The peaks decreased in intensity in the order 3,4-lutidine > 3,5-lutidine > 4-picoline > pyridine. Using this method of analysis, the intensities of the complex bands of the donors which are not sterically hindered parallel closely their basicities. Although comparisons of the steric effect and order of donor strength are not conclusive, these data indicate that the donors act as n-electron donors toward TCNE.

Esr investigations of the TCNE–pyridine systems showed the nine-line spectrum of the TCNE anion radical, but no evidence was found for any other paramagnetic species. The lack of evidence for the presence of the pyridine cation radical implies that the formation of the TCNE anion radical may not be due to the dissociation of the charge-transfer complex.

The radical anion is formed in good yields by the reaction of TCNE with cyanide ion,[14] and this method was used to synthesize the potassium salt of the anion radical in this laboratory. Since the formation of both pentacyanopropenide and tricyanoethenolate ions in the donor–TCNE systems liberates cyanide ion, this ion is very likely responsible for the reduction of TCNE to the anion radical. This possibility is supported by our finding that the concentration of radical increased slowly over a period of hours.

Registry No.—TCNE, 670-54-2; pyridine, 110-86-1; 4-picoline, 108-89-4; 3,4-lutidine, 583-58-4; 3.5-lutidine, 591-22-0.

Deuterium Isotope Effects in the Principal Electronic Transition of Nitrobenzene and Aniline and Their *p*-Alkyl Derivatives

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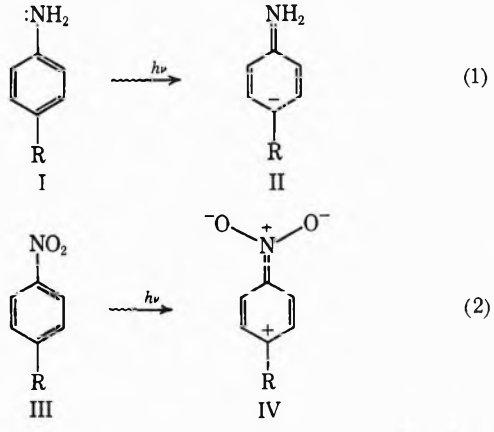
Received September 22, 1969

A study has been made of the effect of *p*-D *vs.* *p*-H, *p*-CD_3 *vs.* *p*-CH_3, and *p*-$CH_2C(CD_3)_3$ and *p*-$CD_2C(CH_3)_3$ *vs.* *p*-$CH_2C(CH_3)_3$ on the principal electronic transition of nitrobenzene and aniline in the gas phase and in heptane solvent. In all but one instance, that of *p*-neopentylnitrobenzene *vs.* *p*-neopentylnitrobenzene-γ-d_9, deuterium substitution shifted the principal band to slightly higher energies. These results are consistent with the polarizability–electronegativity treatment of substituent effects.

It has been reported that *p*-alkyl substituents substantially lower the energy of the "principal" electronic transition of compounds of the type aniline, phenol, and anisole, the excitation energy order in the gas phase and in heptane being neopentyl (neop) < *t*-Bu, Me < H.[1] It is known that in the principal electronic transition of *p*-disubstituted benzenes (also known as the E band or K band), there is a migration of electronic charge in the long axis of the molecule.[2] For *para*-substituted anilines, phenols, and anisoles it has been amply demonstrated by solvent studies that the electron migration takes the expected direction, *i.e.*, away from the heteroatom substituent, toward the *para* substituent.[3-5] Thus it may be symbolized by eq 1, in which the formulas I and II are understood to be only approximately representative of ground and



(1)

(2)

excited states.[6,7] To anyone holding the static viewpoint that alkyl substituents invariably should act as if electron releasing relative to hydrogen, these results are

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(7) For a justification, in quantum mechanical terms, of such a structural depiction of the excitation process see ref 2 and 8.

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somewhat of a surprise. However, the conclusion that under a sufficiently high influx of negativity alkyl substituents exert a stabilizing effect in the polarizability order has been recently verified by the finding of Brauman and Blair that the relative gas-phase stabilities of alkoxide ions are neopo$^-$ (most stable) > t-BuO$^-$ > i-PrO$^-$ > EtO$^-$ > MeO$^-$ > HO$^-$.[9]

In the principal electronic transition of nitrobenzene, acetophenone, and similar compounds, in which the electron migration is in the opposite direction, *i.e.*, away from the substituent (eq 2), alkyl substituents have the expected effect of lowering the excitation energy. However, the excitation-energy order in the gas phase and in nonpolar solvents is also in the polarizability order, not in the hyperconjugative order: neop < t-Bu < i-Pr < Et < Me < H.[10] To account for the alkyl substituent effect, which is to lower the energy of transitions in which the electron migration is toward the substituent as well as those of the opposite sense, it was proposed that the substituent response was a function of its polarizability and its electronegativity (relative to the moieties to which it is bonded in ground and excited states).[1] The postulate had earlier been introduced to account for the effect of *para* halogen substituents, which also gave the polarizability order of excitation energies for both compounds of type I and type III.[3,11] The failure generally of alkyl substituents to respond as apparent electron acceptors relative to hydrogen in nucleophilic *chemical* transitions was attributed to the relatively low demand of the chemical compared with the electronic transitions. In other words, in transitions of lower demand, substituent response is qualitatively governed by relative substituent electronegativity.

To test the polarizability–electronegativity concept and to gain a further insight into the nature of the substituent polarization in the two types of electronic transitions, the effect of p-D, p-CD_3, p-$CD_2C(CH_3)_3$, and p-$CH_2C(CD_3)_3$ has now been studied.

Experimental Section

Compounds were purified with great care and thoroughness, to assure constancy of spectra. Vpc purification was followed by *ca.* five low-temperature recrystallizations, usually from pentane.

Nitrobenzene-p-d.—The reduction of p-nitrobenzenediazonium sulfate with hypophosphorus acid-d_3 according to the method of Hammond yielded nitrobenzene-p-d.[12] Analysis on the mass spectrometer (Consolidated Engineering Corp., type 21-103) showed d_0, 4%; d_1, 96%; d_2 and d_3, 0%.

Aniline-p-d.—The reduction of nitrobenzene-p-d was carried out by the method of Pietra[13] on the following scale: nitrobenzene-p-d (1.19 g), hydrazine hydrate (1.8 ml), 5% Pd on charcoal (52 mg), and ethyl alcohol (5 ml). Only 5 ml of water was used in the isolation procedure. The yield of purified aniline-p-d was 0.5 g. Analysis on the mass spectrometer showed d_0, 6%; d_1, 94%; d_2 and higher, 0%.

p-Nitrotoluene-α-d_3.—Nitration of toluene-α-d_3 (d_0, 0%; d_1, 0.7%; d_2, 14.0%; d_3, 85.3%), kindly furnished by Professor K. B. Wiberg,[14] yielded p-nitrotoluene-α-d_3: mp 50.2–50.8°; bp 146° (76 mm); $n^{25.5}$D 1.5462. The isotopic composition by mass spectral analysis was d_0, 0%; d_1, 0.7%; d_2, 13.9%; d_3, 85.4%.

p-Toluidine-α-d_3.—The method of Smith,[15] applied to the reduction of 1.1 g of p-nitrotoluene-α-d_3, yielded 0.37 g of purified p-toluidine-α-d_3. Mass spectral analysis follows: d_0, 0%; d_1, 0.9%; d_2, 15.5%; d_3, 83.6%.

Reduction of p-nitrotoluene-α-d_3 by the method of Pietra[13] yielded p-toluidine containing very little deuterium. Mass spectral analysis follows: d_0, 93%, d_1, 6%; d_2, 1%; d_3, 0%.

p-Methylanisole-α-d_3.—The isotopic composition of a sample of p-methylanisole-α-d_3, kindly furnished by Professor K. B. Wiberg, by mass spectral analysis follows: d_0, 4.5%; d_1, 0.7%; d_2, 9.8%; d_3, 85.0%.

p-Neopentylnitrobenzene-α-d_2.—Reduction of ethyl benzoate (17.3 g) with $LiAlD_4$ (3 g) in purified tetrahydrofuran (200 ml) yielded benzyl alcohol α-d_2 (11.7 g), bp 100° (13 mm). The benzyl chloride was prepared by refluxing with thionyl chloride. The Grignard reagent was treated with t-butyl chloride according to the method of Berliner[16] to yield p-neopentylbenzene-α-d_2, bp 75° (18 mm). Nitration was carried out as before,[10d] yielding p-neopentylnitrobenzene-α-d_2, mp 30.0–30.1°. The isotopic composition by mass spectral analysis follows: d_0, 1.9%; d_1, 24.7%; d_2, 73.4%.

Isobutylene-d_8 and t-Butyl Chloride-d_9.—A mixture of isobutylene (0.23 mol) and 30% D_2SO_4–D_2O (98.5% d) was shaken for 72 hr at room temperature in a sealed tube. After 12 hr the mixture was homogeneous. The solution was cooled to −80° and transferred to a 200-ml, round-bottom flask which was attached in series to an efficient water-cooled condenser, a Drierite tube, a trap cooled in ice, a Dry Ice–acetone trap, and a Drierite tube. The isobutylene was driven from the solution by gentle heating followed by more vigorous heating until reflux temperature. Refluxing was continued for 12 hr. The liquid that collected in the Dry Ice–acetone trap was bulb to bulb distilled. A total of three equilibrations were run in this manner, yielding finally 6.1 g of deuterated isobutylene. The deuterated isobutylene was distilled through a Drierite tube into a liquid nitrogen trap, the entry tube of which, at the end of the distillation, extended just below the surface of the liquid. Anhydrous ferric chloride (0.2 g) was added to the trap. Deuterium chloride, prepared according to the method of Brown,[17] was slowly passed into this entry tube and the mixture was allowed to stand for 30 min after the addition was complete. The trap was allowed to warm to room temperature in order to enable DCl to escape. The liquid then was distilled bulb to bulb, washed twice with 5 ml of water, dried over anhydrous magnesium sulfate, and distilled, bp 51°, yield 8.0 g. A comparison of the nuclear magnetic resonance spectrum with that of normal t-butyl chloride indicated that the t-butyl chloride-d_9 contained less than 4% protium.

p-Neopentylnitrobenzene-γ-d_9.—The reaction of t-butyl chloride-d_9 with the Grignard reagent of benzyl chloride, according to the procedure of ref 16, gave p-neopentylbenzene-γ-d_9, which was nitrated as above. The isotopic composition of the resulting p-neopentylnitrobenzene-γ-d_9, by mass spectral analysis, follows: d_7, 5%; d_8, 28%; d_9, 67%.

p-Neopentylaniline-γ-d_9.—The reduction procedure of Pietra,[13] applied to 0.915 g of p-neopentylnitrobenzene-γ-d_9, yielded 0.653 g of purified p-neopentylaniline-γ-d_9. Mass spectral analysis follows: d_6, 6%; d_7, 7%; d_8, 27%; d_9, 60%.

Spectral Measurements.—Measurements of gas-phase and solution spectra were made by multirepeated scanning with a Beckman DU instrument as described previously.[10c-e] The values of ν_{max} were determined graphically as described previously.[10c-e] Values of ν_{max} in heptane also were determined from spectral data obtained by means of a Cary Model 14 instrument, run at a slow chart speed with 5 Å/1 cm of chart paper. Both spectrophotometers were in top condition, the latter brand new. For spectra on the Cary, the base line was carefully balanced, air *vs.* air. Solvent *vs.* solvent showed no

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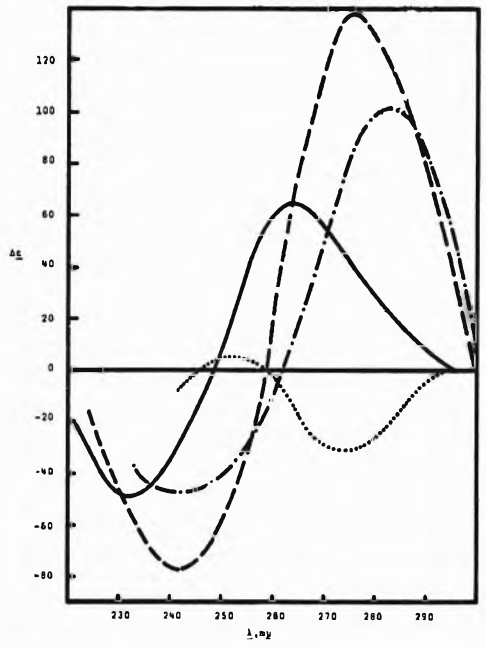

Figure 1.—Difference spectra for *para*-substituted nitrobenzenes, H compound (sample cell) *vs.* D compound (blank cell): D, ——; CD_3, – –; $CD_2C(CH_3)_3$, ·–·–; $CH_2C(CD_3)_3$, · · · · · · .

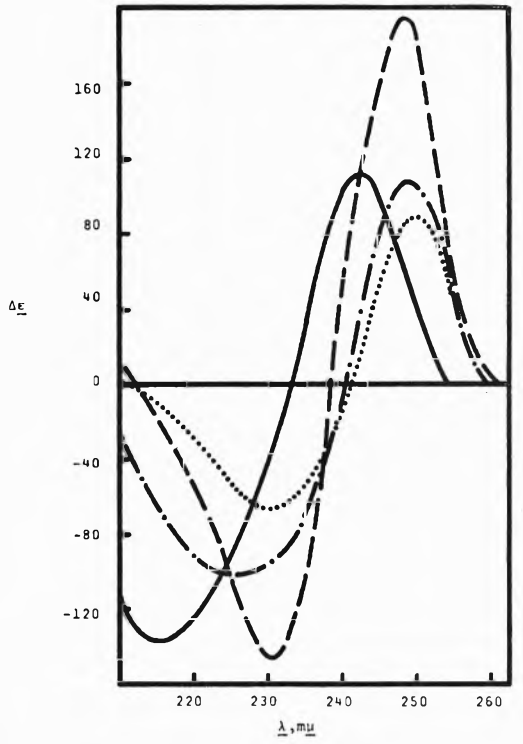

Figure 2.—Difference spectra for *para*-substituted anilines, H compound (sample cell) *vs.* D compound (blank cell): D, ——; CD_3, – –; $CD_2C(CH_3)_3$, ·–·–; $CH_2C(CD_3)_3$, · · · · · · .

deviation from the base line except at λ values lower than those used in the spectral determinations. A special cell holder was constructed to assure precise alignment of the cells each time.

The double-beam instrument was used to determine relative spectra of H and D compounds in heptane. Samples of *ca.* 5 mg were weighed on an analytical balance and diluted to 100 ml, and these solutions ($2–4 \times 10^{-4} M$) were used directly. Hydrogen and corresponding deuterium compounds were of the same molarity to an estimated precision of 0.05%. Difference spectra, in which the solution of hydrogen compound was in the sample cell and that of the deuterium compound in the blank cell, were recorded. The maximum slit width, occurring at *ca.* λ_{max}, was usually below 1.0.

Results

The general appearance of the principal band spectra of the *p*-alkyl nitrobenzenes, anisoles, and anilines has been described.[1,10c,d] Table I lists the values of the difference in ν_{max} between deuterium and protium analogs in the gas phase, as determined at elevated temperatures in a Beckman DU instrument. The ν_{max} differences for averages of three determinations for each compound were reproducible to ±20–30 cm^{-1}. Table II lists ν_{max} differences obtained in heptane. Two sets of values are reported. One set of values was obtained with the Beckman DU instrument and is reproducible to ±20 cm^{-1} or less. The other set of values was obtained with the Cary Model 14 instrument and is reproducible to ±15 cm^{-1} or less.

TABLE I

GAS-PHASE VALUES OF ν_{max} (cm^{-1}) FOR p-RC_6H_4X AND DIFFERENCES IN ν_{max} BETWEEN DEUTERIUM AND PROTIUM ANALOGS[a]

	NO_2	NH_2	OCH_3
ν_H	41,820	43,590	46,510
$\nu_D - \nu_H$	160	150	...
ν_{CH_3}	39,970	42,790	45,500
$\nu_{CD_3} - \nu_{CH_3}$	80	70	130
$\nu_{CH_2C(CH_3)_3}$	39,490	42,280	44,880
$\nu_{CD_2C(CH_3)_3} - \nu_{CH_2C(CH_3)_3}$	30	60	...
$\nu_{CH_2C(CD_3)_3} - \nu_{CH_2C(CH_3)_3}$	−30	40	...

[a] Average of three determinations at 150° on a Beckman DU, duplicable to ±20–30 cm^{-1}.

TABLE II

VALUES IN HEPTANE OF ν_{max} (cm^{-1}) FOR p-RC_6H_4X AND DIFFERENCES IN ν_{max} BETWEEN DEUTERIUM AND PROTIUM ANALOGS[a,b]

	NO_2	NH_2
ν_H	39,700	42,740
$\nu_D - \nu_H$	50,[a] 30[b]	70,[a] 60[b]
ν_{CH_3}	37,870	42,230
$\nu_{CD_3} - \nu_{CH_3}$	50, 40	50, 50
$\nu_{CH_2C(CH_3)_3}$	37,410	41,170
$\nu_{CD_2C(CH_3)_3} - \nu_{CH_2C(CH_3)_3}$	30, 30	30, 40
$\nu_{CH_2C(CD_3)_3} - \nu_{CH_2C(CH_3)_3}$	0, −20	40, 30

[a] The first number reported is the average of three to five determinations at room temperature made on a Beckman DU, reproducible to ±20 cm^{-1} or better. [b] The second number reported is the average of two or three determinations at room temperature made on a Cary, Model 14, duplicable to ±15 cm^{-1} or better.

The plots of Figures 1 and 2 are experimental difference spectra of H compound against corresponding D compound. The experimental definition of $\Delta\epsilon$ is given by eq 3, where A is absorbance, positive or negative, that was determined as a function of wavelength. The quantity $\Delta\epsilon$ is related by eq 4 to $\epsilon_H - \epsilon_D$, the true difference between molar absorptivity of H and D compound. Only in the event that the concentration ratio of H to D compound ([H]/[D]) is exactly unity is $\Delta\epsilon$ at each wavelength *exactly* the molar absorptivity difference, $\epsilon_H - \epsilon_D$. Inherent weighing and volumetric areas impart an unavoidable uncertainty of 0.05% to the ratio [H]/[D]. Thus, if the H compound (sample cell) is in slight excess, $\Delta\epsilon$ is algebraically greater than $\epsilon_H - \epsilon_D$ at all wavelengths.

If the D compound (blank cell) is in slight excess, $\Delta\epsilon$ is algebraically less than $\epsilon_H - \epsilon_D$.[18] It can be shown that for broad, smooth, nearly symmetrical spectral peaks of the type being dealt with here, a slight excess of H or D compound will shift the whole $\Delta\epsilon$ *vs.* λ curve up or down without appreciably changing its shape. Thus the sum of the areas of positive absorption (where $\Delta\epsilon > 0$) and negative absorption (where $\Delta\epsilon < 0$) is practically unaffected, and the algebraic difference $\Delta\epsilon_{max} - \Delta\epsilon_{min}$ is practically unchanged. In other words, for compounds whose peaks are smooth and lie close to each other, the effect of a slight excess of, say, the H compound is to subtract about as much from the intensity of negative absorption as it adds to the intensity of positive absorption. Raising or lowering the $\Delta\epsilon$ curve does appreciably change the point of intersection with the wavelength axis, however.

$$\Delta\epsilon = A/[H] \tag{3}$$

$$\Delta\epsilon = \frac{\epsilon_H[H] - \epsilon_D[D]}{[H]} = \epsilon_H - \epsilon_D\frac{[D]}{[H]} \tag{4}$$

Discussion

Except for *p*-neopentylnitrobenzene-d_9, all the deuterium compounds have experimentally significant higher ν_{max} values than the corresponding hydrogen compounds, though the differences are quite small. The maximum observed $\nu_H - \nu_D$, 160 cm^{-1}, corresponds to 460 cal/mol (Tables I and II). It would, of course, be desirable to be able to measure directly the effect of deuterium on the 0–0* component of the band, which would give the energy difference between zero vibrational levels of ground and excited states. Since the intense principal spectral bands are characteristically smooth, continuous, and nearly bell shaped,[1,10] the 0–0* transition is experimentally inaccessible. However, Figures 1 and 2 show that deuterium substitution does shift the entire spectral band envelope, within the wavelength range of an observable difference spectrum. Thus the differential absorption (H *vs.* D compound) reaches a maximum on one side of the isoabsorptive wavelength and a minimum on the other side. Since the range of 0–n* transitions that contribute to the spectrum is shifted by substitution of D for H,[19] the inference is clear that the 0–0* transition is similarly shifted.

In the interpretation of the results obtained, two assumptions will be made. One is that inherent electronic effects exerted by substituents are qualitatively the same for electronic as for chemical transitions, though quantitatively different, of course. The second assumption is that, although secondary deuterium isotope effects "are vibrational in origin, ... they can be regarded as genuine substituent effects for all practical purposes." The quotation is from p 123 of the review on secondary deuterium isotope effects by Halevi,[20a] who develops the common ground between formal theory and the language and concepts familiar to the physical organic chemist. Indeed, Halevi suggests that the physical organic chemist's approach may be the more meaningful and productive one in many instances of interpretation of secondary isotope effects.

From the magnitude of the experimental ν_{max} differences of Tables I and II, there is not much to choose in the way of deciding where deuterium substitution has its greatest effect. However, there is a trend toward greater magnitudes of $\nu_H - \nu_D$ in *p*-CD_3 and *p*-D compounds than in *p*-$CH_2C(CD_3)_3$. The difference spectra of Figures 1 and 2 are more definitive in this regard. They indicate that for both anilines and nitrobenzenes, the magnitude of the band shift takes the order $CD_3 > D$, $CD_2C(CH_3)_3 > CH_2C(CD_3)_3$.[21]

***p*-D *vs.* *p*-H.**—The substitution of *p*-D for *p*-H leads to a significant increase in the principal electronic transition energy of both nitrobenzene and aniline in both the gas phase (Table I) and in heptane solution (Table II and Figures 1 and 2). Since the electron migration is away from the substituent in the excitation of nitrobenzene and toward the substituent in the excitation of aniline, the effect is not governed by a relative inductive effect, in a fixed direction, between H and D. The results are consistent with the electronegativity–polarizability concept.[1,11] There is ample physical evidence that D is less electronegative than H, and that the C–D bond is less polarizable than the C–H bond.[20b] The effect of *p*-D *vs.* *p*-H on the principal transition of aniline corresponds to both the electronegativity and polarizability order. However, the effect on the principal electronic transition of nitrobenzene corresponds only to the polarizability order, in agreement with the hypothesis that when the transition places a very high electron demand on the substituent, as it does here, a greater polarizability (*i.e.*, a greater response *per increment* of demand) can overcome the retarding effect of a greater electronegativity.[1,11]

The results here are not necessarily in contradiction to the apparent greater activating effect of D than H in certain electron-demanding chemical transitions. Examples in which H (or D) is bonded to trigonal carbon in both states include the ionization of tris-*p*-deuteriophenylmethyl chloride in SO_2 at 0°, for which $K_H/K_D = 0.969 \pm 0.003$ (the corresponding *m*-*d* compound has $K_H/K_D = 0.957 \pm 0.007$),[22] and the solvolysis of bis(pentadeuteriophenyl)methyl chloride in 80% acetone at 25°, for which $k_H/k_D = 0.85$.[23] While these reactions are electron demanding of the substituent, the demand is not nearly comparable with that in the principal electronic transition of nitrobenzene.[24] In other words, the demand may be sufficiently low in the chemical transitions to allow the electronegativity difference between H and D to predominate in the combined polarizability–electronegativity "product."[25]

(18) At the ϵ_{max} of the hydrogen compounds ($\epsilon \cong 10{,}000$), $\Delta\epsilon$ could be as much as 50 units greater (excess H compound) or less (excess D compound) than $\epsilon_H - \epsilon_D$.

(19) For the spectral data in heptane, at room temperature, it may be assumed that the ground state largely occupies the zero vibrational level. Upper levels of the ground state may be somewhat populated in the gas-phase measurements, which were carried out at 150° to avoid adsorption of compound on cell windows.[10c]

(20) (a) E. A. Halevi, "Physical Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1963, pp 109–221; (b) pp 114–123.

(21) For the *para* hydrogen through neopentyl derivatives of the nitrobenzenes and anilines, the spectral band retains the same shape and increases only a little in intensity. Therefore, the change with substituent in the integrated areas of Figure 1 (sum of areas above and below $\Delta\epsilon = 0$) or Figure 2 is qualitative measure of the relative magnitude of the λ shift produced by D replacing H.

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(23) H. S. Klein and A. Streitwieser, Jr., *Chem. Ind.* (London), 180 (1961).

(24) From the effect of *para* substituents with negative σ^+ only, the "reaction" constant, ρ, has been estimated to be -13 ± 1.2.[1]

Reactions that result in negativity at or near trigonal carbon appear generally to be "activated" by H relative to D, in correspondence with both the electronegativity and polarizability order. Examples include the ionization of formic acid (k_{HA}/k_{DA} = 1.06[26] or 1.12[27]) and the ionization of pentadeuteriophenol (k_{HA}/k_{DA} = 1.12).[23]

CD_3 and $CD_2C(CH_3)_3$.—The substitution of α deuterium in either *p*-methyl or *p*-neopentyl raises the energy of both the electron-removing (nitrobenzene) and electron-donating transition (aniline). The effect is greater in methyl than in neopentyl derivatives, as shown especially by the H *vs.* D difference spectra of Figures 1 and 2. However, it is risky to surmise whether this is more or less than a statistical difference owing to three α deuteriums compared with two. Shiner has found a somewhat more than statistical difference, which he attributes to inhibition of C–H hyperconjugation, in the solvolysis of $CD_3CCl(CH_3)_2$ (k_H/k_D = 1.40) and $(CH_3)_3CCD_2CCl(CH_3)_2$ (k_H/k_D = 1.08).[28]

From the facts that H is more electronegative than D and the C–H bond is more polarizable than the C–D,[20] it can be presumed that CH_3 and $CH_2C(CH_3)_3$ are somewhat more electronegative and polarizable than the corresponding α-D substituents. Thus, as with *p*-D compared with *p*-H, the ν_{max} shift on α-D substitution corresponds to both the electronegativity and polarizability order for *p*-methyl and *p*-neopentylaniline, but only to the polarizability order for the nitrobenzenes.

In electron-demanding chemical transitions, CD_3 has been found to sometimes have a retarding effect relative to CH_3, and sometimes an accelerating effect. Deuterium substitution slightly decreases the rate of solvolysis of *p*-methylphenyl-1-chloroethane: $k_{p\text{-}CD_3}/k_{p\ CH_3}$ is 1.08 (30 cal/mol per D) in acetic acid at 50° and only 1.01 in "80%" acetone at 38°.[29] A greater isotope effect is found in the α-methyl substituent, which is under greater electron demand: $k_{\alpha\text{-}CH_3}/k_{\alpha\text{-}CD_3}$ = 1.28 in acetic acid at 50°.[29] Deuterium substitution in the α position of *para* alkyl substituents also reduces solvolysis rates of *p*-alkylbenzhydryl chloride; *e.g.*, $k_{p\text{-}CH_3}/k_{p\text{-}CD_3}$ = 1.06 in "80%" acetone at 0°.[30] The basicity of acetophenone is greater than that of its CD_3 analog, $k^H_{SH^+}/k^D_{SH^+}$ = 0.775 (−51 cal/mol per D).[31] Aromatic substitution gives varied effects. Nitration of CD_3Ph apparently shows no significant effect;[32-34] *e.g.*, k_H/k_T = 1.002 ± 0.002 per tritium.[32] In the more electron-demanding bromination a retarding effect was observed: k_H/k_T = 1.046 ± 0.009 per tritium in 85% acetic acid at 25°.

The β-deuterium isotope effect in solvolysis of purely aliphatic halides and inorganic esters also appears to be demand dependent. Methyl inorganic esters hydrolyze slower in water than the CD_3 esters (*e.g.*, $\Delta F_D^{\ddagger} - \Delta F_H^{\ddagger} = -25$ cal/mol for the bromide).[35] As the SN1 contribution to hydrolysis increases, *i.e.*, as the electron demand in the transition states increases, k_H/k_D increases. Thus the isotope effect for ethyl-α-d_2 derivatives is borderline, and that of isopropyl-α-d_1 is positive (*e.g.*, $\Delta F_D^{\ddagger} - \Delta F_H^{\ddagger} = 22$ for the bromide).[35] With tertiary halides and inorganic esters, β D invariably has a retarding effect.[20,28,36,37] For example, k_H/k_D = 1.40 (64 cal/mol per D) in the solvolysis of $CD_3CCl(CH_3)_2$ in "80%" ethanol at 25°.[28] A somewhat smaller retardation was observed in the hydrolysis of α-deuterio ketals.[38]

The general pattern that emerges from the results of the electron-demanding chemical transitions is that k_H/k_D per deuterium tends to increase as the electron demand on the substituent increases, and has a value less than unity for weakly electron-demanding reactions. This is in agreement with the electronegativity–polarizability hypothesis.[1,11] However, it also agrees with the often advanced argument that inductive electron release (CD_3 better than CH_3) predominates at low demands and that C–H hyperconjugative release (CH_3 better than CD_3) predominates at higher electron demands.

In reactions that place negative charge at the alkyl substituent, deuterium seems generally to exert a retarding effect, but the studies are fewer in number.[20] Deuterium substitution in the α position reduces the acidity of carboxylic acids; *e.g.*, K_H/K_D = 1.06 (12 cal/mol per D) for (CD_3COOH).[20,39] This has been attributed to greater inductive electron release by α-CD than by α-CH substituents, leading to a greater destabilization of the CD_3COO^- anion.[39] A larger effect was encountered in the rate of α proton abstraction from CD_3CH_2Ph by lithium cyclohexylamide in cyclohexylamine at 50°, k_H/k_D = 1.11 ± 0.03.[40] This also was attributed to greater inductive electron release by CD_3,[40] but the suggestion has been made that there may be a contribution by anionoid hyperconjugation.[20]

The fact that in both electron-donating and electron-demanding electronic transitions the ease of substituent polarization takes the order alkyl > deuterioalkyl ≫ H > D requires that any assigned specific mechanism or mechanisms of the substituent role be one that allows the alkyl substituent to respond favorably either to an electron-rich or an electron-poor attached moiety. Thus, if hyperconjugation is of prime importance, it must be cationoid (classical hyperconjugation) at high electron demand and anionoid toward high electron richness. If the effects are largely a consequence of unequal sharing of σ electrons (inductive effect), then the unequal sharing must be able to take either direction. If polarization occurs through space (internal dispersion force), this is by definition operable in either "direction."[41]

(25) Increasing demand increases the relative importance of polarizability, as illustrated graphically in ref 1.

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p-$(CD_3)_3CCH_2$.—The effect that γ-deuterium substitution exerts on the principal band of *p*-neopentylnitrobenzene and *p*-neopentylaniline is the smallest one observed. However, in each successive determination on H and D compounds, ν_{max} for neopentylaniline was consistently less than that for its γ-d_4 derivative. The difference spectrum of Figure 2 shows this even more clearly. For neopentylnitrobenzene in heptane, no difference was found in the average of determinations on a Beckman DU, but, in determinations on the Cary Model 14 spectrometer, ν_{max} for the γ-d_9 derivative was consistently smaller by a tiny amount. The differential absorption curve of Figure 1 shows a rather weak maximum and minimum, but has the shape required for a shift to lower energy of the transition of the D compound.

In previous articles, it has been pointed out that the lowest energy conformation of neopentylbenzenes is probably one in which a portion of two of the terminal methyl groups somewhat overhang one side of the ring (see also ref 28).[10d,e] It was suggested that part of the enhanced effectiveness of the *p*-neopentyl substituent in electronic transitions, both of the type represented by eq 1 and that represented by eq 2, may be due to a polarization across space of these terminal methyl groups (the $h\nu$ order in both instances is neop < *t*-Bu, CH_3 < H). However, the observed opposite effect of γ deuterium on the principal band of *p*-neopentylnitrobenzene and *p*-neopentylaniline is difficult to reconcile with this suggestion. If the effect of γ-D substitution is transmitted through the bonding electrons, then the effect would be expected to be very small in any event.

As regards the effect of γ-D substitution on chemical transitions, γ-d_9 neopentyl methanesulfonate hydrolyzes somewhat slower than the normal compound in water: k_H/k_D = 1.017.[42,43] On the other hand, γ-d_9 may slightly increase the rate of solvolysis of α-methylneopentyl brosylate: k_H/k_D = 0.979 ± 0.017 in 43% ethanol at 40°; k_H/k_D = 0.986 ± 0.014 in 95% trifluoroacetic acid at 10°.[44]

Registry No.—Nitrobenzene, 98-95-3; aniline, 62-53-3; nitrobenzene-*p*-*d*, 13122-36-6; aniline-*p*-*d*, 13122-28-6; *p*-nitrotoluene-α-d_3, 23346-24-9; *p*-toluidine-α-d_3, 23346-25-0; *p*-methylanisole-α-d_3, 23346-26-1; *p*-neopentylnitrobenzene-α-d_2, 23346-27-2; isobutylene-d_8, 20762-54-3; *t*-butyl chloride-d_9, 918-20-7; *p*-neopentylnitrobenzene-γ-d_9, 23346-29-4; *p*-neopentylaniline-γ-d_9, 23359-82-2.

Acknowledgment.—The authors thank Dr. R. G. Minton for preparing and purifying some of the deuterium compounds. Financial support of the Office of Ordnance Research, U. S. Army, also is gratefully acknowledged.

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Kinetics and Stereochemistry of the Gas-Phase Addition of HBr to Methyl-Substituted Allenes

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Received June 9, 1969

The kinetics and stereochemistry of the gas-phase, photocatalyzed addition of HBr to allene, methylallene, 1,1-dimethylallene, 1,3-dimethylallene, and tetramethylallene have been investigated. The rate expression is the same for all: rate of adduct formation = $k[HBr]I_0^{1/2}$. Reactivities relative to allene are 1:1.36:1.31:1.56:1.65 for the compounds as listed. The products, with one minor exception, involve addition of the bromine atom to the center carbon of the allenic system.

The free-radical addition of HBr to simple olefins reaction has been investigated in both solution and gas phases for many years. The general picture that has emerged is that the bromine atoms add to that carbon of the olefinic bond which will yield the most stable radical. In the gas-phase reaction, this radical contains the energy of the new carbon–bromine bond, and may readily dissociate to starting olefin and bromine atom, or be collisionally deactivated to thermal equilibrium, whereupon it may abstract a hydrogen from HBr to give the alkyl bromide product.[1,2]

The situation is more complex with cumulative bond systems. The addition of a radical or atom to the terminal (more electronegative[3]) carbon of an allene produces a vinyl radical. If addition of a radical takes place at the center carbon, however, the radical structure can acquire allylic resonance stabilization by rotation through 90°.[4] The question arises as to whether this rotation can occur fast enough so that this stabilization becomes kinetically important. An examination of the kinetics of the reaction of allene with HBr demonstrated that the initial reaction of the bromine atom with the allene is at the center carbon, and is apparently irreversible.[5] The kinetics does not disclose whether there may be a reversible terminal carbon attack, but only that all of the product of kinetic importance is from reaction at the center carbon.

The stereochemistry of free-radical attack on allene and alkyl-substituted allenes has been investigated for other radials than bromine atoms. Methyl radicals,[6] trifluoromethyl radicals,[6] and trichloromethyl[7] attack exclusively at the terminal carbon, while fluorine

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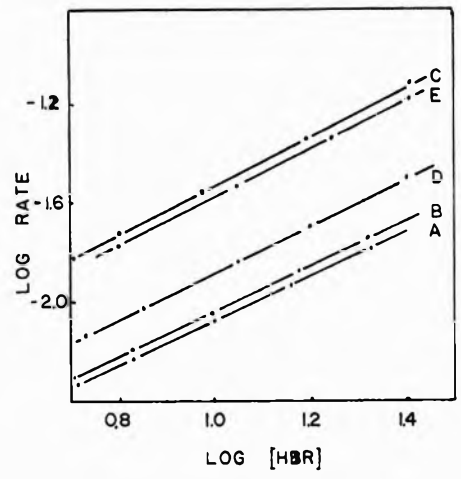


Figure 1.—Rate dependence on HBr concentration at constant allene concentration: A, allene (propadiene); B, methylallene (1,2-butadiene); C, 1,1-dimethylallene (3-methyl-1,2-butadiene); D, 1,3-dimethylallene (2,3-pentadiene); E, tetramethylallene (2,4-dimethyl-2,3-pentadiene).

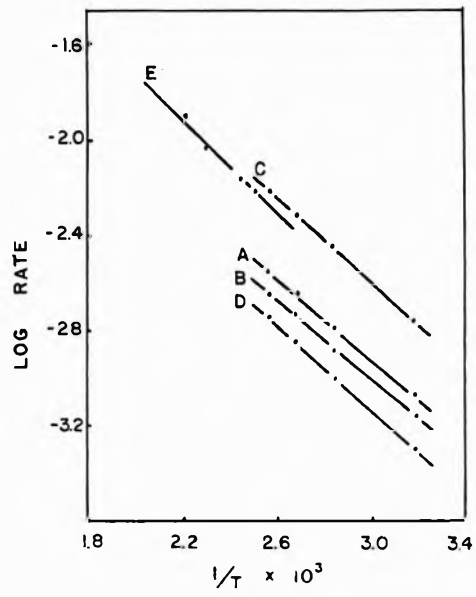


Figure 2.—Arrhenius plots for the addition of HBr to allenes: A, allene (propadiene); B, methylallene (1,2-butadiene); C, 1,1-dimethylallene (3-methyl-1,2-butadiene); D, 1,3-dimethylallene (2,3-pentadiene); E, tetramethylallene (2,4-dimethyl-2,3-pentadiene).

atoms,[8] gas-phase Br atoms,[5] and PH_2 radicals[9] react at the center carbon. Thiyl radicals,[10] trimethyltin radicals,[11] and liquid-phase Br atoms[12] attack at both sites. Heiba and Haag[12] have suggested that attack at terminal carbons may be reversible for the latter radicals, and center-carbon attack irreversible.

Investigation of the various methyl-substituted allenes in their reaction with HBr was undertaken in the hope that the relative energetics and stereochemistry might throw light on the reaction. If the initial attack by bromine atom on the center carbon is indeed irreversible, then the kinetics and thermodynamics will relate to the structure and reactivity of the allylic radicals thus formed.

Results

The various allenes were allowed to react with hydrogen bromide in a cylindrical quartz reaction vessel, irradiated with a 100-W, medium-pressure mercury arc lamp. Kinetic rates were determined by the pressure drop as followed by a quartz spiral manometer and optical lever. Products were isolated by gas chromatography and identified by retention time and/or spectral evidence.

The determination of the kinetic rate expression was by measurement of the change in pressure during a run at constant temperature. When the concentration (pressure) of allene or substituted allene was varied from 15 to 75 Torr and the concentration of HBr was held constant, it was found that the rates did not change, and therefore the allene did not enter into the rate expression. However, when the concentration of HBr was varied from 15 to 75 Torr while the allene concentration was held constant, there was a direct correlation of rate with pressure of HBr. When log (HBr pressure) was plotted *vs.* log (reaction rate), a straight line was obtained for each allene. These plots had slopes of unity, indicating a first-order dependence on HBr concentration (Figure 1).

The dependence of rate on light intensity was obtained by using a calibrated set of Corning 7-54 ultraviolet light filters. Using a variety of conditions of temperature, pressure, and ratio of allenes to HBr, plots of log (relative rate) *vs.* log (light intensity) gave straight lines of slope 0.50 ± 0.04. The experimental rate expression then becomes

$$\text{rate} = k_{\text{exptl}}[\text{HBr}]I_a^{1/2}$$

It is to be noted that this is an initial rate, and not an integrated rate over a reaction carried nearly to completion.

The activation energies were obtained by kinetic runs at a series of temperatures between 40 and 120°. These are shown in Figure 2 and summarized in Table I.

TABLE I
ACTIVATION ENERGY OF HBr–ALLENE REACTIONS

Allene	$\Delta E^{\pm}$, kcal/mol
Propadiene	−3.43
1,2-Butadiene	−3.44
3-Methyl-1,2-butadiene	−4.17
2,3-Pentadiene	−4.06
2,4-Dimethyl-2,3-pentadiene	−4.23

Relative reactivities for the various allenes were obtained by competition experiments with allene for a limited amount of HBr. Analysis of the products by gas chromatography gave the results shown in Table II.

The products of the reactions of the individual allenes with HBr were separated by gas chromatography and identified by nmr and ir spectroscopy. The products and relative amounts are given in Table III, and the spectroscopic data used in structure assignment are given in Table IV.

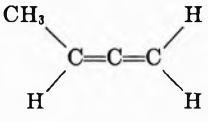
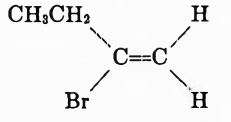
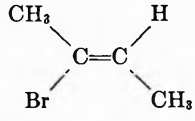
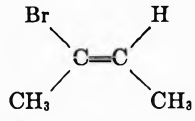
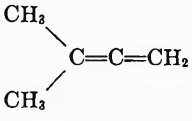
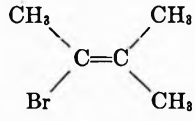
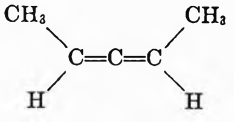
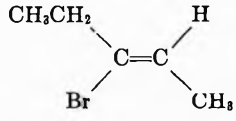
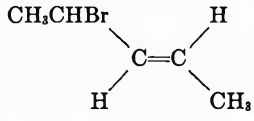
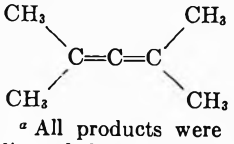
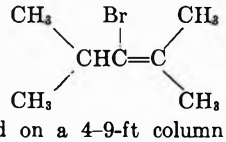
In general the reactions were very clean and the kinetics very straightforward. The reactions proceeded

(8) C. Baumgardner and K. McDaniel, *J. Amer. Chem. Soc.*, **91**, 1032 (1969).
(9) H. Goldwhite, *J. Chem. Soc.*, 3901 (1965).
(10) K. Greisbaum, A. Oswald, E. Quiram, and W. Naegele, *J. Org. Chem.*, **28**, 1952 (1963).
(11) H. Kuivila, W. Rahman, and R. Fish, *J. Amer. Chem. Soc.*, **87**, 2835 (1965).
(12) E. I. Heiba and W. O. Haag, *J. Org. Chem.*, **31**, 3814 (1966).

TABLE II
RELATIVE REACTIVITIES OF ALLENES TOWARD HBr

Allene	60°	90°	120°	$\Delta(\Delta E^{\pm})$ vs. C_3H_4, kcal/mol
Propadiene (standard)	1.00	1.00	1.00	0.00
1,2-Butadiene	1.36	1.36	1.35	0.063
3-Methyl-1,2-butadiene	1.31	1.31	1.32	−0.037
2,3-Pentadiene	1.56	1.55	1.53	0.017
2,4-Dimethyl-2,3-pentadiene	1.65	1.66	1.66	0.042

TABLE III
HBr–ALLENE ADDUCTS

Allene	Yield, %	Product distribution—Compd	%
$CH_2=C=CH_2$	98	$CH_3C(Br)=CH_2$	100[a]
	98		6.5[a]
			83[a]
			10.5[a]
	97		100[a]
	96		94[b]
			6[b]
	89		100?[a]

[a] All products were separated on a 4–9-ft column of 20% dinonyl phthalate on Chromosorb P (60–80 mesh). The retention times for the products are in the order listed. [b] Products were separated on an 8-ft column of a 20% mixture of di-2-ethylhexyl sebacate and dimethylsulfolane on Chromosorb Z.

rapidly to give monoaddition products, and reaction times were short. No products involving addition of 2 mol of HBr were observed. The separation of the products in the tetramethylallene experiments was not very efficient, and there may be some minor products hidden under the single product peak observed.

In only one case was there any product other than material from center-carbon attack by bromine atoms. The minor product from 1,3-dimethylallene was unexpected, but the nmr spectrum leaves little doubt that the structure assignment is correct.

Discussion

The experimental kinetic rate expression indicates that the rate-determining step in the addition of HBr to allenes is the hydrogen abstraction step in the scheme below, and of the various conceivable termination steps, the radical dimerization shown is the important one. The addition of the bromine atom to the center carbon is irreversible, and probably has only a small, or no, activation energy. Therefore, the process should be one of trapping bromine atoms almost as rapidly as they are formed by photolysis of the HBr, and then the more leisurely hydrogen abstraction process follows. Because no appreciable concentration of bromine atoms exists at any given instant, the termination steps involving bromine atoms which are found in reactions with simple olefins[13–15] cannot be involved here.

$$\mathrm{HBr} \xrightarrow{h\nu} \mathrm{H\cdot} + \mathrm{Br\cdot}$$

$$\mathrm{Br\cdot} + \text{allene} \xrightarrow{k_2} \text{bromoallyl radical}$$

$$\text{bromoallyl radical} + \mathrm{HBr} \xrightarrow{k_3} \text{product} + \mathrm{Br\cdot}$$

$$2 \text{ bromoallyl radicals} \xrightarrow{k_t} \text{dimer}$$

If one compares the experimental rate expression with that derived from steady-state assumptions

$$\text{rate} = \left(\frac{k_2}{k_t}\right)^{1/2} I_0^{1/2}$$

it is apparent that the experimental expression can be rewritten in the form of an Arrhenius expression

$$k_{\text{exptl}} = \left(\frac{A_2}{A_t}\right)^{1/2} I_0^{1/2} e^{\frac{-(E_2 - E_{t/2})}{RT}}$$

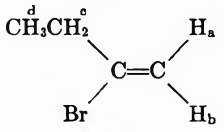
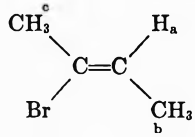
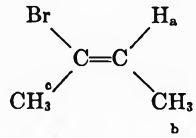
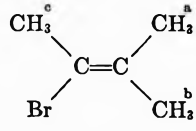
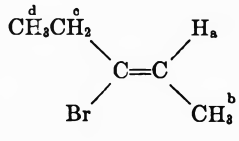
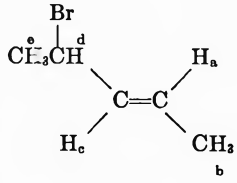
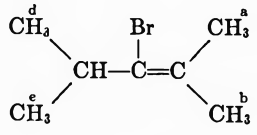
Thus the experimenal activation energy, $\Delta E^{\pm}$, of Table I is equated with $E_2 - E_{t/2}$. It is to be presumed from many atom additions to olefins that $E_2 = 0$. Accordingly, $\Delta E^{\pm} = -E_{t/2}$, and the activation energy as observed is one-half of the termination activation energy. It is somewhat surprising to find activation energies of the order of 6–9 kcal/mol for the dimerization of free radicals, but, when it is recalled that the allyl resonance energy is *ca.* 10 kcal/mol,[16] this is not an unreasonable value. It is unfortunate that the A factor for the reaction cannot be simplified similarly, but, since none of the individual terms in the nonexperimental part of the expression above are known, the experimental A factor is meaningless.

The differences in reactivities of the various allenes (Table II) must be ascribed to some factor which is not temperature dependent. The increased reactivity with increased methyl substitution no doubt reflects the increased hyperconjugative resonance stabilization in the corresponding bromoallyl radicals. However, since the various bromoallyl radical intermediates can only go on to form products by hydrogen abstraction, the relative reactivity values indicate the ease with which they are formed and are not related to how they behave after formation. All this adds up to implication of the

(13) P. I. Abell, *Trans. Faraday Soc.*, **60**, 2214 (1964).
(14) R. J. Field and P. I. Abell, *ibid.*, **65**, 743 (1969).
(15) P. I. Abell and P. K. Adolf, *J. Chem. Thermo.*, **1**, 333 (1969).
(16) D. M. Golden, N. A. Gac, and S. W. Benson, *J. Amer. Chem. Soc.*, **91**, 2136 (1969).

TABLE IV

ANALYTICAL DATA FOR HBr–ALLENE ADDUCTS

Compd	Registry no.	Nmr[a] Peak position, ppm, and coupling constants	Peak ratios	Concn in CCl_4, %	Ir, cm^{-1}
	23074-36-4	a, 5.53 (s) b, 5.34 (s) c, 2.44 (q) d, 1.12 (t) $J_{a,b}$ = 1.10 cps $J_{c,d}$ = 7.0 cps	1 1 2 3	50	3000 s, 1645 s, 1450 s, 1425 s, 1360 s, 1320 s, 1278 s, 1250 s, 1149 s, 1120 s, 1070 w, 912 w, 850 s
	3017-68-3	a, 5.67 (q) b, 1.69 (d) c, 2.25 (s) $J_{a,b}$ = 7.0 cps	1 3	50	3010 s, 1670 m, 1451 s, 1420 s, 1281 s, 1138 s, 1115 s, 980 w, 947 s, 852 s
	3017-71-8	a, 5.81 (m) b, 1.70 (d) c, 2.20 (s) $J_{a,b}$ = 7.0 cps	1 3	50	3010 s, 1668 m, 1450 s, 1428 s, 1281 s, 1139 s, 1115 s, 997 w, 948 s, 851 s
	3017-70-7	a, 1.78 (s)[b] b, 1.85 (s)[b] c, 2.25 (s)	3 3 3	50	3000 s, 1670 s, 1475 s, 1372 s, 1220 s, 1128 s, 1029 s, 981 m, 789 s
	23068-94-2	a, 5.68 (q) b, 1.69 (d) c, 2.43 (q) d, 1.08 (t) $J_{a,b}$ = 7 cps $J_{c,d}$ = 7 cps	1 3 2	50	3002 s, 1660 s, 1450 s, 1371 s, 1300 s, 1120 s, 995 w, 927 m, 879 s, 797 s
	23068-95-3	a, 5.62 (q) b, 1.69 (d)[b] c, 5.73 (m) d, 4.60 (5) e, 1.80 (d)[b] $J_{a,b}$ = 6.5 cps $J_{c,d}$ = 4.0 cps $J_{d,e}$ = 7.0 cps	1 3 1 1 3	50	3000 s, 1670 s, 1450 s, 1285 s, 1191 m, 1045 s, 995 m, 960 s, 893 m, 788 s
	23074-38-6	a, 1.74 (s)[b] b, 1.84 (s)[b] c, 4.84 (m)[b] d, 0.97 (d)[b] e, 1.03 (s)[b] $J_{a,b}$ = 7 cps $J_{c,d}$ = 3 cps $J_{c,e}$ = 3 cps	3 3 1 3 3	50	3020 s, 1650 s, 1452 s, 1290 s, 1130 s, 1114 s, 998 m, 957 m, 851 s, 790 s

[a] s, singlet; d, doublet; q, quartet; m, multiplet. [b] Overlap.

Arrhenius A factor or entropy term as the most reasonable explanation for the reactivity differences. The decrease in entropy that must accompany this increase in relative reactivity probably can be ascribed to increased rotational freedom in going from the allene to the bromoallyl radical. Because of the composite nature of the A factor, more detailed speculation is fruitless.

The determination of the orientation of addition was unambiguous, with one exception. The attack of the bromine atom is effectively on the central carbon of the allenic system. If there is attack on the terminal carbons, it is not kinetically important under our reaction conditions, but can be invoked as an explanation for the small dependence of product distribution on HBr concentration in the addition of HBr to 1,3-dimethylallene. The ratio of center to terminal carbon attack drops from 94:6 down to 85:15 with a tenfold increase in the HBr/allene ratio (1:1 to 10:1). This may well reflect the reversibility of attack at the terminal carbons, because a more statistical process becomes possible when the chain-transfer step is rendered more likely.

One observes much the same sort of situation with the formation of three products from methylallene. The temperature dependence of product distribution (6.5% of nonterminal hydrogen atom abstraction at 40°, 9.7% at 120°) suggests that there is a loss of selectivity with increased temperature. This is not observed with 1,1-dimethylallene, because there is never enough loss of selectivity with increased temperature to produce any detectable nonselective product. Thus one sees here the expected behavior of free radicals—loss of selectivity with increased temperature. This behavior is seldom observed with reactions as sensitive to structural alteration as HBr addition.

Experimental Section

The hydrogen bromide was CP grade from Matheson Co. The allenes, except 1,1-dimethylallene, were commercial chemicals; allene came from Matheson Co., the others from the Chemical Samples Co. 1,1-Dimethylallene was prepared by the method of Doering[17] and Hoffman.[18] All compounds were degassed before use and dried thoroughly over phosphorus pentoxide. The reaction system was a conventional all-glass apparatus except for the quartz reaction vessel, the quartz spiral Bourdon gauge, and the quartz medium-pressure mercury arc lamp (GE 100 W). Gas chromatography was done on apparatus connected directly to the reaction system, using hydrogen as the carrier gas, and either dinonyl phthalate columns or a mixture of di-2-ethylhexyl sebacate and dimethylsulfolane. Reaction times were short, usually less than 5 min, and were kept to less than 10% reaction in the kinetic runs. Product identification was largely by nmr, using 50% solutions in CCl_4 run in a Varian A-60 spectrometer. All gas-phase runs and reactions were carried out at least in triplicate, and under a variety of temperatures and pressures. The yields, relative reactivities, and activation energies are reproducible to *ca.* ±2%.

Registry No.—Allene, 463-49-0; methylallene, 590-19-2; 1,1-dimethylallene, 598-25-4; 1,3-dimethylallene, 591-96-8; tetramethylallene, 1000-87-9.

(17) W. von E. Doering and P. M. LaFamme, *Tetrahedron*, **2**, 75 (1958).
(18) R. Hoffman, *ibid.*, **22**, 521 (1966).

N-Nitrenes. IX. The Reaction of 1,1-Dibenzylhydrazine Anions with Tosyl Azide, Oxygen, and Nitrous Oxide

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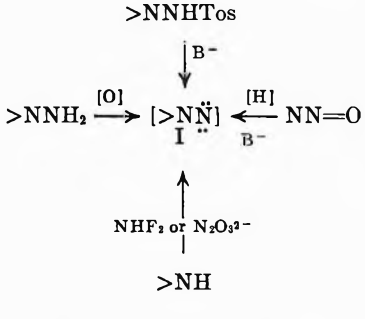
Received September 17, 1969

The diazo transfer reaction of tosyl azide to the anion and to the dianion of 1,1-dibenzylhydrazine gives bibenzyl, benzaldehyde dibenzylhydrazone, and 3,3-dibenzyl-1-tosyltriazene. The effect of temperature, the nature of the anion, and the conditions of the reactions, and the mechanisms by which these products are formed, are discussed. Evidence for the participation of N-azidodibenzylamine as an intermediate has been adduced. The reaction of the monoanion of 1,1-dibenzylhydrazine with nitrous oxide and with oxygen results in the formation of the same products (except for the triazene) as are obtained with tosyl azide.

Through the N-nitrene[2] intermediate I, moderate success has been achieved in the gross rationalization of the products formed in a number of reactions[3-8] (Scheme I). The sequence of events between the time the reactants are brought together and the isolation of the products is a matter of conjecture. The questions as to whether or not N-nitrenes are involved and their behavior under the reaction conditions being used are still unresolved.

SCHEME I



In order to eliminate as many parameters as possible, a method which would produce N-nitrenes directly was needed. By analogy with the generation of carbenes and nitrenes from the corresponding diazo alkanes and azides, N-azides (II) should give N-nitrenes (I) by loss of elemental nitrogen.

$$>\bar{C}-\overset{+}{N}\equiv N \longrightarrow >C: + N_2 \quad (1)$$

$$-\bar{N}-\overset{+}{N}\equiv N \longrightarrow -\ddot{N}: + N_2 \quad (2)$$

$$\underset{\text{II}}{>N-\bar{N}-\overset{+}{N}\equiv N} \longrightarrow \underset{\text{I}}{>N-\ddot{N}:} + N_2 \quad (3)$$

A major portion of our research effort has been devoted to the development of new and mild methods of preparation of azides. Presumably, these techniques could be applied to the preparation of N-azides. The formation of azides and diazo alkanes[9] by the *diazo transfer* reaction to the anions of the appropriate amine derivatives has been reported.[10] Diazo alkanes were obtained from the reaction of oxygen and tosyl azide with anions of hydrazones[11] and by the *azido transfer* reaction of tosyl azide to ketimine anions.[10c]

We are now reporting the results of our investigations of the reactions of the monoanion and of the dianion of 1,1-dibenzylhydrazine with tosyl azide.

Results

The monoanion and the dianion of 1,1-dibenzylhydrazine were prepared by addition of the appropriate

(1) To whom all inquiries should be addressed. Fellow of the Alfred P. Sloan Foundation.
(2) In this discussion, it is by no means implied that the involvement of N-nitrenes as fully developed entities has been proven.
(3) For a summary, see C. G. Overberger, J.-P. Anselme, and J. G. Lombardino, "Organic Compounds with Nitrogen-Nitrogen Bonds," The Ronald Press Co., New York, N. Y., 1966, p 89.
(4) C. G. Overberger, M. Valentine, and J.-P. Anselme, *J. Amer. Chem. Soc.*, **91**, 687 (1969).
(5) L. A. Carpino, *J. Org. Chem.*, **30**, 736 (1965), and previous papers.
(6) (a) D. M. Lemal, *et al.*, *J. Amer. Chem. Soc.*, **85**, 1944 (1963); (b) *ibid.*, **86**, 2395 (1964).
(7) (a) C. L. Bumgardner, K. J. Martin, and J. P. Freeman, *ibid.*, **85**, 97 (1963); (b) C. L. Bumgardner and J. P. Freeman, *ibid.*, **86**, 2233 (1964).
(8) D. M. Lemal and T. W. Rave, *ibid.*, **87**, 393 (1965).

(9) Diazo alkanes can formally be considered as N-nitrenes (iii) and can be viewed as arising from N-azidimines (III).

$$\underset{\text{III}}{>C=N-N_3} \xrightarrow{-N_2} \underset{\text{i}}{>C=\overset{+}{N}-\bar{N}} \longleftrightarrow \underset{\text{ii}}{>\bar{C}-\overset{+}{N}\equiv N} \longleftrightarrow \underset{\text{iii}}{>C-\ddot{N}-N}$$

(10) (a) G. Koga and J.-P. Anselme, *Chem. Commun.*, 446 (1968); (b) J.-P. Anselme and W. Fischer, *Tetrahedron*, **25**, 855 (1969); (c) J.-P. Anselme, W. Fischer, and N. Koga, *ibid.*, **25**, 89 (1969).
(11) (a) W. Fischer and J.-P. Anselme, *J. Amer. Chem. Soc.*, **89**, 5312 (1967); N. Koga and J.-P. Anselme, unpublished results. (b) W. Fischer and J.-P. Anselme, *Tetrahedron Lett.*, 877 (1968).

TABLE I

PRODUCTS OF THE REACTION OF ANIONS OF 1,1-DIBENZYLHYDRAZINE WITH *p*-TOLUENESULFONYL AZIDE, NITROUS OXIDE, AND OXYGEN[a]

Anion	Temp (conditions)	Hydrazine consumed, mmol	Bibenzyl, %	Hydrazone,[b] %	Triazene, %	$TosNH_2$,[c] %	$TosN_3$ recovered, mmo
Mono-	Room	18.6	49	30	...	33	7.4
Mono-	Low	20.1	23	30	16	37	Traces
Mono-	Low[d]	19.2	11	16	28	35	4.2
Di-	Room	24.6	42	10	...	82	Traces
Di-[e]	Low[d]	>95%	Traces	14	13	83	3.8
Mono-[f,g]	Room (O_2)	20.1	27	22	...		
Mono-[f,h]	Room (N_2O)	10.8	12	11	...		

[a] Percentage yields are corrected for recovered 1,1-dibenzylhydrazine. Thirty millimoles of 1,1-dibenzylhydrazine was used except as noted otherwise. An equivalent amount of tosyl azide was used. [b] N,N-Dibenzylbenzalhydrazone; percentage yield based on reaction 10. [c] Percentage yields are based on the amount of uncovered tosyl azide. [d] Reverse addition (anion added to tosyl azide). [e] Twenty millimoles of hydrazine and 40 mmol of tosyl azide were used. [f] See Experimental Section. [g] Dibenzylamine (19%) and benzoic acid (12%) were also isolated. [h] An unknown compound (0.3 g, mp 92–93.5°) having NH (3225 cm^{-1}) and C=O (1690 and 1650 cm^{-1}) absorptions was also isolated. The results of the elemental analysis suggest the formula $C_{14}H_{14}N_2O$.

TABLE II

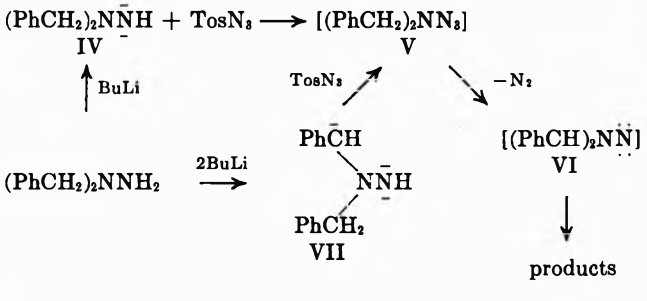
REACTION PRODUCTS OF 1,1-DIBENZYLHYDRAZINE ANIONS WITH TOSYL AZIDE, OXYGEN, AND NITROUS OXIDE[a]

Anion	Temp (conditions)	Hydrazine recovered	Bibenzyl	Hydrazone	Triazene	$TosNH_2$	$TosN_3$
Mono-	Room	2.40	1.65	0.85	...	1.70	1.45
Mono-	Low	2.10	0.85	0.90	1.20	1.90	Traces
Mono-	Low[b]	2.30	0.40	0.46	2.00	1.80	0.25
Di-	Room	1.20	1.90	0.35	...	4.20	Traces
Di-	Low[b]	Traces	Traces	0.43	0.96	2.85	0.30
Mono-	Room[c] (O_2)	2.10	1.00	0.66	...	...	...
Mono-	Room[d] (N_2O)	4.10	0.25	0.18	...	...	...

[a] All weights are in grams; see also footnotes to Table I. [b] Reverse addition (anion added to tosyl azide). [c] Other products identified follow: dibenzylamine, 0.77 g; benzoic acid, 0.3 g. [d] A compound, mp 92–94° ($C_{14}H_{14}N_2O$), was also isolated.

amount of *n*-butyllithium to the hydrazine. Then a solution of tosyl azide in tetrahydrofuran was added and the reaction was allowed to proceed. In addition to recovered 1,1-dibenzylhydrazine and tosyl azide and the expected by-products (tosylamide and nitrogen gas), the following compounds were isolated and characterized in the various runs: bibenzyl (VIII), benzaldehyde dibenzylhydrazone (IX), and 3,3-dibenzyl-1-tosyltriazene (X). The results are collected in Tables I and II along with the data from the reaction of the monoanion of 1,1-dibenzylhydrazine with oxygen and with nitrous oxide.

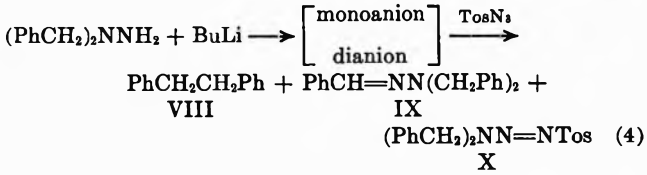
SCHEME II



Discussion

By analogy to the reaction of primary amine anions with tosyl azide, N-azidodibenzylamine (V) may be viewed as the first product of the reaction of the monoanion (IV) of 1,1-dibenzylhydrazine with tosyl azide (Scheme II). Whether or not V has any real existence even as a highly unstable intermediate is not certain at this time, although the evidence presented later would seem to support such an assumption.[12] The results of the reaction depicted below, as well as those of the dianion VII of dibenzylhydrazine[13] with tosyl azide, can be most easily rationalized *via* the intermediacy of the N-nitrene VI. Similarly, the products of the reaction of IV with nitrous oxide and oxygen are also best explained in terms of VI.

An examination of the data of Table I indicates that the expected fragmentation product bibenzyl (VIII) is formed in all cases, even though it is not necessarily the main product. The formation of bibenzyl *via* the intermediacy of dibenzylaminonitrene (VI) had been previously postulated,[3-8] although direct



evidence for this intermediate was still lacking. However, recent reports[14] as well as the early work of Urry, McBride, and coworkers,[15] while not proving

(12) Two N-azidamines have been reported previously: (a) H. Bock and K. L. Kompa, *Z. Anorg. Allg. Chem.*, **332**, 238 (1964); (b) N. Wyberg and A. Gieren, *Angew. Chem., Int. Ed. Engl.*, **1**, 664 (1962).

(13) The deep red color of the dianion suggests that it exists in a large part as the C,N dianion; *i.e.*, the second proton is removed from the α carbon.

(14) R. W. Atkinson and C. W. Rees, *Chem. Commun.*, 1230 (1967); C. W. Rees, *et al.*, *ibid.*, 146, 147, 377 (1969).

(15) W. R. McBride and H. W. Kruse, *J. Amer. Chem. Soc.*, **79**, 572 (1957); W. H. Urry, H. W. Kruse, and W. R. McBride, *ibid.*, **79**, 6568 (1957); W. H. Urry, P. Szecsi, C. Ikoku, and D. W. Moore, *ibid.*, **86**, 2224 (1964).

the existence of VI, add credence to its postulation as the direct source of bibenzyl.

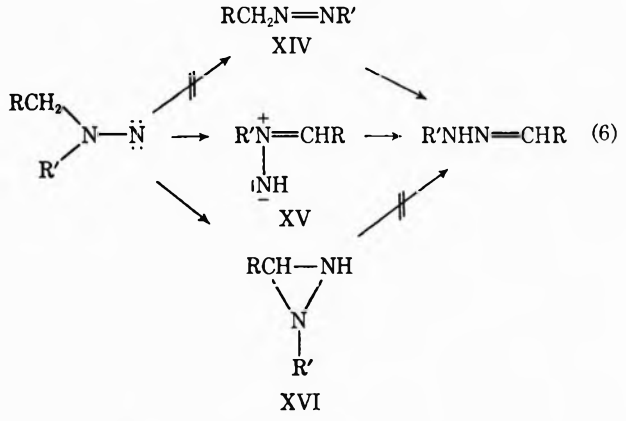
The isolation of benzaldehyde dibenzylhydrazone (IX), sometimes in substantial quantities, was unexpected at first sight. It had never been recognized[16] previously as one of the reaction products of VI. The only report of products of a related nature was that of Urry and Ikoku,[17] who found the hydrazones XII as one of the products of dialkylaminonitrenes (XI).

$$\underset{\text{XI}}{2(RCH_2)_2NN:} \longrightarrow \underset{\text{XII}}{(RCH_2)_2NN{=}CHR} \qquad (5)$$

R = H, alkyl

The formation of benzaldehyde dibenzylhydrazone (IX) as a ubiquitous product of our studies[18] indicated that this was a result of major significance in the overall fate of the dibenzylaminonitrene VI. The reaction of benzyl benzalhydrazone (XIII) with 1,1-dibenzylhydrazine could give IX, since XIII might have been formed by the rearrangement of VI.[6b,19] However, when XIII was treated with 1,1-dibenzylhydrazine or its anion, no IX could be detected. The formation of IX in other reactions[16] further rules out this possibility.

Lemal, Menger, and Coates[6b] had shown that neither the azo alkanes (XIV) nor the diaziridines (XVI) could



be intermediates in the *diazene–hydrazone* rearrangement. These authors reluctantly accepted the azomethine imine (XV)[20] as a tentative intermediate despite what they felt were serious reservations. We suggest that XV is, indeed, the intermediate leading not only to hydrazones of the type reported by Lemal and his group,[6b] but also to IX.[21]

The third compound isolated in the reactions with tosyl azide, 3,3-dibenzyl-1-tosyltriazene (X), is the first member of a novel class of compounds, 3,3-dialkyl-1-tosyltriazenes.[22] Low temperatures and high concentration of tosyl azide favored the formation of X, the generation of which can be viewed as arising directly from the reaction of the anions with tosyl azide (reaction 9). However, in view of the beneficial effect of low temperature on its formation and its yield, it is more likely that X was generated from the reaction

$$(PhCH_2)_2N\bar{N}H + TosN_3 \longrightarrow (PhCH_2)_2NNH\bar{N}Tos \xrightarrow{TosN_3}$$

$$\underset{\text{X}}{(PhCH_2)_2NN{=}NTos} \qquad (7)$$

of either N-azidodibenzylamine (V) or dibenzylaminonitrene (VI) with tosyl azide.

The data of Table I also indicate that the total percentage yield of VIII, IX, and X amounts to 49–79%. The notable exception is that of the low-temperature, reverse-addition reaction of the dianion with a 100% excess of tosyl azide. If the dianion VII is involved, the formation of complex products (as indicated by the formation of tars) would be expected from the reaction of a second molecule of tosyl azide at the α carbon; it is also the only case in which practically none of the starting hydrazine could be recovered.[23]

It is evident from our data that the triazene is being formed at the expense of bibenzyl at lower temperature while the hydrazone yield remains the same. When reverse addition and low temperatures are used, the triazene becomes the major product. This could indicate that V (or VI) may have longer lifetime under these conditions. The complete absence of X in the reaction of tosyl azide with VII, at room temperature, along with the rather high conversion into bibenzyl, suggest that fragmentation is the preferred route. The following mechanisms are suggested as likely paths to explain our results.

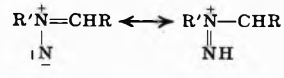
(16) Reexamination of the literature indicated that indeed hydrazones of types IX and XII had been formed. Busch and Weiss [*Ber.*, **33**, 2701 (1900)] isolated IX by heating 1,1-dibenzylhydrazine in ethanol and acetic acid. Evidently, air oxidation had occurred to give VI, which then gave IX. Similarly, the reduction of N-nitrosodibenzylamine also gave IX. In complete agreement with the results, Overberger and Marks [*J. Amer. Chem. Soc.*, **77**, 4101 (1955)] isolated a minor product, mp 86–87°, from the oxidation of 1,1-dibenzylhydrazine with *t*-butyl hypochlorite in basic medium; it was assigned the structure of tribenzylhydrazine and formed a picrate, mp 140–141°. An authentic sample of IX melts at 86–87° and its picrate melts at 137–139°. Subsequently, Overberger, Lombardino, and Hiskey [*J. Amer. Chem. Soc.*, **80**, 3009 (1958)] reported that lithium in liquid ammonia gave, in addition to some bibenzyl, "tribenzylhydrazine." There seems to be little doubt that Overberger and his group indeed obtained IX, both from the reduction of N-nitrosodibenzylamine and from the reaction of 1,1-dibenzylhydrazine with *t*-butyl hypochlorite. Carter and Stevens [*J. Chem. Soc.*, 1743 (1961)] isolated substantial amounts of the hydrazones corresponding to IX. Overberger and Marullo [*J. Amer. Chem. Soc.*, **83**, 1378 (1961)] obtained IX in 65% yield from the oxidation of 1,1-dibenzylhydrazine with potassium bromate in strongly acidic solution.

(17) W. H. Urry and C. Ikoku, Abstracts, 146th National Meeting of the American Chemical Society, Denver, Colo., Jan 1964, p 25c. W. H. Urry, A. L. Olsen, E. M. Bens, H. W. Kruse, and C. Ikoku, *U. S. Gov. Res. Develop. Rep.*, **40**, 107 (1965); *Chem. Abstr.*, **64**, 14078*d* (1966).

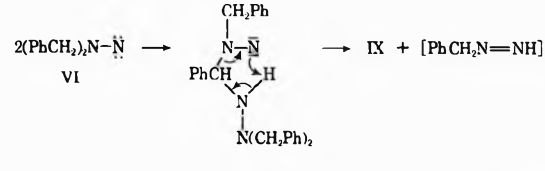
(18) It has also been isolated in other oxidation studies carried out in our laboratories. These results will be the subject of a future paper.

(19) M. Busch and K. Lang, *J. Prakt. Chem.*, **144**, 291 (1936).

(20) In one of its resonance forms, XV could be regarded as a "diimide ylide."



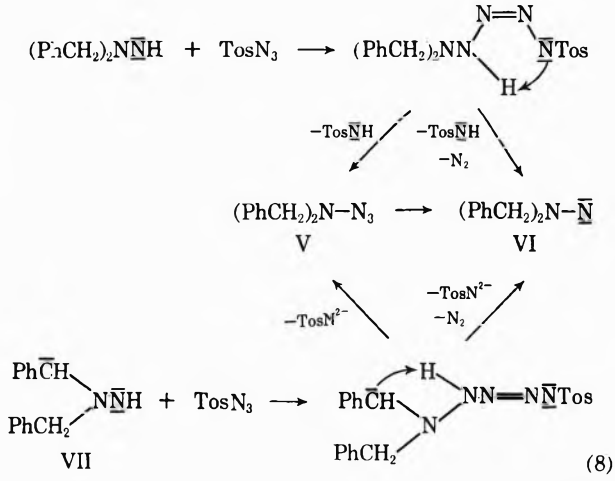
(21) The formation of IX does not necessarily require XV and could involve nitrene insertion and give IX; however, the likelihood of VI reacting with itself, as shown in the reaction below, is remote.



(22) The dimethyl analog has also been prepared and characterized. The nmr spectra of the 3,3-dialkyl-1-tosyltriazenes exhibited *two* sharp, well-defined peaks for the α hydrogens. See G. Koga and J.-P. Anselme, *Chem. Commun.*, 894 (1969).

(23) The oxidation products of the monoanion with oxygen amounts to 63% total yield (benzoic acid divided by 2). Nitrous oxide is known to be a much less effective *diazo transfer* agent.[10a]

Formation of N-azidodibenzylamine (V) and/or dibenzylaminonitrene (VI) is depicted in reaction 8.

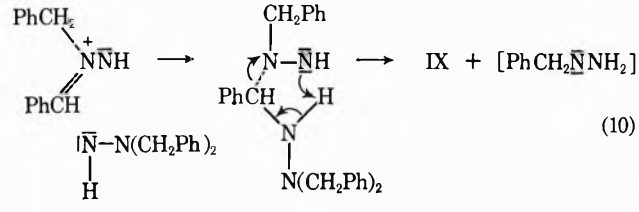


(8)

Formation of bibenzyl (VIII) is depicted in reaction 9.

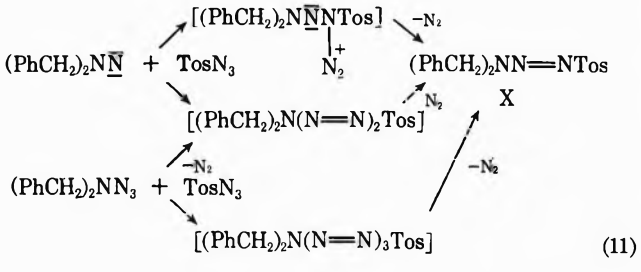
$$(PhCH_2)_2NN \xrightarrow{-N_2} PhCH_2CH_2Ph + N_2 \qquad (9)$$

Formation of benzaldehyde dibenzylhydrazone (IX) is depicted in reaction 10.



(10)

Formation of 3,3-dibenzyl-1-tosyltriazene (X) is depicted in reaction 11.



(11)

The ultimate goal of our program has been to prepare N-azidamines (II) as sources of N-nitrenes (I). The evidence that we have gathered so far suggests that, indeed, both the N-azidamine V and the N-nitrene VI are formed in our reactions. Supporting evidence for the formation of V was obtained from the following experiments. After the anion IV was treated with tosyl azide at −50°, the temperature was allowed to rise to 0–10°. The solvent was evaporated from an aliquot, and infrared spectral examination of the pasty residue showed, in addition to the azide band of tosyl azide at 2120 cm^{-1}, a small absorption at 2060 cm^{-1}. The ratio of the two bands was *ca.* 3:1. The bulk of the reaction mixture was allowed to warm to 15° and quenched with ice–water. Extraction with ether, followed by washing with dilute hydrochloric acid and evaporation of the solvent, gave an oil which showed the same two bands but with the ratio of the 2120- and 2060-cm^{-1} bands increased to 10:1. Upon standing at room temperature, the oil evolved gas; the following day, the band at 2060 cm^{-1} had completely disappeared and a 30% yield of bibenzyl was obtained. If the reaction mixture, having reached room temperature, was cooled back to −50° and triphenylphosphine was added, no significant yield of bibenzyl was obtained. Presumably, the triphenylphosphine reacted with the N-azidodibenzylamine[12a] to form the triphenylphosphine adduct; however, attempts to isolate it from the complex reaction mixture failed.

The reaction of the monoanion of 1,1-dibenzylhydrazine with nitrous oxide can be visualized as proceeding through the same steps as when tosyl azide is used. In the case of oxygen, none of the triazene X can be formed; however, dibenzylamine and benzoic acid were isolated in substantial yields.

The results of the study reported here can be summarized as follows. *Diazo transfer* of tosyl azide to the monoanion (or dianion) of 1,1-dibenzylhydrazine gives N-azidodibenzylamine (V), which is moderately stable at low temperatures. The loss of nitrogen from V generates dibenzylaminonitrene (VI), which can lose nitrogen to give bibenzyl (VIII) or tautomerize to the azomethine imine XV. The reaction of VI (or IX) with tosyl azide would give 3,3-dibenzyl-1-tosyltriazene. Under the strongly basic conditions prevailing in our reaction, benzaldehyde dibenzylhydrazone (IX) is probably formed according to reaction 10. It is clear, however, that a whole gamut of mechanisms may be operative, depending upon the conditions under which VI is generated.

Experimental Section

All melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord. Analyses were performed by the MHW Laboratories, Garden City, Mich. The alkyllithium compounds were used as received from α-Inorganics, Beverly, Mass. The preparation of the anions and all the reactions with tosyl azide were carried out under a nitrogen atmosphere. The compounds obtained were identified by their physical constants and by comparison of their infrared spectra with those of authentic samples.

Dibenzylhydrazine Anion Solution.—*n*-Butyllithium (30 mmol) in hexane was added during the course of 30 min to a solution of 6.4 g (30 mmol) of 1,1-dibenzylhydrazine in 100 ml of tetrahydrofuran under a nitrogen atmosphere with cooling and efficient stirring. The initially colorless solution turned deep wine red toward the end of the addition. Twice the amount of *n*-butyllithium was used with prolonged stirring after the addition to prepare the dianion solution. In this case, the deep red color developed much sooner.

Reaction with Nitrous Oxide.—Dibenzylhydrazine monoanion solution in a 300-ml pressure bottle was stirred at room temperature for 12 hr under 20–40-psi pressure of nitrous oxide. The color of the reaction mixture turned light tan after the introduction of nitrous oxide. The reaction mixture was then poured into cold water and extracted with ether. The ethereal extract was washed with 1 *N* hydrochloric acid to separate the basic fraction and dried over magnesium sulfate. Evaporation of the solvent gave a neutral residue which was chromatographed. The basic fraction was distilled *in vacuo* after a conventional work-up.

Reaction with Tosyl Azide at Room Temperature.—To the dibenzylhydrazine anion solution was added dropwise a solution of 5.9 g (30 mmol) of tosyl azide in 20 ml of tetrahydrofuran at room temperature. From the initially light orange solution, a white solid soon precipitated. After the completion of the addition, the reaction mixture was stirred for 1–2 hr at room temperature. The reaction mixture was worked up as previously described.

Reaction with Tosyl Azide at Low Temperature.—The hydrazine anion solution was cooled to −50 to *ca.* −60° in Dry Ice–isopropyl alcohol. A solution of 5.9 g (30 mmol) of tosyl azide in 20 ml of tetrahydrofuran was added to the above solution during the course of 1 hr with efficient stirring. The reaction mixture became reddish brown and gas began to evolve slowly and amounted to a total of *ca.* 15 mmol (350–400 ml) before all of the tosyl azide was added. After the completion of the addition, the temperature was allowed to rise slowly to room temperature. A white solid precipitated at −10°. The total volume of evolved nitrogen amounted to *ca.* 30–40 mmol (750–800 ml). The reaction mixture was worked up as usual.

Reaction with Oxygen.—A rapid stream of oxygen was bubbled into the solution of dibenzylhydrazine monoanion for 30 min at room temperature. The color changed to light brown and to reddish brown toward the end of the reaction. There was no obvious heat evolution. The reaction mixture was worked up as before, with the exception that the washing with hydrochloric acid was omitted. The aqueous layer, after extraction with ether, gave a positive test for peroxide ion.

The Chromatographic Separation.—The crude reaction mixture, diluted with a small amount of benzene, was adsorbed on a column (i.d. 24 mm, length 600 mm) packed with 150 g of Fisher A540 alumina. The sequence of eluents and main eluates therefrom were as follows (Table III).

TABLE III

Fraction	Eluent	Eluate
1	Hexane	Bibenzyl
2	Hexane–benzene (1:1)	Tosyl azide
3	Benzene	Benzaldehyde dibenzylhydrazone
4	Benzene	Dibenzylhydrazine (O_2 reaction)
5	Benzene	Dibenzylamine (O_2 reaction)
6	Benzene–ether (1:1)	$C_{14}H_{14}N_2O$ compound (N_2O reaction)
7	Benzene–ether (1:1)	3,3-Dibenzyl-1-tosyltriazene

Although there were obtained many minor eluates, including benzaldehyde, along with above compounds, no effort was made to identify them.

In the case of the reaction with oxygen, the basic fraction was not separated from the rest of the reaction mixture.

3,3-Dibenzyl-1-*p*-toluenesulfonyltriazene.—A solution of 30 mmol of 1,1-dibenzylhydrazine monoanion (prepared under a nitrogen atmosphere) from 6.4 g (30 mmol) or hydrazine in 100 ml of dry tetrahydrofuran and 13.5 ml of 22% *n*-butyllithium was cooled to −50 to −60° in Dry Ice–isopropyl alcohol, and 5.9 g (30 mmol) of tosyl azide in 20 ml of tetrahydrofuran was added dropwise. After addition was completed, the solution was allowed to warm up gradually to *ca.* 10°. The initially reddish brown solution turned milky brown by the formation of a white precipitate. The reaction mixture was poured into ice-water and extracted with three 100-ml portions of ether. The combined ethereal extracts were washed successively with water, dilute hydrochloric acid, and water. After having been dried over magnesium sulfate, the solution was evaporated *in vacuo*.

The residual oil was chromatographed, and after the elution of other components, a white solid was obtained from the 1:1 benzene–ether fraction. The compound, mp 79–81°, weighed 1.20 g after recrystallization from carbon tetrachloride. It was characterized and identified as 3,3-dibenzyl-1-tosyltriazene from its elemental analysis and infrared and nmr spectra.[22]

Anal. Calcd for $C_{21}H_{21}N_3SO_2$: C, 66.47; H, 5.58; N, 11.07; S, 8.45. Found: C, 66.73; H, 5.45; N, 10.96; S, 8.34.

Its infrared spectrum, in addition to the expected aromatic and aliphatic bands, exhibited a strong absorption at 1145 and 1180 and at 1325 cm^{-1} ($-SO_2-$). The benzylic protons appeared as two sharp singlets at τ 4.97 and 5.10.[22]

Spectral Detection of N-Azidodibenzylamine.—The monoanion[24] of 1,1-dibenzylhydrazine was treated with 1 equiv of tosyl azide at −50 and −60° and allowed to warm to 0–10° as described above. The solvent was evaporated *in vacuo* below room temperature from a small aliquot. The pasty residue was bubbling on standing and showed two azide bands at 2120 and 2060 cm^{-1}. The former band, *ca.* three times stronger in intensity than the latter, is due to unreacted tosyl azide. The remaining portion of the reaction mixture was worked up as described before. The residual oil showed a much weaker (the ratio of the 2120: 2060-cm^{-1} bands was *ca.* 10:1) but still discrete N-azide band which disappeared completely after standing overnight. Distillation of the residue gave bibenzyl in *ca.* 30% yield; the small discrepancy with the 23% yield given in Table I is due to the different isolation procedures.

Registry No.—Tosyl azide, 941-54-8; oxygen, 7782-44-7; nitrous oxide, 10024-97-2; IV, 23349-33-9; VII, 23349-34-0; X, 23349-35-1.

Acknowledgment.—The generous support of this work by the National Institutes of Health under Grant GM 13689-03 is hereby acknowledged with deep appreciation.

(24) Methyllithium was used to prepare the monoanion in these experiments.

The Acid-Catalyzed Nitramine Rearrangement. IV. The Influence of Aromatic Ring Substituents on Rearrangement Rate[1-3]

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Received September 9, 1969

The rates of rearrangement of 16 *meta*- and *para*-substituted N-nitro-N-methylanilines were determined and correlated by means of Hammett's equation. The best fit of the experimental data was obtained when the results were plotted against σ^+ constants ($\rho = -3.7$). The π-complex and cartwheel mechanisms of the nitramine rearrangement are incompatible with these findings. The experimental observations can be interpreted by a mechanism in which the rate-determining step is the homolytic scission of the nitrogen–nitrogen bond in the protonated nitramine.

Previous investigations in this series[1] have demonstrated that the acid-catalyzed aromatic nitramine rearrangement involves reversible protonation of the substrate followed by a rate-determining unimolecular reaction of the protonated nitramine. Product studies[1] suggest that the latter process may be a cleavage of the N–N bond in the nitramine to yield a pair of solvent-caged radicals, which may either recombine to yield isomerized products or may dissociate, be reduced, and form nitrous acid and aromatic amine. Further information about the rate-determining step should be available from a study of the influence of aromatic ring substituents on the rate of the nitramine rearrangement. Since the reaction is subject to specific acid catalysis, substituent effects must reflect not only the electronic requirements of the protonation step, but also those of the N–N bond-breaking step.

The effect of structure on the rate of the nitramine rearrangement was implicit in the results of some kinetic studies carried out in the early 1900's.[4] The reaction of 2,4-dichloro-N-nitroaniline was 10 times slower than the isomerization of N-nitroaniline and 25 times slower than the rearrangement of 2-bromo-4-methyl-N-nitroaniline, implying that electron-withdrawing groups retard the reaction. Similar effects are apparent in the comparative behavior of 4,N-dinitro-N-methylaniline and 2,4,N-trinitro-N-methylaniline.[5] The former compound, being less encumbered with electron-attracting substituents, rearranges more easily.

These fragmentary results are, however, far from being definitive, and much more precise information about the nature of the N–N bond cleavage should be obtainable from a systematic study of the influence of aromatic ring substituents on the rate of rearrangement.

Results and Discussion

Products of Rearrangement of Substituted Nitramines.—Previous investigations in this series[1] have shown that the nitro group migrates only to the *ortho* and *para* positions of the aromatic ring and that a small fraction of the product corresponds to complete loss of the nitro group. This study was more superficial than the previous ones in that only the major products of rearrangement were identified and accounted for. However, the results summarized in Tables I and II confirm the previous findings. Thus the principal product formed upon rearrangement of a nitramine substituted in the *para* position with an electron-releasing substituent (MeO, MeS, Me, F, Cl, Br, Ph, and PhO) is the *ortho* nitroaniline (formed in 55–85% yields in the cases studied). The presence of strongly electron-withdrawing substituents (NC, O_2N, and $MeSO_2$) in the *para* position causes the yield of the *ortho* nitro compound to drop to 25–45%. The nitrated product from *p*-bromo-N-nitro-N-methylaniline contained 10–17% *p*-nitro-N-methylaniline from bromine atom displacement. A similar displacement occurred in the *p*-chloro compound only to the extent of 0.2%.

Substituent Effects on Rearrangement Rates.—The second-order rate constants for the acid-catalyzed isomerization of 16 *meta*- and *para*-substituted N-nitro-N-methylanilines were determined and are listed in Table III. These rate constants cover a range of over a half-millionfold. Electron-donating groups increase the rate and electron-withdrawing groups slow the reaction indicating that the forward course of the

(1) Previous papers in this series: W. N. White, D. Lazdins, and H. S. White, *J. Amer. Chem. Soc.*, **86**, 1517 (1964); W. N. White, C. Hathaway, and D. Huston, *J. Org. Chem.*, **35**, 737 (1970).

(2) Part of this work has been reported in preliminary form: W. N. White, J. R. Klink, D. Lazdins, C. Hathaway, J. T. Golden, and H. S. White, *J. Amer. Chem. Soc.*, **83**, 2024 (1961).

(3) This work was supported by Grants G-7345 and GP-1970 from the National Science Foundation.

(4) K. J. P. Orton, *Brit. Assoc. Advan. Sci. Rep.*, 115 (1908); A. E. Bradfield and K. J. P. Orton, *J. Chem. Soc.*, 915 (1929).

(5) E. D. Hughes and G. T. Jones, *ibid.*, 2678 (1950).

TABLE I

2-NITRO-4-X-N-METHYLANILINES

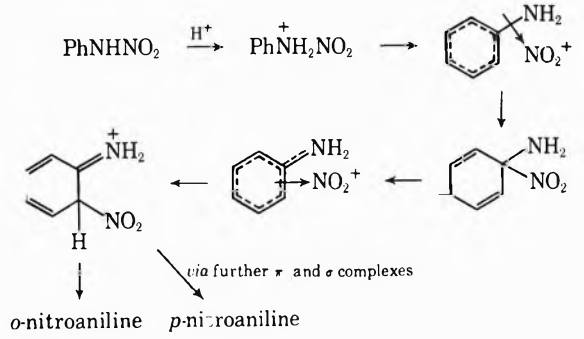
X	Registry no.	Yield, %	Solvent[a]	Mp, °C	Lit. mp, °C
MeS	23042-45-7	63	MeOH–H_2O	64–65	...[b]
MeO		85	MeOH	98–99	97–98[c]
Me		80	MeOH	84.5–85	84–85[d]
F	704-05-2	69	MeOH	74.1–74.6	...[e]
Cl		55	EtOH	107–108	109–110[f]
Br		62	MeOH	101.9–102.4	101–102[g]
Ph		85	EtOH	113–114	112[h]
PhO	23042-47-9	55	Pet. ether	104–105	...[i]
PhCO		60	PhH–MeOH	210–211	200[j]
NC		36	PhH	168.5–169.3	169[k]
$MeSO_2$		25	PhH–MeOH	193.4–193.9	193.5[l]
O_2N		35	PhH	179–180	176–177[f]

[a] Pet. ether = petroleum ether (bp 65–90°). [b] *Anal.* Calcd for $C_8H_{10}N_2O_2S$: C, 48.47; H, 5.08; N, 14.13. Found: C, 48.46; H, 5.20; N, 14.20. [c] A. M. Simonov and P. A. Uglov, *Zh. Obshch. Khim.*, **21**, 884 (1951). [d] L. Gatterman, *Chem. Ber.*, **18**, 1487 (1885). [e] *Anal.* Calcd for $C_7H_7FN_2O_2$: C, 49.41; H, 4.15; N, 16.47. Found: C, 49.00, 49.41; H, 4.18, 4.21; N, 16.33. [f] R. Stoermer and P. Hoffmann, *Chem. Ber.*, **31**, 2523 (1898). [g] J. J. Blanksma, *Rec. Trav. Chim. Pays-Bas*, **21**, 272 (1902). [h] F. Bell and P. H. Robinson, *J. Chem. Soc.*, 1127 (1927). [i] *Anal.* Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.48. Found: C, 63.74; H, 5.05; N, 11.50. [j] J. van Alphen, *Rec. Trav. Chim. Pays-Bas*, **49**, 383 (1930). [k] J. F. Mattaar, *ibid.*, **41**, 24 (1922). [l] E. Scoffone, P. de la Llosa, and M. Justisz, *Bull. Soc. Chim. Fr.*, 1553 (1959).

rearrangement involves electron depletion at the reaction center.

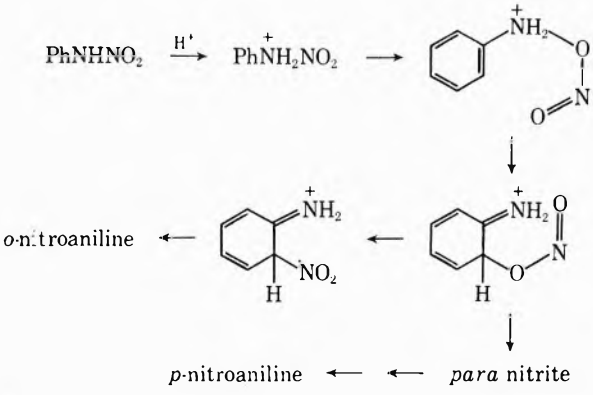
These kinetic results were treated by means of the Hammett equation. The best fit of the experimental data was afforded by σ^+ constants (correlation coefficient = 0.99). The straight-line plot had a slope ρ of -3.7. The correlation coefficients obtained with σ and σ^- constants were less than 0.92 (representative of a poor to fair fit[6]) and the points deviated considerably from a straight line. The σ^+ constants are defined by reactions[7] in which an electron deficiency is generated at the reaction center in such a way that it can be delocalized to the aromatic ring by resonance. The requirement of σ^+ constants for correlation of the nitramine rearrangement suggests that the series of steps leading from the unprotonated nitramine to the rate-limiting transition state must also involve creation of an electron deficiency delocalizable to the aromatic nucleus. The negative reaction constant, ρ, substantiates the conclusion that the substrate becomes more electron deficient as the highest energy transition state is approached. The magnitude of ρ indicates that there must be strong interaction between the reaction center and the substituent.

These findings are not compatible with the "π-complex" mechanism[8] nor the "cartwheel" mechanism[9] for the nitramine rearrangement. In the π-complex mechanism it is proposed that the protonated nitramine is transformed through a series of alternate σ and π complexes into the final products. A reaction proceeding by this path would probably be correlated by σ or σ^- constants and a small value of ρ. The amino-group electrons in the nitramine are not readily available for conjugation with the aromatic ring, since they will be largely delocalized to the highly electron-attracting nitro group. When the nitrogen–nitrogen bond is broken in the transition state for π-complex formation, these electrons should be freed for resonance with the



ring. If the process were this simple, a positive ρ and σ^- constants would be required. However, the liberated nitronium ion will probably interact with the π cloud of the aromatic system and reduce its electron richness somewhat.

In the cartwheel mechanism, it is supposed that the protonated nitramine isomerizes to a nitritoamine, which then undergoes a Claisen-like rearrangement to an *ortho* nitrite. A *para* nitrite can arise from the latter by a similar migration. Isomerization of the nitrites leads to C-nitro intermediates like those formed in direct nitration reactions. Proton loss from these species yields the *o*- and *p*-nitroanilines. The effect of substituents on this overall process is more difficult to predict. Only the protonation step involves a large polarity change, and this should be correlated by σ or σ^- constants and a small negative ρ (-1 to -2). In



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(8) M. J. S. Dewar in "Molecular Rearrangements," Part I, P. de Mayo, Ed., Interscience Publishers, Inc , New York, N. Y., 1963, pp 306–313.

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TABLE II

RATES OF REARRANGEMENT AND PRODUCT YIELDS FOR *m*- AND *p*-X-N-NITRO-N-METHYLANILINES

X	Temp, °C[a]	Concn, *M*	Concn, $HClO_4$[b]	No. of runs	10^4k_2, M^{-1} sec^{-1}	2-NO_2,[c] %	*p*-NO_2,[d] %
p-MeO	30.00	0.00200	0.00100	5	11800 ± 200	68 ± 2	
	15.00	0.00200	0.00100	4	2450 ± 100	69 ± 1	
	0.17	0.0200	0.0100	6	452 ± 3	68 ± 2	
p-MeS	30.00	0.00200	0.00100	4	7450 ± 110		
	15.00	0.00200	0.00100	4	1750 ± 60		
	0.17	0.0200	0.0100	4	345 ± 4		
p-Me	55.00	0.0100	0.00501	4	3660 ± 80	82 ± 1	
	40.00	0.0200	0.00100	6	820 ± 18	82 ± 4	
	25.00	0.0200	0.00100	4	139 ± 3	84 ± 1	
H	55.00	0.0200	0.0100	6	266 ± 6	46 ± 2	28 ± 2
	40.00	0.0200	0.0100	6	34.8 ± 0.8	48 ± 0	28 ± 1
	25.00	0.0802	0.0401	4	4.77 ± 0.04	52 ± 0	28 ± 0
p-F	55.00	0.0200	0.0100	6	233 ± 3	60 ± 1	0
	40.00	0.1002	0.0501	4	41.0 ± 0.5	62 ± 1	0
	25.00	0.0401	0.0200	4	6.47 ± 0.04	61 ± 1	0
p-Cl	55.00	0.1002	0.0501	9	157 ± 6	84 ± 2	0.2 ± 0.1
	40.00	0.1002	0.0501	4	28.4 ± 0.4	80 ± 4	0.2 ± 0.1
	25.00	0.1002	0.0501	4	4.47 ± 0.10		
p-Br	55.00	0.1002	0.0501	4	128 ± 4	67 ± 1	9.4 ± 0.3
	40.00	0.1002	0.0501	4	25.9 ± 0.8	62 ± 2	12.1 ± 0.4
	25.00	0.1002	0.0501	4	3.81 ± 0.09	56 ± 1	16.7 ± 0.1
p-CN	70.00	1.002	0.501	5	12.2 ± 0.4	43 ± 3	
	55.00	1.002	0.501	6	1.93 ± 0.05	46 ± 2	
	40.00	1.002	0.501	4	0.292 ± 0.007	46 ± 2	
p-$MeSO_2$	85.00	0.501	0.251	4	18.7 ± 0.3	32 ± 1	
	70.00	0.501	0.251	6	3.04 ± 0.17	31 ± 1	
	55.00	1.002	0.501	4	0.452 ± 0.006	37 ± 1	
p-NO_2	80.00	1.002	0.501	5	10.1 ± 0.1	41 ± 1	1.0 ± 0.1
	65.00	1.002	0.501	8	2.05 ± 0.06	41 ± 1	2.0 ± 0.1
	55.00	1.002	0.501	4	0.542 ± 0.009	40 ± 3	0.5 ± 0.5
m-MeO	55.00	0.0401	0.0200	4	458 ± 15		
	40.00	0.200	0.1002	4	82.8 ± 1.2		
	25.00	1.002	0.501	5	14.7 ± 0.8		
m-PhO	55.00	0.1002	0.0401	4	148 ± 8		
	40.00	0.501	0.200	6	23.9 ± 0.3		
	25.00	1.002	0.501	4	3.32 ± 0.10		
m-Me	55.00	0.0401	0.0200	4	672 ± 25		
	40.00	0.1002	0.0401	5	120 ± 6		
	25.00	1.002	0.501	4	18.3 ± 0.4		
m-F	70.00	0.1002	0.0401	4	143 ± 4		
	55.00	0.501	0.200	4	26.1 ± 0.3		
	40.00	1.002	0.501	4	4.58 ± 0.16		
m-Cl	70.00	0.1002	0.0401	4	103 ± 2		
	55.00	1.002	0.501	8	18.7 ± 0.8		
	40.00	1.002	0.501	8	2.92 ± 0.05		
m-Br	70.00	0.1002	0.0401	4	100 ± 2		
	55.00	1.002	0.501	5	18.2 ± 0.4		
	40.00	1.002	0.501	6	2.82 ± 0.06		

[a] Temperature of reaction, ±0.02°. [b] Ionic strength maintained constant at 1.002 *M* by addition of $NaClO_4$. [c] Per cent of 2-nitro-4-X-N-methylaniline formed. [d] Per cent of *p*-nitro-N-methylaniline formed.

TABLE III

RATE CONSTANTS FOR REARRANGEMENT OF *m*- AND *p*-X-N-NITRO-N-METHYLANILINE[a]

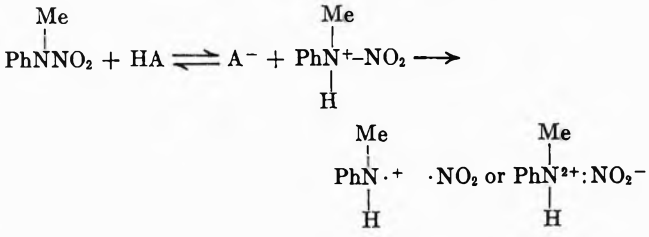
X	10^6k_2, mol^{-1} sec^{-1}	X	10^6k_2, mol^{-1} sec^{-1}
p-MeO	3,060,000[b]	*p*-Br	2590
p-MeS	1,840,000[b]	*m*-PhO	2390
p-Me	82,000	*m*-F	458
m-Me	12,000	*m*-Cl	290
m-MeO	8,280	*m*-Br	282
p-F	4,100	*p*-CN	29.2
H	3,480	*p*-NO_2	8.05[b]
p-Cl	2,840	*p*-$MeSO_2$	5.40[b]

[a] T = 40.00 ± 0.02°. [b] Extrapolated from other temperatures.

the nitramine–nitritoamine isomerization, a less electronegative center becomes attached to the amino nitrogen, and thus this process should require σ constants and a positive ρ. The *ortho* nitrite formed by rearrangement has considerable electron deficiency centered at the two positions *meta* to the amino group but not *para* to it. The substituent–rate data indicate that a sizable electron deficiency, which is delocalized to the *para* (but not the *meta*) position of the aromatic ring, is developed at the reaction center. The C-nitrite–C-nitro isomerization should be effected by substituents in the reverse manner of their influence on the N-nitro–N-nitrite change. Proton loss from the final intermediates is not kinetically significant, and thus need

not be considered in the prediction or interpretation of substituent effects. Regardless of what is chosen as the rate-determining step in the cartwheel mechanism, it is impossible to interpret the observed rate effects of substituents in terms of their influence on this and the preceding steps.

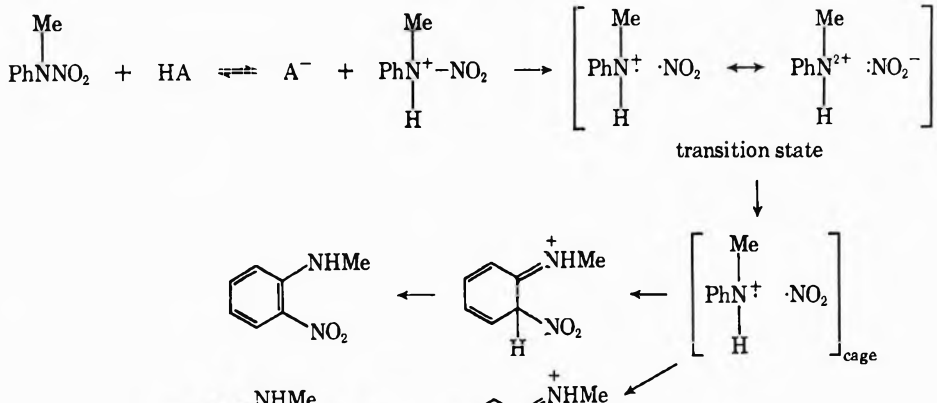
However, a mechanism involving cleavage of the nitrogen–nitrogen bond in the protonated nitramine could lead to the observed results. This would be true if this bond broke symmetrically to yield a pair of radicals in a solvent cage or if it broke unsymmetrically, both bond electrons becoming associated with the nitro group so that the amino nitrogen would be doubly electron deficient. Homolytic cleavage would produce an aromatic aminium cation radical. The electron



deficiency associated with the nitrogen atom in this species could be delocalized to the aromatic ring. Thus it would be expected that correlation of substituent effects on such a process would involve σ^+ constants and a large negative value of ρ. This supposition is supported by a number of studies that demonstrate that the generation of aromatic aminium cation radicals is correlated best by σ^+ constants. Polarographic oxidation of primary aromatic amines[10] requires σ^+ constants and large negative values of ρ (-4.3[10a] and -6.8 [10b]) for fitting the effect of substituents. Oxidation of substituted anilines with N,N-diphenyl-N-picrylhydrazyl[11] is correlated by σ^+ constants and a ρ of -1.5. Methyl proton and nitrogen hyperfine splitting constants for substituted N,N-dimethylanilinium cation radicals[12] are linearly related to σ^+ constants. Thermolyses of *t*-butyl N-arylperoxycarbamates yield arylamine radicals[13] and are correlated by σ^+ constants ($\rho = -2.2$). Hydrogen atom abstraction from the hydroxyl group of phenols and from the α carbons of α-substituted toluenes have been found to give better linear plots with σ^+ than with σ constants.[14] All of these reactions involve generation of a radical center adjacent to an aromatic ring. Most processes of this type are correlated by σ^+ constants and a negative ρ. Thus the substituent–rate data for the nitramine rearrangement should exhibit a similar dependence on σ^+ constants if this process involves homolytic nitrogen–nitrogen bond breaking in the protonated nitramine.

Unsymmetrical cleavage of this nitrogen–nitrogen bond so that both electrons became associated with the departing nitro group would produce a highly electron-deficient, dipositive amino nitrogen. Substituents would have a very large effect on such a process. Correlation would require σ^+ constants and a large negative value of ρ. Reactions in which a single positive charge is developed on the less electronegative α carbon in substituted toluenes have ρ values of -2.3 to -4.7[7]. The observed reaction constant for the nitramine rearrangement (-3.7) is not large enough for a mechanism in which the nitrogen–nitrogen bond breaks to form an anilinium dication.

Thus it is likely that the protonated nitramine undergoes bond cleavage to form an anilinium cation radical and nitrogen dioxide. The transition state for this process is undoubtedly a resonance hybrid and partakes of the character of both modes of nitrogen–nitrogen bond scission described above. The magnitude of the substituent effect suggests that the least ionic structure makes the largest contribution. The mechanism most compatible with the results of this study is the following.



Experimental Section

Preparation of *m*- and *p*-X-N-Nitro-N-methylaniline.—The substituted N-nitro-N-methylanilines were obtained from the corresponding substituted anilines. Those aromatic amines bearing substituents that do not react with phenyllithium were subjected to alkaline nitration and the resulting nitramines were methylated with methyl sulfate to prepare[15] the title compounds. Anilines substituted with nitro, cyano, keto, and sulfonyl groups were converted into the corresponding diazonium salt and the latter was oxidized to the nitramine,[16] which was methylated.[17] The resulting *m*- and *p*-X-N-nitro-N-methylanilines were purified

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(14) J. A. Howard and K. U. Ingold, *Can. J. Chem.*, **41**, 1744 (1963); G. A. Russell and R. C. Williamson, *J. Amer. Chem. Soc.*, **86**, 2357 (1964).

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(16) E. Bamberger and K. Landsteiner, *Chem. Ber.*, **26**, 485 (1893).

(17) H. J. Backer, *Rec. Trav. Chim. Pays-Bas*, **31**, 142 (1912).

TABLE IV

m- AND *p*-X-N-NITRO-N-METHYLANILINES

X	Registry no.	Solvent	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
H	7119-93-9	*a*	36.6–37.6[b]	...	...	...	...	...	...
p-MeS	23042-28-6	*c*	71.0–72.0	48.47	5.08	14.13	48.65	5.19	14.07
p-MeO	22809-78-5	*a*	68.1–69.1	52.74	5.53	15.38	52.57	5.77	15.53
p-Me	23042-30-0	*d*	73.6–74.6[e]	...	...	...	...	...	...
p-F	655-56-1	*a*	68.6–69.1	49.41	4.15	16.47	49.18	4.26	16.50
p-Cl	23042-32-2	*a*	51.9–52.4[f]	...	...	...	...	...	...
p-Br	23042-33-3	*d*	84.0–84.9[g]	...	...	...	...	...	...
p-PhS	23042-34-4	*h*	137.8–138.5	68.40	5.30	12.28	68.60	5.32	12.23
p-PhO	23042-35-5	*c*	107.5–108.0	63.93	4.95	11.48	64.17	5.18	11.44
p-PhCO	23042-36-6	*c*	136.7–137.3	65.59	4.72	10.93	65.98	4.53	11.15
p-NC	23042-37-7	*h*	104.1–104.6	54.23	3.99	23.72	54.16	4.17	23.53
p-$MeSO_2$	23042-38-8	*h*	158–159	41.77	4.38	12.17	41.86	4.39	12.20
p-O_2N	16698-03-6	*i*	138.2–139.5[j]	...	...	...	...	...	...
m-Me	23042-40-2	*k*	...[k]	57.83	6.02	16.87	57.71	6.30	17.04
m-F	23102-81-0	*a*	24–25	49.41	4.15	16.47	49.31	4.28	16.50
m-Cl	23042-41-3	*a*	48.5–49.2	45.05	3.78	15.01	45.29	3.74	14.99
m-Br	23042-42-4	*a*	43.2–43.8	36.38	3.05	12.12	36.43	3.29	12.10
m-PhO	23042-43-5	*a*	44.0–44.5	63.93	4.95	11.48	64.14	4.87	11.39
m-MeO	23042-44-6	...[k]	...[k]	52.74	5.53	15.38	52.90	5.31	14.62

[a] Petroleum ether (bp 35–60°). [b] Literature mp 38.5–39.5°: E. Bamberger, *Chem. Ber.*, **27**, 359 (1894). [c] Cyclohexane. [d] Petroleum ether (bp 65–90°). [e] Literature mp 74.5–75.5°: J. Pinnow, *Chem. Ber.*, **30**, 833 (1897). [f] Literature mp 48–49°: E. Bamberger, *ibid.*, **30**, 1248 (1897). [g] Literature mp 83.5–84.5°: reference in *f*. [h] Benzene–cyclohexane. [i] Benzene. [j] Literature mp 140°: reference in *f*. [k] Liquid.

by chromatography on neutral alumina using ether as an eluent and then by crystallization from a suitable solvent. The appropriate data regarding these compounds are summarized in Table IV.

Isolation of Rearrangement Products of *p*-X-N-Nitro-N-methylaniline.—A solution of 1.00 g of the *p*-X-N-nitro-N-methylaniline in 50 ml of methanol and 50 ml of concentrated hydrochloric acid was refluxed for 2 hr and then allowed to stand for 20 hr at 25°. The solution was cooled to 0° and the solid product was collected by suction filtration. It was purified by chromatography on neutral alumina using benzene as eluent and by crystallization. Physical constants and crude-yield data are recorded in Table I.

Kinetic Measurements.—An aliquot of 1.022 *M* perchloric acid was pipeted into a 50-ml volumetric flask and diluted with 1.022 *M* sodium perchlorate solution to within 1 cm of the mark. After the flask had stood in a constant-temperature bath for 40 min, the volume was adjusted to the mark with 1.022 *M* sodium perchlorate solution. A 1.00-ml aliquot of a nitramine solution of accurately known concentration (*ca.* 10^{-2} *M*) in dioxane was added, the contents of the flask were mixed immediately, and the flask was returned to the thermostatic bath at once. Measured samples were withdrawn at appropriate intervals and quickly quenched by rapid addition to a volume of saturated lithium acetate solution sufficient to neutralize the acid. The absorbances of the quenched samples were determined at the wavelength of maximum extinction in the visible region. The optical density at "infinite" time was approximated from a reaction sample taken after 10 half-lives.

Pseudo-first-order rate constants were calculated from the experimental data in the usual way and these were converted into second-order constants by dividing by the constant concentration of acid, which was in large excess. The kinetics of rearrangement of each nitramine were studied at three different temperatures. Two different acid concentrations were used for each temperature, and at least two runs were made with each compound at a single acid concentration and temperature. The results of these kinetic investigations are summarized in Table II.

Spectrophotometric Determination of Yields of 2-Nitro-4-X-N-methylanilines from Rearrangement of *p*-X-N-Nitro-N-methylanilines.—After completion of the kinetic runs described above, a 5.00-ml aliquot of the cooled reaction mixture was transferred to a 10.0-ml volumetric flask and 1.00 ml of 20% ammonium sulfamate was added. The resulting solution was heated at 100° for 30 min to destroy nitrous acid and remove N-nitroso groups. After cooling, the volume of liquid in the flask was brought to 10.0 ml by addition of acetic acid (8.8 *M*)–sodium acetate (1.1 *M*) buffer. The absorbance of the resulting solution was determined at five different wavelengths near the visible absorption maximum of the 2-nitro-4-X-N-methylaniline being determined.

Solutions of the pure 2-nitro-4-X-N-methylanilines in dioxane were treated in the same way as described above for solutions of the corresponding *p*-X-N-nitro-N-methylanilines in order to obtain extinction coefficients for the rearrangement products.

The concentration of 2-nitro-4-X-N-methylaniline in the reaction mixtures was calculated using Beer's law. Since the absorbance was determined at five wavelengths, there were five equations in one unknown (the concentration). The method of least squares was applied to these equations to obtain the best value.

Four of the nitramines produced two colored products on rearrangement—varying amounts of *p*-nitro-*N*-methylaniline were formed in the rearrangements of unsubstituted, *p*-chloro-, *p*-bromo-, and *p*-nitro-N-nitro-N-methylaniline in addition to the expected 2-nitro compound. The concentration of each colored substance was obtained by using the equation $A = abc + a'b'c'$, which has two unknown concentrations. Application of the method of least squares to the absorbances measured a five different wavelengths for each sample gave the best values for the concentrations of each of the products.

The results of this analysis are shown in Table II.

Mechanistic Aspects of the Photochemistry of Unsaturated Nitriles

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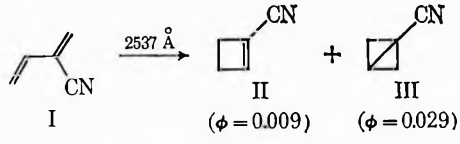
Received August 21, 1969

Simple unsaturated nitriles [acrylonitrile, crotononitrile, and 2-cyanobutadiene (I)] were shown to undergo well-defined photochemical reactions. Mechanistic aspects of these reactions were studied with the aid of quantitative measurements. The isolation of 1-cyanobicyclobutane (III) as the major product from the photolysis of I suggests a diradical intermediate (IV).

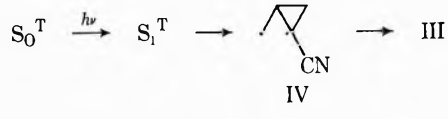
This investigation was initiated to determine the effect of the nitrile function on the solution photochemistry of simple olefins and dienes.[1] At the start of our study, only scattered accounts[2,3] of photochemistry which might involve nitrile participation had appeared. Recently, examples of triplet-state α,β-unsaturated nitriles have been reported.[4-6]

Photoisomerization of 2-Cyanobutadiene.—The solution photochemistry of acyclic 1,3-dienes has been studied in detail.[7] In general, singlet dienes tend to undergo photocyclization, while triplet dienes tend to dimerize. 2-Cyano-1,3-butadiene (I) was irradiated in dilute ether solution with 2537-Å light. The products, 1-cyanocyclobutene (II) and 1-cyanobicyclobutane (III), were isolated by gas chromatography and compared with authentic samples prepared by standard



methods.[8-10] The bicyclobutane was also indentified *via* a crystalline diiodide. Quantum yields for the formation of II and III (in ether) were determined by crystal violet leucocyanide actinometry at 30°. Measurements in other solvents were hampered by the tendency of I to undergo photopolymerization. Repeated large-scale photolysis in ether consistently allowed isolation III as the major product (usually the ratio of III/II was 1.5). Similar large-scale results were obtained in 1,2-dichloroethane and carbon tetrachloride. Attempts to sensitize the photoisomerization of I with acetone ($E_T \approx 80$, 3000 Å), triphenylene ($E_T = 67$, 3500 Å), benzophenone ($E_T = 69$, 3500 Å), acetophenone ($E_T = 74$, 3500 Å), and 9,10-dibromoanthracene ($E_{T_1} = 42$, $E_{T_2} \approx 75$; 3500 Å) gave essentially no reaction. The inability of triplet sensitizers to cause photoisomerization tends to exclude the triplet of I as the precursor of II and III; the absence of substantial dimerization suggests that the triplet of I is nonreactive.[11] No fluorescence or phosphorescence was observed for I in dilute ethanol solution at −190°. These data exclude luminescence as a major path for energy loss.

The mechanism of diene photoisomerization is of current theoretical interest,[12] as is the mechanism of bicyclobutane[13] and cyclobutene[14] ring opening. Quantum mechanical considerations have amply demonstrated their usefulness in this problem,[12,13,15] but, thus far, these deal only with concerted processes. Even so, it is not clear from these treatments whether the formation of a bicyclobutane from a transoid diene (S_1^T) is a concertedly allowed process. Moreover, the vast majority[7,16] of acyclic dienes photoisomerize to cyclobutenes as their sole product; this presents a paradox when it is recalled that simple acyclic dienes are largely transoid.[7] Although bicyclobutanes may have been recently[17] implicated in acyclic diene photolysis, the isolation of III as the major product from reaction of I is surprising. A reasonable mechanism for its formation is shown. The formation of III *via* intermediate



IV supports Srinivasan's generalization.[12] In comparing the reaction of I with that of the parent butadiene in which bicyclobutane was only a minor product, we see no reason why concerted ring closure to III should be favored by substitution of a nitrile group. A number of paths exist for the conversion of I into II. The disrotatory closure[12,15] of S_1^C is appealing, but it may not be correct. Particular care must be taken in assigning mechanism since stereochemical arguments are not available, and an independent criterion of concertedness is lacking.

(1) A preliminary account of the photodimerization of acrylonitrile has appeared: R. S. H. Liu and D. M. Gale, *J. Amer. Chem. Soc.*, **90**, 1897 (1968).

(2) J. G. Atkinson, D. E. Ayer, G. Buchi, and E. W. Robb, *ibid.*, **85**, 2257 (1963).

(3) J. A. Barltrop and R. Robson, *Tetrahedron Lett.*, 597 (1963); P. DeMayo, R. W. Yip, and S. T. Reid, *Proc. Chem. Soc.*, 54 (1963).

(4) J. Runge and R. Kache, *Zeit. Chem.*, **8**, 382 (1968); S. Hosaka and S. Wakamatsu, *Tetrahedron Lett.*, 219 (1968).

(5) W. L. Dilling and R. D. Kroening, *ibid.*, 5101 (1968).

(6) J. A. Barltrop and H. A. J. Carless, *ibid.*, 3901 (1968).

(7) R. Srinivasan, *Advan. Photochem.*, **4**, 113 (1966).

(8) I am indebted to Dr. H. K. Hall, Jr., for the sample of III[9] and to Dr. W. G. Kenyon for the sample of II[10] used in this study.

(9) H. K. Hall, Jr., U. S. Patent 3,457,194 (1969).

(10) R. Tietz and W. G. Kenyon, U. S. Patent 3,468,861 (1969).

(11) One may argue here that the triplet was never formed under the reaction conditions.

(12) R. Srinivasan, *J. Amer. Chem. Soc.*, **90**, 4498 (1968), and references cited therein.

(13) G. L. Closs and P. E. Pfeffer, *ibid.*, **90**, 2452 (1968), and references cited therein.

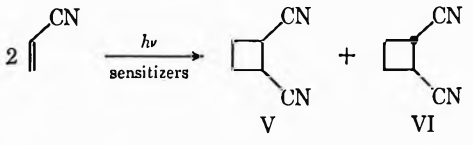
(14) H. M. Frey, B. M. Pope, and R. F. Skinner, *Trans. Faraday Soc.*, **63**, 1166 (1967); H. M. Frey and R. Walsh, *Chem. Rev.*, **69**, 103 (1969).

(15) H. C. Longuet-Higgins and E. W. Abrahamson, *J. Amer. Chem. Soc.*, **87**, 2045 (1965). R. B. Woodward and R. Hoffmann, *ibid.*, **87**, 395 (1965); *Accounts Chem. Res.*, **1**, 17 (1968). K. B. Wiberg, *Tetrahedron*, **24**, 1083 (1968). R. Hoffmann, Abstracts, 21st National Organic Symposium of the American Chemical Society, Salt Lake City, Utah, June 1969, p 116; R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

(16) K. J. Crowley, *Tetrahedron Lett.*, **21**, 1001 (1965); *Proc. Chem. Soc.*, 245, 334 (1962); 17 (1964).

(17) (a) R. E. K. Winter and P. Kalicky, Abstracts of the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968. ORGN 36. (b) J. A. Barltrop and H. E. Browning, *Chem. Comm.*, 1481 (1968).

Photodimerization of Acrylonitrile.—Acrylonitrile photocyclodimerizes[1,4,6] to a mixture of *cis*- and *trans*-1,2-dicyanocyclobutane[18] (V and VI, respectively) in



the presence of triplet sensitizers. Less than 2% 1,3-dicyanocyclobutanes[19] were detected; these isomers were shown to be stable to the reaction conditions. Table I summarizes the 1,2-dicyanocyclobutane products ratios and quantum yields as a function of sensitizer and solvent. The product ratio varies with the medium but not with sensitizer, suggesting the intermediacy of triplet acrylonitrile. The almost exclusive head-to-head dimerization argues against the Schenk[20] scheme for "chemical relay" of energy; a complex of a sensitizer, such as benzophenone, and acrylonitrile would likely give rise to 1,3-dinitrile on reaction with another molecule of acrylonitrile. The Schenk mechanism does not explain why 1- and 2-acetonaphthone are ineffective sensitizers or why benzophenone and 9,10-dibromoanthracene give essentially identical results. The preference for head-to-head dimerization is indicative of a diradical intermediate. Successful dimer formation in ethanol and furan as solvents tends to exclude a strained isomer of acrylonitrile as the reactive species. Attempts to observe direct singlet–triplet absorption for acrylonitrile in ethyl iodide solution (10-cm cell) were unsuccessful. Sensitization by the anthracenes probably occurs *via* their T_2 states.[1,21] An interesting aspect of this study is the unequivocal demonstration of nitrile participation in the excited state. The quantum yield measurements require that acrylonitrile (≈65 kcal/mol) have a lower triplet energy than that expected for ethylene (>80 kcal/mol).

TABLE I

PHOTOSENSITIZED DIMERIZATION OF ACRYLONITRILE (AN)[a]

Sensitizer (E_T)	[AN], *M* (solvent)[a]	Ratio of VI/V[b]	$\Sigma\phi$[c]
Xanthone (74)	10 (B)	0.8	*d*
Acetophenone (74)	Neat	0.82[e]	*d*
	1.8 (F)[f]	1.7[e]	
Triphenylene (67)	Neat	0.82[e]	*d*
Benzophenone (69)	Neat	0.84[e]	0.062
	10 (B)	0.8	
	1.0 (B)	1.3	
	0.3 (B)	2.33[e]	
	10 (A)	0.8	
	1.0 (A)	0.8	
	0.9 (P)	1.08[e]	
2-Acetonaphthone (59)	Neat	None	<0.002[g]
1-Acetonaphthone (56)	Neat	None	<0.002[g]
9-Fluorenone (51)	Neat	None[e]	<0.002[g]
9,10-Dibromoanthracene	Neat	0.82[e]	0.078
(DBA)	10 (B)	0.7	
	1.0 (B)	1.2	
	0.3 (B)	2.33[e]	
	10 (A)	0.7	
	1.0 (A)	0.7	
	0.2 (EA)[f]	0.82[e]	
	2.7 (T)[f]	1.8[e]	
Cu^+, Cu^{2+} possible[h]	0.4 (E)	1.6[e]	
(9-Fluorenone + DBA)[i]	Neat	0.01	
9-Bromoanthracene	Neat	0.9	0.067

[a] Irradiated in Pyrex tubes in a "merry-go-round" apparatus with Dow-Corning 0-52 and 7-60 filters. Solvent: benzene (B), acetonitrile (A), ether (E), pyridine (P), furan (F), ethanol (EA), or trichloroethylene (T). [b] ~10% error, unless specified. [c] Benzophenone–benzhydrol actinometry. Analysis by gc on a silicone gum nitrile column at 175 or 200°. Values are not corrected for intersystem-crossing efficiency. [d] Qualitatively similar to benzophenone. [e] Large-scale experiment with ir and nmr identification. [f] Other products noted. [g] Limit of detection. [h] Saturated with "CuCl;" quartz apparatus and 2537-Å light used. [i] 1.67×10^{-2} 9-fluorenone, 6.67×10^{-4} *M* DBA; *ca.* 80% of the light absorbed by 9-fluorenone.

***cis–trans* Isomerization in Crotononitrile.**—Crotononitrile undergoes facile photosensitized *cis–trans* isomerization. Stationary states were determined for high energy sensitizers by approach from both directions (Table II). With lower energy sensitizers, such as 1-acetonaphthone, Michler's ketone (E_T = 61), the rate of isomerization was much diminished, suggesting triplet energies for these isomers in the sixties, in good agreement with the value obtained for acrylonitrile. Among the lower energy sensitizers, several anomalous results were obtained. Rapid equilibration was observed with 2-acetonaphthone (*cis/trans* ratio, 1.6), 9,10-dibromoanthracene, and 9-methyl-10-bromoanthracene. The ketone may be catalyzing the isomerization *via* a radical addition mechanism.[20] The brominated anthracenes appear to be photoprecursors of atomic bromine (see Table III) which, in turn, catalyzes the isomerization.[22] This result is in sharp contrast to the need to invoke T_2 states of brominated anthracenes[21] to explain the rapid dimerization of acrylonitrile.

TABLE II

STATIONARY STATES FOR CROTONONITRILE

Sensitizer	*cis/trans* ratio at equilibrium[a]
Xanthone	1.05
Acetophenone	0.95
Benzophenone	0.87
Triphenylene	0.97

[a] Estimated error ±0.05.

TABLE III

CATALYZED ISOMERIZATION OF CROTONONITRILE

Catalyst	[Crotononitrile]	*cis/trans* ratio
9,10-Dibromoanthracene	0.6 *M* in benzene	1.49
9,10-Dibromoanthracene	50% in benzene	1.29
9,10-Dibromoanthracene	Neat	1.24
9-Methyl-10-bromoanthracene	0.6 *M* in benzene	1.49
Bromine	0.6 *M* in benzene	1.49
Bromine	50% in benzene	1.29
Bromine	Neat	1.25

(18) E. C. Coyner and W. S. Hillman, *J. Amer. Chem. Soc.*, **71**, 324 (1949).
(19) K. C. Stueben, *J. Polym. Sci.*, **4**, 829 (1966).
(20) For a review of this point of view, see R. Steinmetz, *Fortsch. Chem. Forsch.*, **7**, No. 3, 445 (1967).
(21) R. S. H. Liu and J. R. Edman, *J. Amer. Chem. Soc.*, **91**, 1492 (1969).
(22) The uncatalyzed thermal equilibration of crotononitrile has been studied in the vapor phase: J. N. Butler and R. D. McAlpine, *Can. J. Chem.*, **41** (10), 2487 (1963).

Experimental Section

Photolysis of 2-Cyanobutadiene (I).—A 2% solution of I[23] in anhydrous ether, saturated with Cu_2Cl_2, was photolyzed for 5 days employing a quartz apparatus, cooled with tap water (*ca.* 15°) and equipped with 16 low-pressure mercury lamps.[24] The most intense wavelength produced by these lamps is 2537 Å. When the photolysis was completed, the reaction mixture was filtered and the ether was removed from the filtrate under reduced pressure (*ca.* 10–20 mm). A sample of the residue, stabilized with hydroquinone, was shown to contain III and II by nmr comparisons with authentic samples.

In another experiment, a 2.9-g sample of I dissolved in 350 ml of anhydrous ether saturated with Cu_2Cl_2 was photolyzed for 131.5 hr. The same work-up procedure led to 2 g of yellow liquid. Nmr analysis showed that III was formed in about 28.5% yield and II in about 15.5% yield. Short-path distillation of this residue led to mixtures of III and II, isolated in somewhat lower yields than determined by nmr. Similar results were obtained in ether without the Cu_2Cl_2, in 1,2-dichloroethane, and in CCl_4 (lower yield). Thus, the addition of Cu_2Cl_2 seems to have little effect on the process. Both II and III could also be isolated by gas chromatography (butanediol succinate column).

Quantum Yield Determinations.—A 2×10^{-4} *M* solution of crystal violet leucocyanide[25,26] in ethanol was used for a standard solution. The molar extinction coefficient of the dye at 5900 Å was taken as 1.1×10^5. A quartz cell (path length, 1 cm; volume, 3 ml) was separated (5.5 cm) from a low pressure mercury lamp ("pencil source") by a shutter assembly. The intensity of the light source was measured before and after each determination measuring the change in the absorbance at 5900 Å employing a Cary spectrophotometer (actually the intensity of this source was constant for long periods of time). The quantum yields for the formation of II and III were determined by exposing 0.13 *M* (~100% absorption of light) ether solutions (no Cu_2Cl_2; degassed with argon) of gc-pure I to the source for definite time intervals and analyzing for the concentration of products by gas chromatography (standard samples employed). Measurements were made at ambient temperature (~30°).

1,3-Diiodocyclobutanecarbonitrile.—To a 13-g sample of solid iodine (0.052 mol) mostly dissolved in 100 ml of CCl_4 was added 4.6 g (0.058 mol) of III dissolved in 25 ml of CCl_4. The purple mixture was stirred at room temperature for 16 hr and filtered to remove 1.7 g of a yellow solid. The filtrate was evaporated to dryness and the residue was crystallized from methanol. A total of 11.86 g (80%), mp 82–86° dec, of diiodonitrile was obtained. Recrystallization from methanol gave an analytical sample, mp 91–94° dec. The infrared spectrum showed saturated CH at 3.35 and —C≡N at 4.51 μ and no ≡CCH_3 absorption. The mass spectrum showed a parent ion at *m/e* 333 and the expected fragmentation. The nmr spectrum showed complex absorption at τ 5.3 (area 1) and 6.5 (area 4). *Anal.* Calcd for $C_5H_6NI_2$: C, 18.03; H, 1.51; N, 4.21; I, 76.25. Found: C, 18.15; H, 1.65; N, 4.30; I, 76.14.

A 200-mg sample of a mixture of III (three parts) and II (one part) obtained from the photolysis of I was dissolved in 25 ml of CCl_4 and stirred for 17 hr at room temperature with 610 mg of iodine (excess). The solvent and most of the unreacted iodine were removed leaving 0.6 g of crude diiodide, which was recrystallized from methanol (most soluble) to give 95% pure 1,3-diiodocyclobutanecarbonitrile (by nmr and ir comparisons with an authentic sample), mp 80–84° dec.

Photodimerization of Acrylonitrile.—In a typical experiment, 100 mg of recrystallized benzophenone (from ethanol) dissolved in 100 g of polymer-grade acrylonitrile (which had been further purified by washing with 5% sodium bicarbonate solution and three times with water, dried over magnesium sulfate, passed through Al_2O_3, and distilled under vacuum through a spinning-band column), in a glass vessel formed from 4-cm Pyrex tubing and cooled to 10° by internal coil, was degassed with Ar and irradiated with a bank of 16 germicidal uv lamps coated with a "black light" phosphor for 2 weeks (intensity of light estimated from lamp output was 0.2 einsteins/day absorbed). The solution remained clear except for the last few days when a small amount of polymer formed. The absorbance (1-cm cell) at 3500 Å changed from 0.7 to 0.6 (>99% absorption at end). The reaction mixture was concentrated to 6.7 g for gc analysis (butanediol succinate at 150°): 38% acrylonitrile, 28% VI (1.9% yield), 33% V (2.2% yield), and two peaks of less than 1% each with the retention times of *cis*- and *trans*-1,3-dicyanocyclobutanes. Attempts to collect the dinitrile products by gc were unsuccessful owing to decomposition. Further concentration for infrared and nmr analysis established the presence of the 1,2-dinitriles by comparison with spectra of authentic materials (see Table I).

Photoisomerization of Crotononitrile.—Stationary states were determined by dissolving sufficient sensitizer in near crotononitrile (both *cis* and *trans*) to make the solution "totally absorbing," and irradiating in Pyrex tubes in a "merry-go-round" apparatus with Dow-Corning 0-52 and 7-60 filters. All of the data in Tables II and III were obtained by starting with both pure isomers. Analyses were made by gc on a silicone gum nitrile column at 150°.

Registry No.—I, 5167-62-4; acrylonitrile, 107-13-1; *cis*-crotononitrile, 1190-76-7; *trans*-crotononitrile, 627-26-9; 1,3-diiodocyclobutanecarbonitrile, 23264-15-5.

(23) C. S. Marvel and N. O. Brace, *J. Amer. Chem. Soc.*, **70**, 177 (1948).

(24) D. M. Gale, U. S. Patent 3,459,647 (1969).

(25) See J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," John Wiley & Sons, Inc., New York, N. Y., 1966, p 788.

(26) I am indebted to Dr. A. MacLachlan for his assistance with these measurements.

Methoxonium Ions in Solvolysis. Neighboring Acetal Participation

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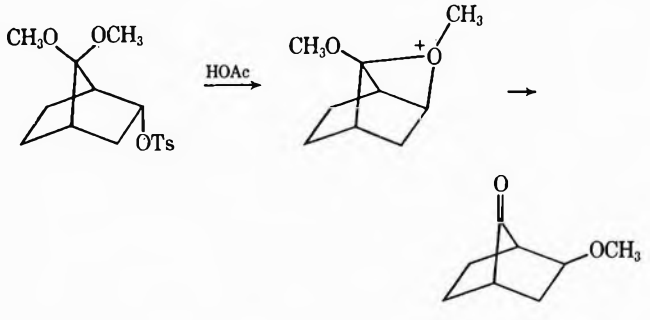
The dimethoxy-1 alcohols **1** (n = 2–4) were synthesized and the corresponding tosylates **2** (n = 2–4) were solvolyzed in both methanol and trifluoroethanol to examine the possibility of methoxyl participation by the dimethyl acetal functional group. The solvolysis rates were measured and compared with that of n-octyl tosylate as a model compound and with that of 5-methoxy-1-pentyl tosylate, which is known to solvolyze with methoxyl participation. The 4,4- and 5,5-dimethoxy compounds **2** (n = 2 and 3) showed rate enhancement of *ca.* 3900 and 245, respectively, relative to n-octyl tosylate in trifluoroethanol, indicating that acetal methoxyl participation dominates the solvolysis in both cases. Comparison of 5,5-dimethoxy-1-pentyl tosylate and 5-methoxy-1-pentyl tosylate showed that the acetal methoxyl group is a much poorer intramolecular nucleophile than the simple methyl ether group in both solvents. Product studies of the trifluoroethanolysis of 4,4-dimethoxy-1-butyl and 5,5-dimethoxy-1-pentyl tosylate confirmed the neighboring-group phenomenon in both cases in that the major products were the mixed acetals **8** and **9** resulting from 1,4 and 1,5 migration, respectively, of an acetal methoxyl group. The kinetic features of the trifluoroethanolysis reactions of 5-methoxy-1-pentyl tosylate and 5,5-dimethoxy-1-pentyl tosylate are discussed in terms of the ion-pair chemistry of the solvolysis intermediates.

Although a large number of functional groups have been examined for their ability to serve as intramolecular nucleophiles in solvolytic displacement reactions,[2] conspicuous by its absence is a systematic study of the neighboring acetal or ketal group. Since participation by the methyl ether oxygen has been exhaustively studied,[3,4] an examination of the dimethyl acetal or ketal group participation would allow an instructive comparison of the relative nucleophilicities of the methoxy group in the two functional groups. To date only one example of neighboring ketal participation has been reported. Thus backside MeO-4[5] participation has been invoked in the acetolysis of *endo*-7,7-dimethoxy-2-norbornyl tosylate to account for the migration of the methoxyl group to the 2-*exo* position and concomitant ketone formation. The corresponding *exo*



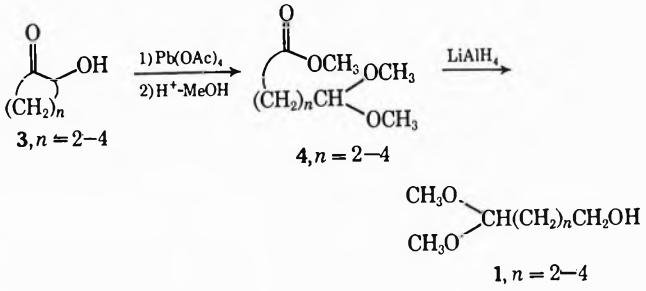
tosylate, in which methoxyl participation cannot occur, gives only unrearranged substitution products (the corresponding *exo* and *endo* acetates), the ketal function remaining intact.[6] Several examples of acetal participation have previously been noted in the carbohydrate field.[7]

It was therefore of interest to examine a series of homologous dimethoxy tosylates for evidence for the generality of acetal participation, for elucidation of mechanism, and for a direct comparison with the structurally related methoxyalkyl tosylates studied previously.

Results

Syntheses.—The required dimethoxy-1 alcohols **1** (n = 2–4) were prepared from the appropriate cyclic acyloins essentially by the method of Saunders and Hurd,[8] as outlined in Scheme I. The acyloins were

SCHEME I



treated first with lead tetraacetate in methanol and then with methanolic sulfuric acid. The resulting acetal esters **4** were then reduced with lithium aluminum hydride to yield the dimethoxy alcohols **1**.

The precursor acyloins were synthesized by known methods. Adipoin (**3**, n = 4) was readily prepared by the hydrolysis of 2-chlorocyclohexanone, which in turn was synthesized by the chlorination of cyclohexanone.[9] The remaining acyloins (**3**, n = 2, 3) were prepared by the acyloin condensation with diethyl succinate and diethyl glutarate, respectively, employing the recent modification with chlorotrimethylsilane.[10–12] With this modification the acyloins were isolated as the 1,2-bistrimethylsiloxy-1-cyclo alkenes **6**, (see Scheme II). The acyloins **3** (n = 2, 3) were then generated simply by

(1) Address correspondence to Division of Natural Science, University of California, Santa Cruz, Calif. 95060.

(2) B. Capon, *Quart. Rev.* (London), **18**, 45 (1964).

(3) S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, **3**, 1 (1958).

(4) (a) E. Allred and S. Winstein, *J. Amer. Chem. Soc.*, **89**, 3991 (1967); (b) E. Allred and S. Winstein, *ibid.*, **89**, 3998 (1967); (c) E. Allred and S. Winstein, *ibid.*, **89**, 4008 (1967); (d) E. Allred and S. Winstein, *ibid.*, **89**, 4012 (1967).

(5) This terminology is explained in ref 3.

(6) P. G. Gassman and J. L. Marshall, *Tetrahedron Lett.*, 2429, 2433 (1968).

(7) See *e.g.*, (a) R. U. Lemieux and B. Fraser-Reid, *Can. J. Chem.*, **42**, 539 (1964); (b) N. A. Hughes and P. R. H. Speakman, *J. Chem. Soc., C*, 1182 (1967); (c) C. L. Stevens, R. P. Glinski, K. G. Taylor, P. Blumbergs, and F. Sirokman, *J. Amer. Chem. Soc.*, **88**, 2073 (1966); (d) J. G. Buchanan, A. R. Edgar, and D. G. Large, *Chem. Commun.*, 558 (1969).

(8) C. L. Hurd and W. H. Saunders, Jr., *J. Amer. Chem. Soc.*, **74**, 5324 (1952).

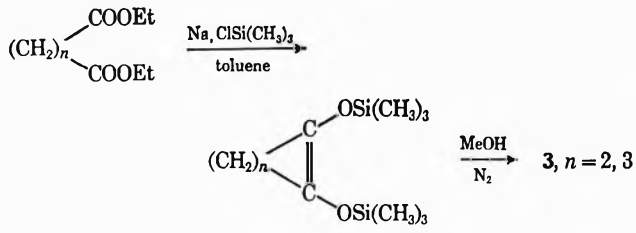
(9) M. S. Newman, M. D. Farbman, and H. Hipsher, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 188.

(10) U. Schrapler and K. Ruhlmann, *Chem. Ber.*, **97**, 1383 (1964).

(11) J. J. Bloomfield, *Tetrahedron Lett.*, 587 (1968).

(12) G. E. Gream and S. Worthley, *ibid.*, 3319 (1968).

SCHEME II



6

stirring in absolute methanol under a nitrogen atmosphere.

The tosylates **2** were prepared from the alcohols by the sodium hydride method.[13] None of the tosylates was crystalline; since they proved to be moderately unstable even in the cold, they were prepared as needed.

Kinetic and Product Studies.—The tosylates were solvolyzed in absolute methanol and in buffered trifluoroethanol, and their rate constants were determined titrimetrically. Methanol was a suitable choice, since its use obviated the problem of acetal exchange and the need to neutralize the acid liberated in the solvolysis. Trifluoroethanol, being considerably more ionizing and less nucleophilic than methanol,[14] is an ideal nonacidic solvent, since it allows neighboring-group participation to predominate over direct solvent displacement. The first-order rate data are summarized in Tables I and II.

TABLE I
SUMMARY OF KINETIC DATA IN METHANOL AT 59.86 ± 0.05°

Compd	10^5k, sec^{-1}	Rel rate	Fk_Δ,[a] %
$CH_3(CH_2)_6CH_2OTs$	0.765	1.0	...
$(CH_3O)_2CH(CH_2)_2CH_2OTs$	5.73 ± 0.05	7.49	87
$(CH_3O)_2CH(CH_2)_3CH_2OTs$	1.49 ± 0.02	1.95	49
$(CH_3O)_2CH(CH_2)_4CH_2OTs$	~1.1	~1.4	~30
$CH_3OCH_2(CH_2)_3CH_2OTs$	2.08 ± 0.02	2.72	63

[a] Calculated from the kinetic data.

The application of the kinetic rate-enhancement criterion for neighboring-group participation requires a means of estimating the expected value of the rate constant in the absence of participation, the observed rate constant (k_{obsd}) being the sum of the assisted (k_Δ) and unassisted (k_s) rate constants.

$$k_{obsd} = Fk_\Delta + k_s$$

A measure of the unassisted portion of the solvolysis rates of the dimethoxy-1-alkyl tosylates was taken to be the rate of solvolysis of *n*-octyl tosylate.[15] No attempt was made to assess the extent of internal return ($1 - F$) to covalent starting material.

The solvolysis of 5-methoxy-1-pentyl tosylate, which is dominated by methoxyl participation,[4d] was also examined to provide a comparison with the corresponding 5,5-dimethoxy-1-pentyl system (Tables I and II).

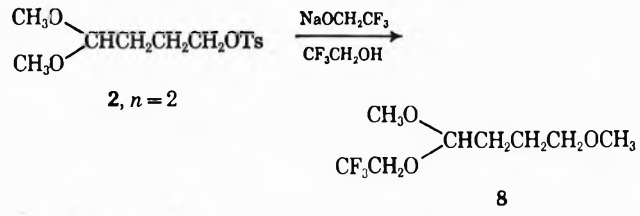
(13) J. K. Kochi and G. S. Hammond, *J. Amer. Chem. Soc.*, **75**, 3443 (1953).

(14) F. L. Scott, *Chem. Ind.* (London), 224 (1959); V. J. Shiner, Jr., W. Dowd, R. D. Fisher, S. R. Hartshorn, M. A. Kessick, L. Milakofsky, and M. W. Rapp, *J. Amer. Chem. Soc.*, **91**, 4838 (1969).

(15) The actual choice of which primary alkyl tosylate (*n*-butyl, *n*-pentyl, or *n*-hexyl) to use as a model compound is relatively unimportant, since they all solvolyze at very nearly the same rate (in ethanol and in water); see P. M. Laughton and R. E. Robertson, *Can. J. Chem.*, **33**, 1207 (1955).

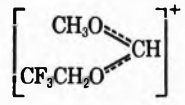
The 5-methoxy-1-pentyl derivative solvolyzes with first-order behavior in methanol, but in trifluoroethanol exhibits behavior typical of the internal return rearrangement to methyl tosylate (and tetrahydropyran) *via* the cyclic methoxonium ion observed previously for this system in acetic acid.[4d] The rearrangement is kinetically detectable as a downward-drifting rate constant and a low acid infinity titer in unbuffered solvent, and as an upward-drifting rate constant (and a theoretical infinity titer) in sodium trifluoroethoxide buffered trifluoroethanol.[16] However, similar rearrangement to methyl tosylate does not accompany the trifluoroethanolysis of 5,5-dimethoxy-1-pentyl tosylate, since there was observed no drift in the first-order rate constant through at least 80% reaction.

The products from the trifluoroethanolysis of 4,4-dimethoxy-1-butyl (**2**, $n = 2$) and 5,5-dimethoxy-1-pentyl (**2**, $n = 3$) tosylates were examined to substantiate the kinetic evidence for the neighboring-group phenomenon. From the trifluoroethanolysis of **2** ($n = 2$) was detected a single major product, formed in 70% yield, as estimated by gas chromatography using internal standards. This material was isolated by distillation, purified by preparative gas chromatography, and identified as the mixed acetal 1,4-dimethoxy-1-trifluoroethoxybutane (**8**) on the basis of elemental analy-



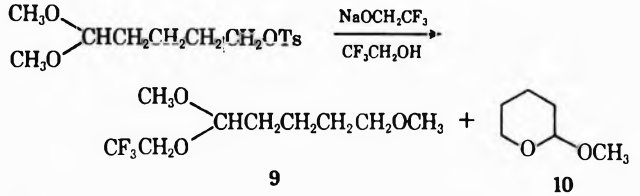
8

sis and infrared, nmr, and mass spectra. In particular, the nmr spectrum showed two singlets corresponding to the nonequivalent methoxyl groups. Also the base-peak ion in the mass spectrum occurred at m/e 143 and was assigned structure a, a typical fragment ion in the mass spectra of acetals.[17]



a, m/e 143

Similarly, the trifluoroethanolysis of 5,5-dimethoxy-1-pentyl tosylate (**2**, $n = 3$) gave 1,5-dimethoxy-1-trifluoroethoxypentane (**9**) in *ca.* 25% yield. The structure assignment was again based on the fact that the material showed two distinctly nonequivalent methoxyl singlets in the nmr, and had a base-peak ion at m/e 143 owing to ion a in its mass spectrum. The



9 10

(16) The interesting kinetic features of this system in trifluoroethanol have been reported elsewhere; see J. R. Hazen, *Tetrahedron Lett.*, 1897 (1969).

(17) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1964, pp 52–54.

TABLE II

SUMMARY OF KINETIC DATA IN TRIFLUOROETHANOL AT 69.90 ± 0.05°

Compd	CF_3CH_2ONa, M	k, sec^{-1}	Rel rate	Fk_Δ,[a] %
$CH_3(CH_2)_6CH_2OTs$	...	3×10^{-7}	1.0	...
$(CH_3O)_2CH(CH_2)_2CH_2OTs$	0.0505	$1.18 \pm 0.02 \times 10^{-3}$	3.9×10^3	100
$(CH_3O)_2CH(CH_2)_3CH_2OTs$	0.0560	$7.35 \pm 0.10 \times 10^{-5}$	2.45×10^2	>99
$CH_3OCH_2(CH_2)_3CH_2OTs$	0.0560	$2.04 \pm 0.02 \times 10^{-4}$	6.80×10^2	>99
	...	$1.59 \pm 0.03 \times 10^{-4}$	5.30×10^2	

[a] Calculated from the kinetic data.

major product in the trifluoroethanolysis of **2** ($n = 3$) is 2-methoxytetrahydropyran (**10**), identified by comparison of its gas chromatography retention time with that of an authentic sample.

Discussion

There are several *a priori* considerations with regard to a comparison of MeO-*n* participation in the dimethoxy and simple methoxy compounds. First, a statistical factor of two must be recognized, since either of the two methoxyl groups of the acetal function can serve as the neighboring group. Second, it is well known that alkyl substituents on the aliphatic chain serve to enhance cyclization reactions. For example, 5-methoxy-1-hexyl brosylate solvolyzes about six times more rapidly than 5-methoxy-1-pentyl brosylate in acetic acid.[4a] It is reasonable to assume that the methoxyl group has a steric bulk which is intermediate between that of methyl and an ethyl group. The presence of the second methoxyl group may therefore be estimated to increase the rate of a ring-closure reaction by a factor of roughly 10–15.[2,4a,18] On the basis of this factor and the statistical factor, it might be estimated that the dimethoxy compounds would solvolyze some 20–30 times faster than the methoxyl compounds. A third factor, however, should counterbalance these first two. The electron-withdrawing inductive effect of each methoxyl group on the other in the dimethoxy compounds should significantly reduce the ability of the methoxyl oxygen atoms to donate their nonbonded electrons to a neighboring electron-deficient carbon atom in the solvolysis transition state. That is, the methoxyl groups of the acetal are expected to be much less nucleophilic in intramolecular displacements than the methyl ether group. The relative importance of these factors will become apparent from the discussion below.

It is clear from the data in Table I that the rate enhancement owing to acetal participation is quite modest in methanol, being only a factor of 7.5 in the case of 4,4-dimethoxy-1-butyl tosylate.[19] However, the magnitude of the neighboring-group effect in the series of tosylates is in the expected order in that **2** ($n = 2$) is more reactive than **2** ($n = 3$), which in turn is more reactive than **2** ($n = 4$). This observation is in accordance with the expectation that formation of the five-membered-ring transition state is the most favorable and formation of the seven-membered-ring transition state is the least favorable.[2,3] It is significant to note that 5-methoxy-1-pentyl tosylate solvolyzes 40% faster than 5,5-dimethoxy-1-pentyl tosylate, indicating that acetal methoxyl participation is less favorable than simple methoxyl participation. This observation reflects the overriding importance of the inductive or electronic factor on the nucleophilicity of the acetal methoxyl groups.

The fact that the k_s route represents a large portion of the solvolysis pathway in methanol is undoubtedly due to its relatively high nucleophilicity. An ionizing but weakly nucleophilic solvent would make any participation effects more apparent, since k_s for primary tosylates is reduced in a less nucleophilic solvent. Since the usual acidic solvents are unsuitable, the tosylates were solvolyzed in trifluoroethanol in the presence of sodium trifluoroethoxide as a buffer to prevent acetal exchange.

The large rate accelerations for the tosylates **2** in the cases where $n = 2$ and 3 relative to *n*-octyl tosylate (Table II) clearly indicate that methoxyl-assisted ionization completely dominates the solvolysis in both cases. Furthermore, both compounds solvolyze with good first-order behavior, indicating the absence of any S_N2 displacement by sodium trifluoroethoxide. On the other hand, both *n*-octyl tosylate and 6,6-dimethoxy-1-hexyl tosylate (**2**, $n = 4$) undergo predominant bimolecular displacement by the alkoxide and do not follow first-order kinetics. The solvolysis rate of *n*-octyl tosylate was therefore determined in unbuffered solvent. The observation of a substantial contribution from the second-order displacement by alkoxide with 6,6-dimethoxy-1-hexyl tosylate in competition with the methoxyl-assisted displacement is consistent with the long-recognized fact that participation *via* seven-membered ring intermediates is a relatively minor pathway.[2,3] It is also pertinent to note that the solvolysis rate of 4,4-dimethoxy-1-butyl tosylate is 16 times faster than that of 5,5-dimethoxy-1-pentyl tosylate (Table II). This result compares favorably with the observation that the corresponding 4-methoxy-1-butyl system solvolyzes 14 times more rapidly than the 5-methoxy-1-pentyl system at 75° in formic acid, in which solvent both compounds solvolyze exclusively *via* methoxyl participation.[3]

It should again be noted that the apparent neighboring-group rate accelerations of 3900 for **2** ($n = 2$)

(18) See, for example, T. C. Bruice and W. C. Bradbury, *J. Amer. Chem. Soc.*, **87**, 4846 (1965); D. S. Bailey, "The Gem-Dialkyl Effect," Organic Chemistry Seminar, University of Rochester, Rochester, N. Y., 1967, pp 60–68.

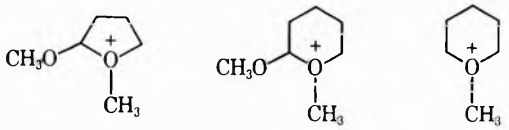
(19) Corrections for the inductive effect of the $(CH_3O)_2CH$ group have not been applied to any of the data. The inductive effect, though small, is not negligible. The σ^* value for $(CH_3O)_2CH$ has recently been determined to be +1.14,[20] about twice that of the CH_3OCH_2 substituent. Using the reaction constant $\rho^* = 1.03$ (the value for ethanol[3]) and σ^* $[CH_3(CH_2)_n-CH_2] = -0.10$,[3] the inductive rate *retardation* for the 4,4-dimethoxy compound (**2**, $n = 2$) relative to the unsubstituted compound may be calculated to be a factor of *ca.* 1.80. Thus the actual rate enhancement due to MeO-5 participation would be 7.5 × 1.80 or 13.5. Similarly, the inductive effect in the 5,5-dimethoxy analog will produce a rate retardation factor of *ca.* 1.4, indicating that the true neighboring-group rate acceleration for **2** ($n = 3$) amounts to a factor of 1.95 × 1.4 or 2.8.

The inductive effects in trifluoroethanol are probably even somewhat larger, since the reaction constant ρ^* is probably larger in this more ionizing solvent.

(20) T. Minamida, Y. Ikeda, K. Uneyama, and S. Oae, *Tetrahedron*, **24**, 5293 (1968).

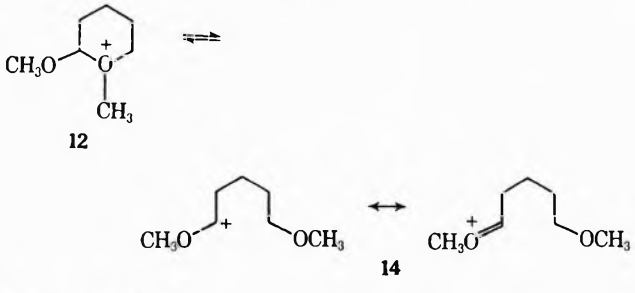
and 245 for **2** (n = 3) (Table II) are approximations, since no corrections have been applied to allow for the differences in the inductive effect in n-octyl tosylate and the substrates of interest.[19] Also no allowance has been made for the fact that the solvolyses of n-octyl tosylate and the dimethoxy tosylates were not conducted under conditions of identical ionic strength, since the latter compounds were solvolyzed in the presence of sodium trifluoroethoxide buffer. However, these effects are relatively small (and tend to counterbalance one another), compared with the magnitude of the rate accelerations, and may be neglected without affecting the validity of the kinetic conclusions.

The domination of the trifluoroethanolyses by methoxyl participation indicates that the initially formed intermediates from **2** (n = 2) and **2** (n = 3) are the methoxonium ions **11** and **12**, respectively.



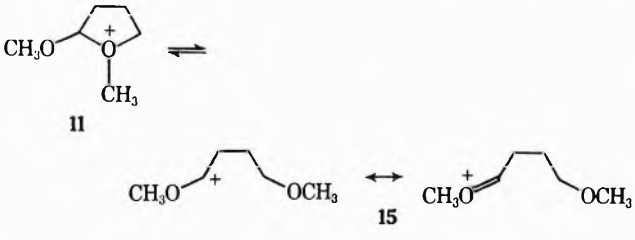
11 **12** **13**

A comparison of the kinetic behavior of 5-methoxy-1-pentyl and 5,5-dimethoxy-1-pentyl systems allows further mechanistic insight. It is again clear that the acetal methoxyl groups are considerably less nucleophilic than the simple methyl ether group, since the dimethoxy tosylate reacts nearly three times more slowly than 5-methoxy-1-pentyl tosylate. Especially interesting is the observation that, while the solvolysis of 5-methoxy-1-pentyl tosylate in buffered trifluoroethanol is accompanied by internal return rearrangement to methyl tosylate (*via* the methoxonium ion **13**),[16] no such rearrangement occurs from methoxonium ion **12**. The absence of O-methyl cleavage by the tosylate anion in the solvolysis of the 5,5-dimethoxy system may reasonably be interpreted as being indicative of a rapid equilibrium between the cylic oxonium ion **12** and the highly resonance-stabilized α-methoxycarbonium ion **14**. Since such an equilibrium would involve a rapid



12 **14**

change in the geometries of the intermediates as well as a rapid shifting of the site of the electron deficiency, it seems unlikely that the tosylate anion would often



11 **15**

be in a proper position to collapse with either of the O-methyl groups. Hence, solvent capture of the intermediates **12** and **14** is the favored process, with little or no methyl tosylate formation. The cyclic ion **11** is similarly postulated to give rise to the α-methoxycarbonium ion **15** prior to solvent capture.

The kinetic evidence for the neighboring-group effect was substantiated by the product study. The formation of the rearranged, mixed acetals **8** and **9**, respectively, from **2** (n = 2) and **2** (n = 3) requires the migration of a methoxyl group to the carbon initially bearing the leaving group in both cases. No unrearranged dimethyl acetal product was detected in the solvolysis of either substrate.[21] The formation of the mixed acetals is also consistent with (but does not prove) the intermediacy of the α-methoxycarbonium ions **14** and **15**.

While it is obvious that methoxyl participation in the acetals is important, it is less so than in the simple methyl ether analogs. The lesser reactivity of the dimethoxy compounds relative to the methoxy compounds clearly indicates that the most important factor in determining their relative reactivities is the electronic factor. Thus although the statistical and steric factors should make the dimethoxy compounds roughly 20–30 times more reactive than the corresponding methoxy compounds (*vide supra*), the electron-withdrawing inductive effect exerted by each methoxyl group on the other in the acetals more than counterbalances these factors. The fact that 5-methoxy-1-pentyl tosylate is nearly three times *more* reactive than 5,5-dimethoxy-1-pentyl tosylate indicates that the intrinsic nucleophilicity of the acetal methoxyl group is roughly 3 × 20–30 or *ca.* 10^2 less than that of the simple methoxyl group. It is interesting that this factor is also about the same as the magnitude of the inductive effect found for the generation of positive charge on a *carbon* atom with a β-methoxyl group (as in the solvolysis of 2-methoxycyclohexyl brosylate).[22]

Experimental Section

1,2-Bistrimethylsiloxy-1-cyclobutane (6, n = 2).—In a 500-ml, three-necked flask equipped with mechanical stirrer, condenser and drying tube, and a dropping funnel with a nitrogen inlet tube was placed 180 ml of dry toluene and 14.0 g (0.61 mol) of freshly cut cubes of sodium. The mixture was heated to reflux under nitrogen with vigorous stirring to disperse the globules of melted sodium. Then a solution of 26.2 g (0.15 mol) of diethyl succinate and 70 g (0.644 mol) of chlorotrimethylsilane plus 25 ml of dry toluene was added dropwise to the refluxing, vigorously stirred mixture under nitrogen at such a rate as to maintain refluxing. After the addition of the diester solution (*ca.* 1.5 hr), refluxing the stirring were continued for an additional 19 hr. The mixture was cooled and filtered, and the filtered salts were washed with ether. The solvent was removed from the filtrate under reduced pressure and the residue was distilled to give 23 g (67% yield) of product, bp 103–107° (25–30 mm), n^{28}D 1.4292. The nmr spectrum (neat) showed a singlet at τ 7.90 (4 H, methylene protons) and a singlet at τ 9.82 (18 H, trimethylsiloxy protons).

4,4-Dimethoxy-1-butanol (1, n = 2).—To 90 ml of absolute methanol was added dropwise 22.0 g (0.096 mol) of 1,2-bistrimethylsiloxy-1-cyclobutene under a nitrogen atmosphere.[11] After the addition was complete, the solution was stirred for an

(21) The possibility of acetal participation suggested by J. P. Ward [*Tetrahedron Lett.*, 3905 (1965)] for 4,4-diethoxy-1-butyl chloride in potassium hydroxide–ethylene glycol was not confirmed by the reported product study, since only the unrearranged product 4,4-diethoxy-1-butanol was formed.

(22) S. Winstein, E. Grunwald, and L. L. Ingraham, *J. Amer. Chem. Soc.*, **70**, 821 (1948).

additional 0.5 hr, followed by the portionwise addition of *ca.* 50 g of lead tetraacetate with occasional external cooling (ice bath).[8] About 0.5 hr after the lead tetraacetate addition was complete, a solution of 18 g of concentrated sulfuric acid in 45 ml of absolute methanol was added dropwise with vigorous stirring and, when the mixture became thick, with manual agitation. The reaction mass was allowed to stand for 3 days, after which it was filtered. The filtrate was poured into 150 ml of 30% potassium carbonate solution, and the resulting mixture was immediately extracted with a total of 400 ml of ether. The combined extracts were washed with 75 ml of water, dried over sodium sulfate and then 3A molecular sieves, and distilled. The product, methyl 4,4-dimethoxybutyrate (**4**, n = 2), was collected at 84° (12 mm), $n^{25.5}$D 1.4140–1.4144 [lit.[23] bp 85.5–86° (13 mm), n^{20}D 1.4171]. The infrared spectrum (liquid film) showed a strong carbonyl absorption at 1735 cm^{-1}. The yield was 6.6 g (42%). The acetal ester was then reduced with lithium aluminum hydride in ether to yield, after base hydrolysis, a 61% yield of 4,4-dimethoxy-1-butanol (**1**, n = 2), bp 97.5–99.5° (12 mm), n^{25}D 1.4246. The infrared spectrum (liquid film) showed a hydroxyl at 3450 cm^{-1}, but no carbonyl absorption.

Anal. Calcd for $C_6H_{14}O_3$: C, 53.71; H, 10.52. Found: C, 53.70; H, 10.67.

4,4-Dimethoxy-1-butyl Tosylate (**2**, n = 2).[13]—4,4-Dimethoxy-1-butanol (4.75 g, 0.0355 mol) was stirred and refluxed under nitrogen with an equivalent amount of oil-free sodium hydride in ether for 18 hr. Then, after cooling, 6.6 g (0.0346 mol) of freshly recrystallized tosyl chloride in ether was added over 0.5 hr. After 9.5 hr in the cold the mixture was centrifuged (3000 rpm, 20 min) and the supernatant solution was filtered through a sintered glass disk. The solvent was removed under reduced pressure (the final traces with a vacuum pump) to give 6.8 g (68%) of a clear, pale yellow oil, n^{25}D 1.4911. All attempts to induce crystallization failed. However, the infrared spectrum showed no hydroxyl absorption, and the material contained no tosyl chloride (as determined by treatment with 0.0516 *M* sodium trifluoroethoxide in trifluoroethanol and back titration with perchloric acid in 95% ethanol). The tosylate showed good first-order kinetics and had a 96% infinity titer in both methanol and trifluoroethanol.

Anal. Calcd for $C_{13}H_{20}O_5S$: C, 54.14; H, 6.99. Found: C, 54.14; H, 7.11.

1,2-Bistrimethylsiloxy-1-cyclopentene (**6**, n = 3).—This compound was prepared as described above for bistrimethylsiloxycyclobutene, bp 65° (2 mm) and 88° (9–10 mm), n^{25}D 1.4390 [lit.[10] bp 93–94° (10–12 mm), n^{20}D 1.4426].

Methyl 5,5-Dimethoxyvalerate (**4**, n = 3).—The above-prepared bistrimethylsiloxycyclopentene (34.6 g) was added dropwise over 0.5 hr to 160 ml of stirred absolute methanol. After 4 hr the reaction solution was treated with *ca.* 80 g of lead tetraacetate, portionwise over a 0.5-hr period. After an additional 1.5 hr, 29.5 g of concentrated sulfuric acid in 75 ml of methanol was added dropwise with cooling and vigorous agitation. After 2 days the reaction mixture was filtered, poured into 30% potassium carbonate solution (from 150 g in 350 ml of water), extracted with 800 ml of ether, washed with a total of 150 ml of water, and dried over sodium sulfate and molecular sieves. The solvent was then removed and the product was distilled to give 14.5 g (58%) of pure material, bp 70–72° (2.3 mm), n^{26}D 1.4206.

Anal. Calcd for $C_8H_{16}O_4$: C, 54.53; H, 9.15. Found: C, 54.36; H, 9.06.

5,5-Dimethoxy-1-pentanol (**1**, n = 3).—A solution of 14.5 g of the acetal ester (**4**, n = 3) in 20 ml of ether was added cautiously, dropwise, to a stirred suspension of 2.2 g of lithium aluminum hydride in 100 ml of ether over the course of 45 min. After several hours the mixture was hydrolyzed with 2 ml of water, 2 ml of 15% aqueous sodium hydroxide, and 6 ml of water. After filtration and drying over 3A molecular sieves, the solvent was removed and the product was distilled to give 7.9 g (66%) of the dimethoxy alcohol, bp 67–69° (0.2 mm), $n^{25.5}$D 1.4315 [lit.[24] bp 57–63° (0.07 mm), n^{20}D 1.4344].

Anal. Calcd for $C_6H_{14}O_3$: C, 56.73; H, 10.88. Found: C, 57.07; H, 10.88.

5,5-Dimethoxy-1-pentyl Tosylate (**2**, n = 3).—The tosylate was prepared from the alcohol (**1**, n = 3) by the sodium hydride method as described above. Several preparations of varying reaction time, temperature, etc., all gave the tosylate as a pale yellow oil containing 8.5–10.4% by weight of tosyl chloride as estimated by quantitatively diluting the impure ester in standardized sodium trifluoroethoxide in trifluoroethanol and back-titrating the excess trifluoroethoxide with standardized perchloric acid in ethanol to the bromphenol blue end point. Control experiments showed that this assay method is accurate. The refractive indices of the various preparations varied from n^{26}D 1.4979 to n^{25}D 1.5008. After correction for the tosyl chloride impurity, the tosylate exhibited good first-order kinetic behavior and a 99% infinity titer.

6,6-Dimethoxy-1-hexanol (**1**, n = 4).—This alcohol was prepared as described by Saunders and Hurd, bp 65–67° (0.2 mm), n^{25}D 1.4336 [lit.[8] bp 84° (1.0 mm), n^{20}D 1.4358]. The tosylate (**2**, n = 4) was prepared as described above and was isolated as an impure, pale yellow oil containing tosyl chloride. Repeated sodium bicarbonate washings of an ethereal solution of the ester failed to remove the tosyl chloride completely. A sample of material, n^{26}D 1.5002, contained 8.0% tosyl chloride. The presence of tosyl chloride precluded an accurate determination in Table I.

5-Methoxy-1-pentyl Tosylate (**7**).—The tosylate was prepared from 5-methoxy-1-pentanol by the usual low-temperature method and was isolated as a clear, colorless oil, $n^{27.5}$D 1.4990. This material solvolyzed with well-defined kinetics and liberated the theoretical amount of *p*-toluenesulfonic acid in both methanol and trifluoroethanol. The nmr and infrared spectra were consistent with the expected structure.

1-Octyl Tosylate.—The ester, prepared in 67% yield from *n*-octanol (Eastman) by the usual low-temperature method in pyridine, had n^{27}D 1.4878 (lit.[25] n^{20}D 1.4946) and solvolyzed with steady, first-order kinetics.

Kinetics.—The kinetic runs were followed titrimetrically by standard techniques, and the rate constants were calculated from the first-order rate law. Commercial absolute methanol containing *ca.* 0.04% water was used without further purification. The titrations for the methanolyses were performed with standard aqueous ethanolic sodium carbonate using bromphenol blue as the indicator. Trifluoroethanol was used as received from Matheson Coleman and Bell. Sodium trifluoroethoxide–trifluoroethanol solutions were standardized by titration with perchloric acid in 95% ethanol, which in turn was standardized against aqueous ethanolic primary standard sodium carbonate. The trifluoroethanolysis kinetics were followed by titration with standardized perchloric acid in ethanol to the bromphenol blue end point. A typical rate run is given in Table III.

TABLE III

SOLVOLYSIS OF 0.0374 *M* 5,5-DIMETHOXY-1-PENTYL TOSYLATE IN 0.0507 *M* SODIUM TRIFLUOROETHOXIDE IN TRIFLUOROETHANOL AT 69.88 ± 0.02°

Time, sec	0.0254 *M* $HClO_4$–EtOH,[a] ml	[ROTs], *M*	10^5k,[b] sec^{-1}
0	3.76	0.0352	...
1,472	3.495	0.0318	6.95
3,255	3.195	0.0279	7.42
5,170	2.90	0.0241	7.22
7,450	2.60	0.0202	7.46
9,280	2.40	0.0176	7.47
12,550	2.12	0.01040	7.35
15,400	1.915	0.01135	7.36
∞	1.035	...	...

[a] Per 1.98 ml of aliquot. [b] Average k = 7.32 ± 0.13.

Trifluoroethanolysis Products from 4,4-Dimethoxy-1-butyl Tosylate (**2**, n = 2).—The tosylate (3.0 g) was diluted with 50 ml of 0.25 *M* sodium trifluoroethoxide–trifluoroethanol and heated at 70° for 115 min. The mixture was cooled, filtered, concentrated, and distilled. A single fraction was collected (1.15 g, 51%), bp 84–87° (20 mm), n^{26}D 1.3715. This material consisted of a single component with trace amounts of several other products as determined by gas chromatography (10 ft × 0.25 in. 20% FFAP on Chromosorb P column at 125°). An analytical sample was obtained by preparative gas chromatography and identified as 1,4-dimethoxy-1-trifluoroethoxybutane (**8**): n^{26}D 1.3703; nmr ($CDCl_3$) τ 5.40 [t, 1, $(CH_3O)_2CH$], 6.32

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(q, 2, J = 9 Hz, CF_3CH_2), 6.65 (s, 3, CH_3OCH), 6.68 (s, 3, CH_3OCH_2), and *ca.* 8.3 (m, 4, methylene); mass spectrum (70 eV) *m/e* 143 (base peak); ir (neat) 1280 cm^{-1} (CF_3).

Anal. Calcd for $C_8H_{15}F_3O_3$: C, 44.44; H, 6.99; F, 26.36. Found: C, 44.14; H, 7.04; F, 26.48.

A better estimate of the yield of **8** was obtained by gas chromatographic analysis using internal standards. In a typical experiment the accurately weighed ester (*ca.* 0.4 g) was solvolyzed as above, the reaction mixture was cooled, and cyclohexyl acetate and *n*-octyl alcohol were accurately weighed into the reaction mixture. The mixture was vigorously shaken and analyzed directly on a 20% FFAP on Chromosorb P column. The yield of **8**, determined from the relative peak areas suitably corrected for minor differences in detector response, was 70%.

Trifluoroethanolysis Products from 5,5-Dimethoxy-1-pentyl Tosylate (2, n = 3).—The tosylate (2.82 g) was diluted with 95 ml of 0.130 M sodium trifluoroethoxide–trifluoroethanol and heated at 70° for 14 hr. The mixture was cooled, filtered, and concentrated. Ether (*ca.* 35 ml) was added to precipitate the remaining salts. The mixture was filtered, concentrated, and distilled. A single high-boiling component was isolated (0.5 g), bp 95° (17 mm), $n^{27}D$ 1.3816. This material was further purified by preparative gas chromatography and identified as 1,5-dimethoxy-1-trifluoroethoxypentane (**9**): nmr (CCl_4) 5.50 [t, 1, J = *ca.* 5 Hz, $(CH_3O)_2CH$], 6.23 (q, 2, J = 9 Hz, CF_3CH_2); 6.70 (s, 3, CH_3OCH), 6.75 (s, 3, CH_3OCH_2–), and *ca.* 8.5 (m, 6, methylene); mass spectrum (70 eV) *m/e* 143 (base peak); ir (neat) 1280 cm^{-1} (CF_3).

Anal. Calcd for $C_9H_{17}F_3O_3$: C, 46.95; H, 7.44; F, 24.76. Found: C, 46.85; J, 7.51; F, 24.79.

The yield of **9**, determined by gas chromatography using an internal standard, was *ca.* 25%. Although no attempt was made to recover the major solvolysis product, it was identified as 2-methoxytetrahydropyran on the basis of its identical gas chromatography retention time with that of an authentic sample.

Registry No.—**1** (n = 2), 23068-87-3; **2** (n = 2), 23068-88-4; **2** (n = 3), 23068-89-5; **2** (n = 4), 23068-90-8; **4** (n = 3), 23068-91-9; **6** (n = 2), 17082-61-0; **7**, 23074-20-6; **8**, 23074-21-7; **9**, 23074-22-8; 1-octyl tosylate, 3386-35-4.

Acknowledgment.—The author gratefully acknowledges the interest of Professor D. S. Tarbell and financial support by the National Institutes of Health (Grant AI-08424) and the Petroleum Research Fund of the American Chemical Society (Grant 2252-C). The author is also indebted to Mr. Charles Wetter and Miss Betty Lankford for their skillful assistance in obtaining the mass spectra.

Cyclopropylcarbinyl *p*-Toluenesulfonate Solvolysis. IV. Correlation with Cholesteryl Tosylate Solvolysis Rates

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Received September 15, 1969

The solvolysis rates of cholesteryl and cyclopropylcarbinyl (**3**-H) tosylate have been determined in a series of solvents of varying ionizing strength. The correlation of the cholesteryl tosylate solvolysis rates with those of **3**-H reflects a mechanistic similarity between the two substrates. The solvolysis rates of 1-*p*-nitrophenylcyclopropylcarbinyl tosylate (**3**-NPh) have been determined in acetic acid and ethyl alcohol. The solvolysis of **3**-NPh relative to **3**-H is retarded by a factor of 10^{-1}. Comparison of the substituent effect upon the solvolytic reactivity of **3**-H with related compounds supports a transition state with little charge localized at the methinyl carbon.

The rates of ionization of *p*-methoxyneophyl tosylate, log k_{ion}, in several solvents provide a useful scale of solvent polarity for measuring the response of an anchimerically assisted reaction to solvent variation.[2] Earlier work[3] revealed that solvolysis rates of cyclopropylcarbinyl arenesulfonates, although obeying a limiting SN1 mechanism, are poorly correlated by such a scale.

This finding, coupled with more recent observations,[4,5] suggests that a substrate subject to homoallylic rather than phenyl anchimeric assistance would be a more suitable model reaction for correlating cyclopropylcarbinyl arenesulfonate solvolysis rates.

That cholesteryl tosylate solvolyses are assisted by homoallylic interaction[6] has been well established.[6,7] Accordingly, reaction rates of cholesteryl tosylate have been measured in a solvent series of varying ionizing and nucleophilic strength.[8]

The kinetic data are given in Table I. The course of each reaction was followed by titrating the liberated *p*-toluenesulfonic acid. The solvolysis reactions of cyclopropylcarbinyl tosylate (**3**-H) in the aqueous binary solvents demonstrated the previously reported "internal return" rearrangement,[9,10] which accounted for 5–15% of the starting material. The purities of the starting materials were, therefore, checked by methanolysis, where a rearrangement to less reactive tosylates does not occur.[10] The solvolysis rates of cholesteryl tosylate in aqueous dioxane solvents obeyed first-order kinetics up to 85% conversion, with the exception that the first 5% of reaction was accelerated.

All other reactions were strictly first order in *p*-toluenesulfonate and furnished, within experimental error, 100% of the theoretical amount of acid present.

Discussion

The correlation of the cholesteryl tosylate solvolysis rates with those of cyclopropylcarbinyl tosylate results in a dispersion of points into two accurately straight lines (*cf.* Figure 1) in contrast to scatter diagrams

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TABLE I

Tosylate	Solvent, vol. %[a]	Temp, °C	k_1, 10^5 sec^{-1}
b	MeOH	50	31[c]
b	MeOH	40	16
b	50% MeOH–EtOH	50	21[c]
b	50% MeOH–EtOH	40	11
b	75% MeOH–EtOH	50	12
b	EtOH	50	10[c]
b	EtOH	40	3.5
b	*n*-PrOH	50	6.6[c]
b	*n*-PrOH	40	2.2
b	80% aq EtOH	50	42
b	80% aq EtOH	40	19
b	85% aq EtOH	50	33
b	90% aq EtOH	50	21[c]
b	90% aq EtOH	40	9.0
b	AcOH[d]	50	13.2
b	80% aq dioxane	50	11[b]
b	80% aq dioxane	40	3.4[c]
b	85% aq dioxane	50	9.0[c]
b	90% aq dioxane	50	4.0[c]
b	90% aq dioxane	40	1.0[c]
b	85% aq Me_2CO	50	10
b	85% aq Me_2CO	40	3.5
b	90% aq Me_2CO	50	5.8[c]
b	90% aq Me_2CO	40	1.9
e	50% MeOH–EtOH	20	7.0
e	75% MeOH–EtOH	20	4.7
e	*n*-PrOH	20	2.2
e	85% aq EtOH	20	84
e	90% aq EtOH	20	32
e	80% aq dioxane	20	11
e	85% aq dioxane	20	7.0
e	90% aq dioxane	20	1.4
e	85% aq Me_2CO	2;	9.0
e	90% aq Me_2CO	20	3.15
f	50% MeOH–EtOH	20	7.1
f	75% MeOH–EtOH	20	5.0
f	*n*-PrOH	20	2.2
f	85% aq EtOH	20	33.0
f	90% aq EtOH	20	20.0
f	80% aq dioxane	20	5.5
f	90% aq dioxane	20	1.4
f	85% aq Me_2CO	20	4.3
f	90% aq Me_2CO	20	2.4

[a] x vol. % binary solvent YZ means x volumes of Z plus $100 - x$ volumes of Y. [b] Cholesteryl. [c] Duplicate runs. [d] Taken from data of S. Winstein and R. Adams, *J. Amer. Chem. Soc.*, **70**, 838 (1948). [e] Cyclopropylcarbinyl tosylate. [f] 1-Phenylcyclopropylcarbinyl tosylate.

obtained for both mY[11] and log k_{ion} correlations. The dispersion of the data into more than one correlation line is typical[12] for a study involving several solvent systems and is in accord with the significantly different solvolytic behavior of cyclopropylcarbinyl tosylate in the two solvent series. Thus, in the ionizing solvents (correlation line I, Figure 1) significantly less than the theoretical amount of acid liberated at infinity and $\Delta S^{\pm}$ values of *ca.* −20 eu are observed, while in nucleophilic solvents (correlation line N, Figure 1) liberation of nearly the theoretical amount of acid at infinity and $\Delta S^{\pm}$ values of *ca.* −7 eu are observed.

Correlation of the solvolysis rates of **3**-H with those of cholesteryl tosylate over such a wide spectrum of

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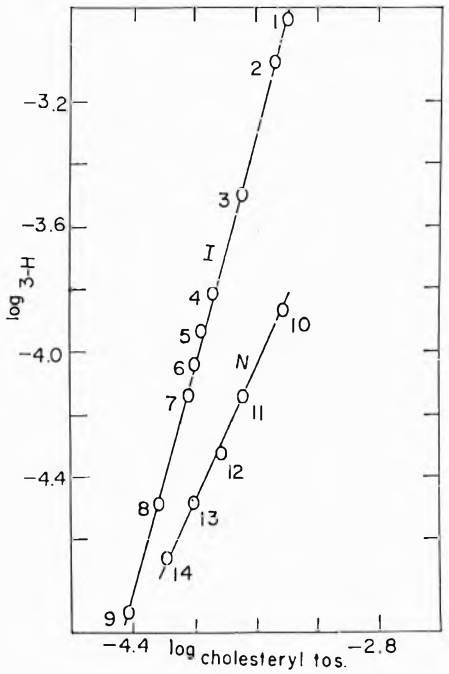
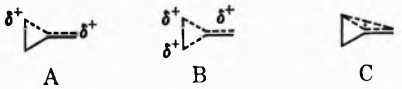


Figure 1.—The linear dependence of log (**3**-H) on log (cholesteryl tosylate): 1, 80% aqueous EtOH; 2, 85% aqueous EtOH; 3, 90% aqueous EtOH; 4, AcOH; 5, 80% aqueous dioxane; 6, 85% aqueous acetone; 7, 85% aqueous dioxane; 8, 90% aqueous acetone; 9, 90% aqueous dioxane; 10, methanol; 11, 50:50 methanol–ethanol; 12, 25:75 methanol–ethanol; 13, ethanol; 14, *n*-propyl alcohol.

solvents reflects a mechanistic similarity between the two substrates. This possibility is strengthened by the failure of a solvent polarity scale (log k_{ion}) based upon a compound known to undergo ionization assisted by neighboring-group participation to correlate with **3**-H solvolysis rates.

Many structures have been considered for the cyclopropylcarbinyl cation to accommodate various modes of electron delocalization. Among these are the homoallyl[13,14] (A), symmetrical homoallyl[14,15] or bisected form[16,17] (B), and bicyclobutonium[18,19] (C) ions.



A B C

Recently,[10,20] it was proposed, based upon solvolytic behavior, that the mode of electron delocalization in the cyclopropylcarbinyl cation varied with the nature of the solvent—structure A is favored in nucleophilic solvents while structure C (or possibly structure B) is favored in ionizing solvents. On the other hand, the mode of charge dispersal in the cholesteryl ion, stereoelectronically restricted to unsymmetrical homoallylic delocalization, is insensitive to medium effect. The partitioning of the solvents, therefore, into two correlation lines is in keeping with the solvent-variable

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TABLE II
SUMMARY OF SOLVOLYSIS RATES FOR *p*-SUBSTITUTED 1-PHENYLCYCLOPROPYLCARBINYL TOSYLATES

para substituent[a]	Solvent	Concn of salt, *M*	Temp, °C	k_1, 10^5 sec^{-1}	*b* value[b]	$\Delta H^{\pm}$, kcal/mol	$\Delta S^{\pm}$, eu
H	AcOH		30	53.0		21.0	−4
H	AcOH	0.025[c]	30	84.0	23		
H	AcOH	0.051[d]	18	16.3[e]	1.4		
CH_3O	AcOH		25	62.0[f]		19.9	−6
CH_3O	AcOH	0.025[c]	25	90.0	18		
CH_3O	AcOH	0.024[d]	25	62.0	0.0		
NO_2	AcOH		25	1.5		21.9	−7
NO_2	AcOH	0.025[c]	30	5.1	34		
NO_2	AcOH	0.024[d]	30	3.0	4.4		
NO_2	AcOH		35	4.9			
NO_2	AcOH		45	16.2			
NO_2	AcOH		55	47.0			
NO_2	EtOH		45	7.1		19.0	−18
NO_2	EtOH		50	11.0			
NO_2	EtOH		60	30.0			
NO_2	EtOH		65	43.0			

[a] Initial concentration 0.020–0.030 *M*. [b] Calculated from the equation $k_t = k_t^0$ [1 + *b* (salt)]; A. H. Fainberg and S. Winstein, *J. Amer. Chem. Soc.*, **78**, 2763, 2767, 2777, 2780 (1956). [c] $LiOClO_4$. [d] NaOAc. [e] Taken from data of J. W. Wilt and . D. Roberts, *J. Org. Chem.*, **27**, 3430 (1962). [f] Taken from data of ref 4.

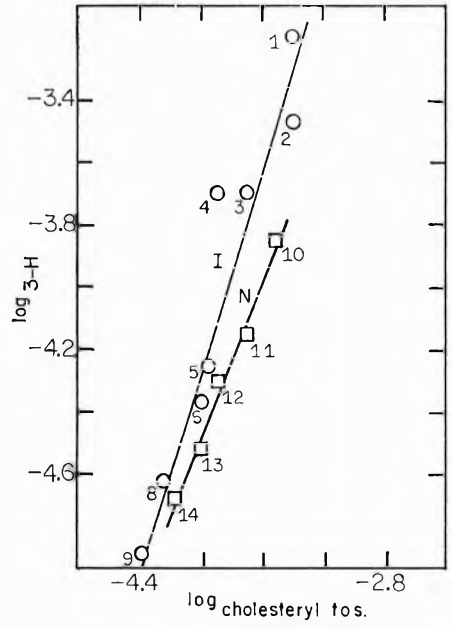

Figure 2.—The linear dependence of log (3-Ph) on log (cholesteryl tosylate): 1, 80% aqueous EtOH; 2, 85% aqueous EtOH; 3, 90% aqueous EtOH; 4, AcOH; 5, 80% aqueous dioxane; 6, 85% aqueous acetone; 8, 90% aqueous acetone; 9, 90% aqueous dioxane; 10, methanol; 11, 50:50 methanol–ethanol; 12, 25:75 methanol–ethanol; 13, ethanol; 14, *n*-propyl alcohol.

modes of charge dispersal in the cyclopropylcarbinyl cation.

Previously,[3] it was reported that the solvolysis rates of 1-phenylcyclopropylcarbinyl tosylate (**3**-Ph) were well correlated with log k_{ion} in four solvents. The incorporation of additional solvents in the study, however, yielded data which failed to fit this correlation. The correlation of the solvolysis rates of **3**-Ph with those of cholesteryl tosylate follows the same general pattern (*cf*, Figure 2) as that observed for **3**-H. The poorer fit for the **3**-Ph data can be attributed to the introduction of additional solvation mechanisms by the phenyl group. Interestingly, in all the ionizing solvents, with the exception of acetic acid, the inclusion of the phenyl group has a slight rate-retarding effect.

The failure of **3**-H to respond to 1-ring substitution in solvolysis reactions has been explained[4,5] by a transition-state geometry more closely resembling a homoallylic-like ion than a bicyclobutonium-like ion. Support for this explanation is based on the study of both substituent-[4] and leaving-group[5] effects. The kinetic data given in Table II reveal that *p*-nitrophenyl substitution at the 1-ring position has a rate-retarding effect of *ca.* 10^{-1} on the solvolytic reactivity of **3**-H. The calculated salt orders also summarized in Table II are of the right magnitude[21] for an SN1-type reaction.

The products of acetolysis of **3**-NPh and **3**-Ar (1-*p*-anisylcyclopropylcarbinyl tosylate) are 1-*p*-nitrophenylcyclobutyl and 1-*p*-anisylcyclobutyl acetate, respectively. In order to establish that the initial products of acetolysis are rearranged cyclobutyl esters, the stabilities of 1-*p*-anisylcyclopropylcarbinyl and 1-*p*-nitrophenylcyclopropylcarbinyl acetate were determined in buffered acetic acid containing *p*-toluenesulfonic acid. Both cyclopropylcarbinyl esters were stable in the reaction medium for at least 10 half-lives.

The fact that both *p*-anisyl[4] and *p*-nitrophenyl substitution at the 1-ring position has only a small effect on the solvolytic reactivity of **3**-H is inconsistent with a solvolysis transition state with significant charge development at the methinyl carbon. Furthermore, from theory[22] and experimental evidence, one would predict both significant rate enhancement by *p*-methoxy substitution and significant rate retardation by *p*-nitro substitution on a phenyl ring, assisting in the dispersal of positive charge in a solvolysis transition state. For example, the calculated value of k^{OMe}/k^{NO_2}, the ratio of acetolysis of the *p*-methoxy-substituted compound to that of the *p*-nitro-substituted compound, is 25,000 for neophyl brosylate[23] and 440,000 for *exo*-2-benznorbornenyl brosylate.[24,25] The fact that the value of k^{OMe}/k^{NO_2} for 1-phenylcyclopropylcarbinyl tosylate ace-

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tolysis is 39, orders of magnitude less than that of the above, related compounds, is consistent with a homoallylic-like ion transition-state geometry where very little charge is localized at the methinyl carbon and where rearrangement[4] to a cyclobutyl cation is much faster than capture by solvent.

Experimental Section

Melting points were not corrected for stem exposure and were taken on a Mel-Temp apparatus. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer; ultraviolet spectra were obtained on a Beckman DK-2A spectrophotometer; and the nmr spectrum was obtained on a Varian HA-100 instrument with tetramethylsilane as internal reference standard. An F & M Model 700 gas chromatograph equipped with a hydrogen-flame detector and a 6 ft × 0.125 in. column of 10% Carbowax 20M on Chromosorb W was used for analytical gc work. All microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Cyclopropylcarbinol was prepared in 84% yield by lithium aluminum hydride reduction of cyclopropanecarboxylic acid, bp 125° (760 mm) [lit.[15] bp 126° (760 mm)].

1-Phenylcyclopropylcarbinol was prepared in 87% yield by lithium aluminum hydride reduction of 1-phenylcyclopropanecarbonyl chloride, mp 32–33° (lit.[26] mp 32.5–33°).

Cyclopropylcarbinyl tosylate (3-H) was prepared according to published procedure.[15] The purity, calculated from "infinity" titers in methanolysis reactions, was 95%.

1-Phenylcyclopropylcarbinyl tosylate (3-Ph) was prepared according to established procedure,[26] mp 52° dec (lit.[26] mp 52° dec).

Cholesteryl tosylate was prepared in 85% yield by the usual method,[27] mp 131–132.5° (lit.[27] mp 131.5–132.5°).

Nitration of 1-Phenylcyclopropylcarboxylic Acid.—To a stirred solution of 48 g (0.3 mol) of 1-phenylcyclopropylcarboxylic acid[28] and 75 ml of acetic anhydride at 25° was added a cold solution of 62 g (0.92 mol) of 90% nitric acid and 140 ml (1.48 mol) of acetic anhydride at such a rate that the temperature did not rise above 25°. After stirring for an additional 1 hr at 25°, the mixture was poured into 1400 ml of ice–water and the product was extracted with benzene. The benzene extract was dried (Na_2SO_4) and concentrated, and the residue was allowed to solidify upon a watch glass to yield 50 g of crude, nitrated product. Gc analysis of a 1-g portion (converted into methyl ester by treatment with diazomethane) revealed the presence of two major and one minor bands, all with longer retention times than that for methyl 1-phenylcyclopropylcarboxylate.

Methyl 1-*p*-Nitrophenylcyclopropylcarboxylate (1).—The above mixture of nitrated acids (49 g) was converted into the corresponding methyl esters by treatment with diazomethane (*ca.* 0.8 mol) in ether. Distillation through a 20 × 1.5 cm glass helix packed column, monitored by gc, yielded 10 g of the pure *para* ester 1, mp 86–87°.

Anal. Calcd for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.64; H, 5.09; N, 6.31.

That the isomer with the longer gc retention time and higher melting point is the para compound is confirmed by the absorption maximum at 280 mμ characteristic of *p*-nitrophenylcyclopropane.[29] Additional definitive evidence for the assigned structure is provided by the nmr spectrum of 2.

1-*p*-Nitrophenylcyclopropylcarboxylic Acid (2).—Methyl 1-*p*-nitrophenylcyclopropylcarboxylate (5.5 g) dissolved in 100 ml of 85% (v/v) aqueous ethanol (0.3 *N* in NaOH) was maintained at 45° for 3 hr and then poured into 250 ml of ice water, filtered (no detectable quantity of precipitate was observed), and acidified with cold, dilute HCl. The precipitated acid was separated and air dried to yield 5.0 g (96%) of 2: mp 192–193.5°; λ_{max}^{EtOH} 280 mμ (ε 7900); nmr δ 1.16, 1.90 (complex multiplets, 4, cyclopropyl), 7.53 (d, 2, J = 8 Hz, aromatic), and 8.04 (d, 2, J = 8 Hz, aromatic).

Anal. Calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 58.04; H, 4.45; N, 6.60.

1-*p*-Nitrophenylcyclopropylcarbinol (3).—A solution of borane in tetrahydrofuran (23 ml, 0.5 *M*) was added in 10 min to 4.8 g of 2. The addition was accompanied by the vigorous evolution of a gas. After 30 min at room temperature, the mixture was poured into 250 ml of ice and extracted with ether. The combined extracts were washed once with 1.0 *N* aqueous NaOH and twice with cold water and dried (Na_2SO_4), and after air evaporation of solvent yielded 3.9 g (87%) of crude alcohol, mp 52–54°. Two recrystallizations from petroleum ether (bp 30–60°)–benzene gave the analytical sample of alcohol 3: mp 55–56°; ir (Nujol) 3300 (OH) and 1023 cm^{-1} (primary alcohol CO).

Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.25; H, 5.82; N, 7.14.

1-*p*-Nitrophenylcyclopropylcarbinyl *p*-Toluenesulfonate (3-NPh).—The tosylate ester was prepared by reaction of 7.5 mol of the alcohol 3 in 7 ml of pyridine with 9 mmol of tosyl chloride at 0° over a period of 2 hr. After the usual work-up and recrystallization from petroleum ether–benzene, 2.0 g (77%) of the tosylate 3-NPh was obtained, mp 69° dec. The sample was stable at room temperature for longer than 2 weeks.

Anal. Calcd for $C_{17}H_{17}NO_5S$: C, 58.83; H, 4.93; N, 4.03; S, 9.23. Found: C, 59.10; H, 4.99; N, 3.85; S, 9.44.

Solvolysis of 1-*p*-Anisylcyclopropylcarbinyl Tosylate (3-An).—The tosylate 3-An (5 mmol) was solvolyzed in 25 ml of acetic acid (containing 6 mmol of sodium acetate) at 25° for 10 half-lives. The mixture was poured into 200 ml of ice–water and extracted with ether. The combined extracts were washed with saturated $NaHCO_3$ until neutral, dried over Na_2SO_4, and filtered, and the solvent was removed by rotovaporization. Analysis of the residue by gc revealed a single product peak with a retention time different from that of 1-*p*-anisylcyclopropylcarbinyl acetate (the sample was unstable and upon distillation or prolonged standing set to a tacky, polymeric substance). Analysis by infrared revealed a strong band at 1728 cm^{-1} (ester carbonyl) and a medium-intensity band at 945 cm^{-1}. The sample was transparent in the 990–960-cm^{-1} region.[30]

1-Phenylcyclobutyl acetate, as well as the acetolysis products of 3-NPh and 3-An, absorbs at 945 cm^{-1} and is transparent in the 990–960-cm^{-1} region.

Solvolysis of 1-*p*-Nitrophenylcyclopropylcarbinyl Tosylate (3-NPh).—The tosylate 3-NPh (5 mmol) was solvolyzed in 25 ml of acetic acid (containing 6 mmol of sodium acetate) at 35° for 10 half-lives. Work up as above and analysis by gc and infrared revealed that 1-*p*-nitrophenylcyclobutyl acetate was the exclusive product (99%).

Solvents.—The aqueous acetone solvents were prepared from conductivity water and acetone purified by distillation from potassium permanganate. Absolute methanol was prepared by distillation from magnesium turnings, and purified *n*-propyl alcohol was obtained by distillation from aluminum foil and mercuric chloride. Absolute ethanol and dioxane were prepared according to the methods of Fieser.[31]

Kinetic experiments were carried out as previously described.[3,10]

Registry No.—1, 23348-98-3; 2, 23348-99-4; 3, 23349-00-0; 3-H, 1015-45-8; 3-Ph, 1034-83-9; 3-NPh, 23349-01-1; 3-*p*-anisyl, 16728-04-4; cholesteryl tosylate, 1182-65-6.

Acknowledgment.—This work was supported in part by the donors of the Petroleum Research Fund administered by the American Chemical Society. This support is gratefully acknowledged.

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Permanganate Oxidations. III. Kinetics and Mechanisms of the Oxidation of Furfurals in Alkaline Media[1-3]

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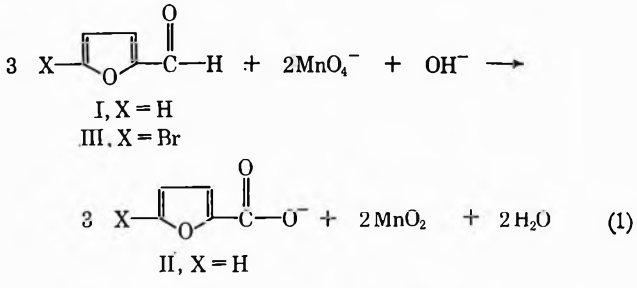
Received May 28, 1969

A spectrophotometric stopped-flow kinetic study of the permanganate ion oxidation of furfural (I) and six 5-substituted furfurals at pH 11.5–13.3 reveals that the reaction follows two reaction paths. The minor pathway (Scheme I) is independent of hydroxyl ion concentration, and the major mechanism (Scheme II) is dependent on the first power of hydroxide ion concentration. Both reaction pathways are first order with respect to the concentration of I and permanganate ion. A correlation of the second-order rate constants with Hammett σ *meta*-substituent constants has been observed for the substituents 5-Me, 5-Et, 5-*n*-Bu, H, 5-Cl, and 5-Br at 25° with $\rho = +1.30$ (Scheme II). At pH 13.3 (Scheme II), $\Delta H^{\ddagger}$ is 10.2 kcal/mol, $\Delta S^{\ddagger}$ is −22.8 eu, and k_H/k_D is >1.8. Oxygen-18 experiments show that the solvent is the major source of oxygen introduced into I *via* Scheme II. The kinetic data are consistent with the formation of the hydrate anion of I followed by a hydride anion transfer to permanganate ion in the rate-determining step for the mechanism of Scheme II. It is postulated that the mechanism of Scheme I involves a direct attack of permanganate ion on I to give the permanganate ester, which decomposes in a subsequent slow step.

Although a few kinetic studies of the permanganate ion oxidation of aliphatic and aromatic aldehydes have been published,[5-7] no reports have appeared concerning the oxidation of heterocyclic aldehydes. Since there is the possibility of simultaneous attack at the furan ring and at the carbonyl group, several conflicting reports have appeared concerning the permanganate ion oxidation of furfural (I). For example, Obata,[8] using an excess of oxidant, obtained maleic acid from the alkaline permanganate oxidation of I. In contrast, Wagner and Simons[9] reported a greater than 80% yield of 2-furoic acid (II) from I, and Gilman and Wright[10] oxidized 5-bromofurfural (III) to the corresponding



I, X = H
III, X = Br

II, X = H

(1)

acid in basic media. The complexity and pH dependence of the permanganate ion oxidation of I are further demonstrated by the observations that II is not the major oxidation product in neutral and acid solution.[11,12] Presumably, the furan ring is more susceptible to attack than the carbonyl carbon in nonalkaline media.

Owing to the absence of previous kinetic studies, we have investigated the alkaline permanganate ion oxidation of I spectrophotometrically in a stopped-flow reactor.[1,13] A study of the effect of substituents on the rates of reaction, of kinetic isotope effects, of activation parameters, and of oxygen-labeling experiments permits a fairly clear mechanistic picture to be presented. Also, one of the few examples of an application of the Hammett equation to the furan nucleus is discussed.[14-17]

Experimental Section

All melting points are uncorrected and were determined on a Thomas–Hoover apparatus. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Mass spectral analyses were performed by Professor P. C. Ford.[18]

Reagents.—Distilled water was purified by passing through an ion-exchange cartridge (Type R-2, Illinois Water Treatment Company, Rockford, Ill.). Reagent grade sodium nitrate (Baker) was used to adjust solutions to desired ionic strengths. Potassium permanganate stock solutions were prepared from Acculute standard volumetric solutions. The stock solution was stored under nitrogen and the absorbancy index of permanganate ion was checked before each set of kinetic runs. Sodium hydroxide solutions were prepared from standard concentrated (Acculute). All solutions were prepared immediately before the kinetic runs, and the pH of the solutions were taken as those measured potentiometrically.

Potassium permanganate-^{18}O was prepared by the isotopic exchange reaction between normal permangatate ion (Mallinckrodt) and water-^{18}O (Bio-Rad).[5,19] Isotopic analyses were performed by thermal decomposition of the sample followed by mass spectrometric analysis of the oxygen formed.[5,20] The *m/e* 34:32 ratio was used to calculate per cent ^{18}O.

Furfural (Aldrich) was purified by distillation, bp 91–93° (11 mm).

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5-Nitrofurfural was prepared according to the method of Gilman and Wright,[21] using 5-nitrofurfural diacetate (Eastman). Under an atmosphere of nitrogen, 24.3 g (0.1 mol) of 5-nitrofurfural diacetate was refluxed with a solution of 54 g (0.56 mol) of concentrated sulfuric acid in 108 g (6.0 mol) of water for 15 min with constant stirring. The ether extract of the cooled hydrolyzed product was washed with water, dried over Na_2SO_4, and filtered. The ether was removed and the residue was distilled at 132–134° (11 mm) to give 10 g (71%) of product, mp 34–36° (lit.[21] mp 35–36°).

5-Methylfurfural was prepared from 2-methylfuran (Aldrich) according to the method of Traynelis, *et al.*,[22] except that a ratio of 2 mol of DMF and 2 mol of $POCl_3$ to 1 mol of 2-methylfuran was used. Distillation at 78–80° (16 mm) [lit.[22] bp 72–73° (13 mm)] gave 88 g (76.1%) of product.

5-Ethylfurfural was prepared from 2-ethylfuran, which was prepared by reduction[23,24] of 2-acetylfuran (Aldrich). 2-Ethylfuran was formylated as described above. Distillation gave 11.9 g (64%) of product, bp 88–90° (11 mm) [lit.[22] bp 88–90° (11 mm)].

5-Isobutylfurfural was prepared from 2-isobutylfuran, which was prepared by reduction of isobutyl furyl ketone. Isobutyl furyl ketone was prepared by the Friedel–Crafts reaction of furan and isobutyryl chloride.[24]

In a 1-l., round-bottomed flask, 38.8 g (0.28 mol) of isobutyl furyl ketone, 28 ml (0.5 mol) of 85% hydrazine hydrate, 28 g (0.7 mol) of sodium hydroxide, and 225 g (3.64 mol) of ethylene glycol were heated for 2.5 hr until the vigorous evolution of gas diminished. A two-phase distillate was obtained after distillation. The aqueous layer was separated and extracted twice with 50-ml portions of ether. The combined organic solution was dried (Na_2SO_4), filtered, and distilled to give 14.3 g (41.2%) of 2-isobutylfuran, bp 126.5–128° (lit.[24] bp 123–127°). Formylation of the product as described above gave 13.6 g (72%) of 5-isobutylfurfural, bp 168–170° (40 mm). The 2,4-dinitrophenylhydrazone, mp 150–152°, was prepared and analyzed.

Anal. Calcd for $C_{15}H_{16}N_4O_5$: C, 54.22; H, 4.85; N, 16.86. Found: C, 54.05; H, 4.90; N, 16.76.

5-*n*-Butylfurfural was prepared from 2-*n*-butylfuran. *n*-Butyl furyl ketone, which was prepared by the Friedel–Crafts reaction of furan and *n*-butyryl chloride,[24] was reduced as described above[23,24] to give 2-*n*-butylfuran, bp 140–142° (lit.[24] bp 137–138°). Formylation gave 50.1 g (91%) of 5-*n*-butylfurfural, bp 117–119° (11 mm). The 2,4-dinitrophenylhydrazone, mp 160–162°, was analyzed.

Anal. Calcd for $C_{15}H_{16}N_4O_5$: C, 54.22; H, 4.85; N, 16.86. Found: C, 54.00; H, 4.86; N, 16.75.

5-Chlorofurfural was prepared, mp 31–33° (lit.[25] mp 31.5–33°).

5-Bromofurfural was prepared, mp 83–85° (lit.[26,27] mp 83–85°).

Furfural-d_1 was prepared in 85% isotopic purity (pmr) by the Rosenmund reduction[28] of 2-furoyl chloride.[29] Attempts to prepare furfural-d_1 by the lithium deuteride reduction of furil[30] or the manganese dioxide oxidation of α,α-d_2-furfuryl alcohol[31] were unsuccessful.

Since furfurals are easily oxidized, they were stored as the bisulfite addition compound. The only exception was the water-soluble bisulfite addition compound of I.

Oxidation with Potassium Permanganate-^{18}O.—A modification of the method of Wiberg and Stewart[5] was used to prepare 5-bromofuroic acid for mass spectral analysis. In a 2-l. flask fitted with stirrer, thermometer, and nitrogen inlet flow, which contained 1.28 g (0.0072 mol) of 5-bromofurfural in 750 ml of deionized water equilibrated in a water bath at 25.0°, was rapidly added 250 ml of deionized water containing 0.76 g (0.0048 mol) of labeled potassium permanganate (0.833% ^{18}O) and 150 ml of 2 *N* sodium hydroxide (added just prior to addition). The resulting solution had a pH of 13.3. After 5 min the solution was quenched with 50 ml of 0.5 *M* sodium bisulfite, concentrated sulfuric acid was added to dissolve precipitated manganese dioxide, and the solution was extracted three times with 75-ml portions of benzene. The extract was washed with water and extracted with 40 ml of 0.5 *M* potassium carbonate solution. Acidification of the basic solution with concentrated sulfuric acid gave, after cooling, filtering, and drying, 0.24 g of 5-bromofuroic acid, mp 183–185° (lit.[32] mp 185–186°). The ^{18}O content of the acid was analyzed and the per cent transfer of oxygen from potassium permanganate was calculated according to the formula of Wiberg and Stewart:[5,33] % O from $KMnO_4$ = 100 [2(y − 0.204)/x − 0.204], where y = 100 [^{18}O/(^{16}O + ^{18}O)] and x = % ^{18}O in $KMnO_4$ = 0.833%.

Kinetic Method.—All experiments were performed under pseudo-first-order conditions using a large excess of furfural.

Because of the large rate constants, the rates of reaction were determined by following spectrophotometrically the disappearance of permanganate ion (522 mμ) in a stopped-flow system.[1,13] The rate constants, which were obtained from plots of $-\ln[\log(T_\infty/T)]$ *vs.* time, where T_∞ is the per cent transmission at a point just before colloidal manganese dioxide begins to form, were calculated on an IBM 1620 computer.[34] The rates were followed until the reactions were 75–90% complete, and the rate constants were calculated three times using the data to the first half-life, to the second half-life, and then to the third half-life. In this method, any deviation from linearity was readily observed.

Results and Discussion

The rate of oxidation of I was determined using an eightfold range of furfural concentration, a threefold range of permanganate ion concentration, and a sevenfold range of hydroxide ion concentration (Tables I and II). A plot of k_ψ (pseudo-first-order rate constant) *vs.* concentration of I gives a straight line that goes through the origin, indicating the rate of oxidation to have a first-order dependence on furfural concentration. At constant furfural and hydroxide ion concentrations, the pseudo-first-order rate constant is not altered appreciably with increasing permanganate ion concentrations, which indicates a first-order dependence on permanganate ion. With a large excess of I and hydroxide ion, good first-order plots are obtained, which further demonstrates that the reaction has a first-order dependence on permanganate ion. A plot of the second-

TABLE I
RATE DEPENDENCE ON FURFURAL AND PERMANGANATE CONCENTRATIONS[a]

[Furfural], 10^2 *M*	[OH$^-$], *M*	[MnO_4^-], 10^4 *M*	k_ψ,[b] sec^{-1}	k_2,[c] M^{-1} sec^{-1}
0.25[d]	0.20	4.0	0.02	8.0
0.50[d]	0.20	4.0	0.04	8.0
2.01[d]	0.20	4.0	0.159	7.9
4.02[d]	0.20	4.0	0.34	8.4
4.02	0.20	4.0	0.54	13.4
4.02	0.20	6.0	0.60	14.9
4.02	0.20	8.0	0.55	13.7
4.02	0.20	12.0	0.65	16.1

[a] λ = 522 mμ, μ = 1.0 *M*, *T* = 25.0°. [b] Pseudo-first-order rate constant. [c] Second-order rate constant = k_ψ/[furfural]. [d] *T* = 5.0°.

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TABLE II

RATE DATA FOR THE NEUTRAL AND BASE-CATALYZED REACTIONS OF FURFURAL AND 5-METHYL- AND 5-NITROFURFURAL[a]

Substrate	pH	[OH⁻], *M*	k_ψ,[b] sec^{-1}	k_2,[c] M^{-1} sec^{-1}	k_0,[d] M^{-1} sec^{-1}	$k_3 = (k_2 - k_0)/[OH^-]$,[e] $l.^2$ mol^{-2} sec^{-1}
I[f]	12.5	0.03	0.18	4.50	2.70	60.0
I[f]	12.8	0.063	0.26	6.50	2.70	60.3
I[f]	13.25	0.18	0.54	13.50	2.70	60.0
I[f]	13.3	0.20	0.59	14.75	2.70	60.3
IV[g]	12.3	0.02	0.14	3.50	2.60	45.0
IV[g]	12.5	0.03	0.15	3.75	2.60	38.3
IV[g]	12.8	0.063	0.20	5.00	2.60	38.1
IV[g]	13.25	0.18	0.39	9.75	2.60	39.7
V[h]	11.5	0.003	0.61	127.6[i]	47.8	26.6×10^3
V[h]	11.8	0.006	1.03	215.5[i]	47.8	27.9×10^3
V[h]	12.3	0.02	2.74	573.2[i]	47.8	26.3×10^3

[a] $\lambda = 522$ mμ, $T = 25.0°$, $\mu = 1.0$ *M*. [b] Pseudo-first-order rate constant. [c] Second-order rate constant = k_ψ/[Furfural]. [d] Intercept from plot of k_2 *vs.* [OH⁻]. [e] Third-order rate constant which agrees well with the slope from a plot of $(k_2 - k_0)$ *vs.* [OH⁻]. [f] [I] = 4.02×10^{-2} *M*. [g] [IV] = 4.00×10^{-2} *M*. [h] [V] = 4.78×10^{-3} *M*. [i] $T = 14.5°$.

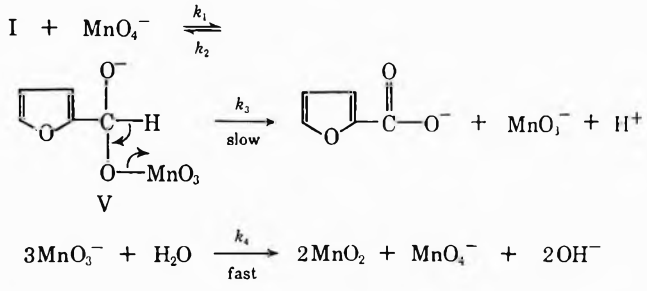
order rate constant ($k_2 = k_\psi$/[furfural]) *vs.* hydroxide ion concentration gives a straight line that does not go through the origin. Similar plots were obtained with 5-methylfurfural (IV) and 5-nitrofurfural (V). This implies that there are both zero-order and first-order terms describing the effect of hydroxyl ion on the rate of reaction. These data suggest the following rate law

$$-d[MnO_4^-]/dt = k_0[\text{furfural}]\,[MnO_4^-] + k_3[\text{furfural}]\,[MnO_4^-][OH^-] \quad (2)$$

where k_0 (the intercept of a plot of k_2 *vs.* [OH⁻]) is the rate constant for oxidation of neutral I, IV, or V, and k_3 is the constant for the base-catalyzed reaction.[35] Table II shows the constancy of k_3 for I, IV, and V, respectively.

A possible mechanism for the neutral reaction, which involves a direct attack of permanganate ion at the carbonyl carbon of I to give the permanganate ester V, is shown in Scheme I. The slow step is probably

SCHEME I



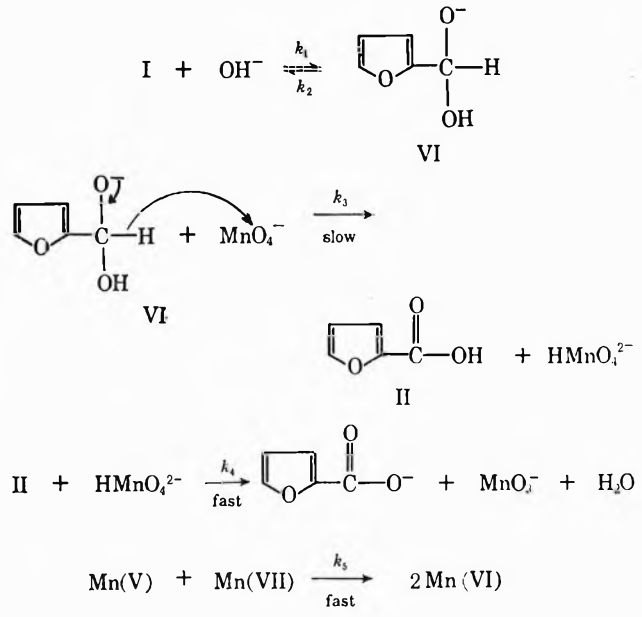
the decomposition of V *via* proton transfer and cleavage of the manganese–oxygen bond. The rate equation derived from this mechanism is eq 3, where K_{eq} denotes the equilibrium constant for the formation of V.[7]

$$v = k_\psi[IV] = k_0K_{eq}[I][MnO_4^-] \quad (3)$$

The mechanism shown in Scheme II, for the base-catalyzed reaction, presumably involves a hydride transfer in the rate-determining step. The rate equation derived from this mechanism is eq 4, where K_{eq} is the equilibrium constant for the formation of VI.

$$v = k_\psi[VI]\,[MnO_4^-] = k_{OH^-}K_{eq}[I]\,[MnO_4^-]\,[OH^-] \quad (4)$$

SCHEME II



The mechanism correctly predicts that the rate will be a linear function of hydroxide ion concentration and that the reaction will be subject to specific hydroxide ion catalysis.

The observed rate of disappearance of permanganate ion is the sum of the rates of the neutral (Scheme I) and base-catalyzed (Scheme II) reactions. This means that a plot of $(k_2 - k_0)$ *vs.* hydroxide ion concentration should give a straight line passing through the origin if the reaction is first order in hydroxyl ion. Using the data from Table II shows that this is indeed true for I, IV, and V.

Scheme I suggests that the permanganate ion will be the source of oxygen introduced into I, while Scheme II predicts that the oxygen will come from the solvent. In order to determine the source of oxygen, 5-bromofurfural (III)[36] was oxidized with enriched potassium permanganate-^{18}O and then analyzed *via* mass spectrometry (Table III). The low value at pH 13.3 and the larger value at pH 12.3 support Scheme II. The low incorporation of ^{18}O into I, at pH 13.3, could arise

(35) Our results in neutral and acid media indicate that k_0 might also contain the rate constant for permanganate attack on the furan nucleus.[11]

(36) Compound III was selected because 5-bromo-2-furoic acid is less water soluble than 2-furoic acid (II).

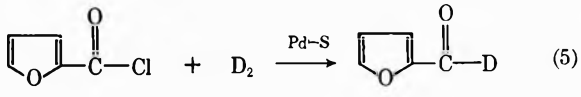
TABLE III
OXIDATION OF 5-BROMOFURFURAL WITH POTASSIUM PERMANGANATE-^{18}O AT 25°

pH	% O from MnO_4^-
13.3	7.6
12.3	21.3

from the slow exchange between permanganate ion and solvent.[37-41]

The enthalpy of activation (10.2 kcal/mol) and the entropy of activation (−22.8 eu) at pH 13.3 for the base-catalyzed oxidation of I are of the same order of magnitude as the values for the reaction of other anions with permanganate.[1,42,43]

Furfural-d_1 was prepared in 85% isotopic purity *via* the Rosenmund reduction of furoyl chloride (eq 5).[28,29,44]



(5)

An uncorrected k_H/k_D value of 1.8 was observed at pH 13.3. Although no quantitative significance can be ascribed to this value, the results do support the breaking of a C–H(D) bond in the rate-determining step (Scheme II).

Table IV shows a slight increase in reaction rate owing to increased salt concentration, which is expected for a reaction between two negative ions.[46]

TABLE IV
KINETIC DEPENDENCE ON IONIC STRENGTH AT 25.0°[a]

μ	k_ψ,[b] sec^{-1}
0.1	0.37
0.2	0.42
0.3	0.43
0.5	0.51

[a] [Furfural] = 4.02×10^{-2} *M*, [MnO_4^{2-}] = 4.00×10^{-4} *M*, pH = 13.3, λ = 522 mμ. [b] Pseudo-first-order rate constant.

Since the furan ring is a planar pentagon with sp^2-hybridized carbon atoms and possesses considerable aromatic character arising from the delocalization of the two paired electrons on the oxygen atom and the four carbon π electrons, one would expect a Hammett correlation similar to substituted benzenes. In order to test this possibility, for the base-catalyzed mechanism, several 5-substituted furfurals were prepared and oxidized under identical conditions. Figure 1 shows that I is oxidized faster with electron-withdrawing groups than with electron-releasing groups.

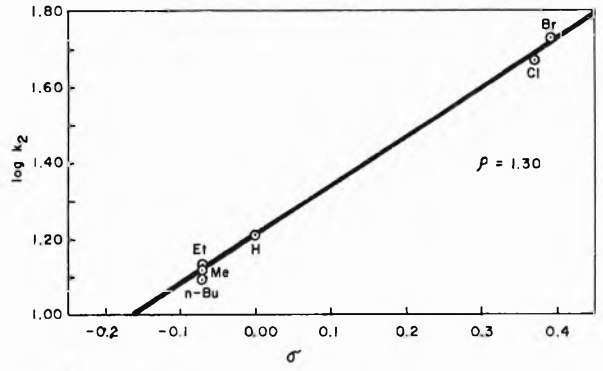


Figure 1.—Hammett plot for furfurals at pH 13.3.

Indeed, V is immeasurably fast in our stopped-flow system. Statistical treatment[47] of the rate data, using Hammett σ *meta*-substituent values, gives a ρ value of +1.30 with a correlation coefficient r of 0.9974 and a standard deviation s of 0.0235. Using σ *para*-substituent values, the statistical treatment gives a ρ of +1.52 with r = 0.9766 and s = 0.0706. The excellent correlation with σ-*meta* values is surprising, since molecular orbital calculations[48] and dipole moment measurements[49] that the *ortho*, *meta*, and *para* positions of benzene corresponds to the 3, 4, and 5 positions in 2-substituted thiophenes. Also, Noyce and Kaiser[16] obtained an excellent correlation (0.99) by using σ^+ *para*-substituent constants for the 5 position and σ^+ *meta*-substituent constants for the 4 position in the solvolysis of furylmethylcarbinol derivatives. However, it has been noted that 5-substituted 3-furoic acids correlate equally well with σ *meta*- and σ *para*-substituent constants.[17,50]

Although the observed kinetic data support Scheme II and are consistent with Scheme I, additional kinetic studies are required to fully elucidate the mechanisms in the neutral and acid regions. It is also of interest to note that the kinetics of permanganate ion oxidation of I are remarkably similar to the alkaline permanganate ion oxidation of benzaldehyde.[5,50-52]

Registry No.—I, 98-01-1; III, 1899-24-7; IV, 620-02-0; V, 698-63-5; 5-ethylfurfural, 23074-10-4; 5-chlorofurfural, 21508-19-0; 5-isobutylfurfural, 23115-88-0; 2,4-dinitrophenylhydrazone of 5-isobutylfurfural, 23074-12-6; 5-*n*-butylfurfural, 23074-13-7; 2,4-dinitrophenylhydrazone of 5-*n*-butylfurfural, 23074-14-8.

(37) Exchange between the carboxylate group and hydroxide ion is unlikely because of electrostatic repulsion. However, it has been found that benzoic acids will undergo slight exchange under drastic conditions, *e.g.*, 10 days at 100°.[38]

(38) C. A. Bunton, A. E. Comyns, J. Graham, and J. R. Quayle, *J. Chem. Soc.*, 3817 (1955).

(39) N. F. Hall and O. R. Alexander, *J. Amer. Chem. Soc.*, **62**, 3455 (1940).

(40) G. A. Mills, *ibid.*, **62**, 2833 (1940).

(41) Saturated potassium permanganate solution exchanges slowly with water at 100° in neutral solution.[39] The rate of exchange appears to be only slightly faster in basic solution,[5,39,40] which is negligible for this work.

(42) S. M. Taylor and J. Halpern, *J. Amer. Chem. Soc.*, **81**, 2933 (1959).

(43) F. Freeman and A. Yeramyan, *Tetrahedron Lett.*, 4783 (1968).

(44) Curiously, attempts to prepare furfural-d_1 *via* the lithium aluminum deuteride reduction of furil were unsuccessful.[30] Although furfuryl alcohol was oxidized to I by manganese dioxide, the increased bond strength in α,α-d_2-furfuryl alcohol appeared to make the rate of oxidation of the aldehyde faster than the rate of oxidation of deuterated alcohol.[45]

(45) F. Freeman and A. A. Kamego, unpublished data, 1967.

(46) The ionic strength is too high to permit any detailed interpretation according to the Debye–Hückel theory.

(47) (a) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953). (b) One would expect the rate-determining step to have a negative ρ value, since electron-releasing groups should facilitate a hydride ion transfer (Scheme II). Since the observed rates depend on the equilibrium concentration of VI, it appears that ρ_{eq} in the equation

$$\log(k/k_0)_{obsd} = \log (K/K_0)_{eq} + \log (k/k_0)_{rate} = \sigma(\rho_{eq} + \rho_{rate})$$

is opposite in sign and larger in magnitude than ρ_{rate}. This has also been observed in the permanganate oxidation of benzaldehyde and in the chromic acid oxidation of alcohols.[5]

(48) L. Melander, *Ark. Kemi*, **11**, 397 (1957).

(49) R. Keswani and H. Freiser, *J. Amer. Chem. Soc.*, **71**, 1789 (1949).

(50) On the other hand, since the measured relative substituent effect (alkyl and halogen) arises from polar effects and electrostatic interactions, the excellent correlation with σ_{meta} values is not unexpected. When the data (Me, Et, H, Br, Cl) from the oxidation are correlated with the σ normal (σ_{para}) parameter[17b] and the σ_{meta}^0, and σ_{para}^0 parameters (Me, H, Br, Cl),[17c] the ρ values, r, and s are 1.54, 0.988, and 0.013; 1.29, 0.998, and 0.012; and 1.47, 0.978, and 0.080, respectively.

(51) Early work in the benzaldehyde–permanganate ion reaction indicated a fractional dependence on hydroxyl ion concentration.[5] However, more recent studies have shown that this is not the case.[52]

(52) K. B. Wiberg and F. Freeman, unpublished results.

Silver(II) Complexes in Oxidative Decarboxylation of Acids

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Received August 21, 1969

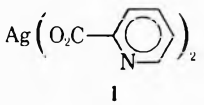
Silver(II) picolinate, bis(α,α'-bipyridine)silver(II) nitrate, and silver oxide have been employed directly in the oxidative decarboxylation of acids. Excellent yields of carbon dioxide, isobutylene, and *t*-butyl derivatives are obtained from pivalic acid by oxidation with all three silver(II) oxidants under a variety of conditions. The *t*-butyl cation is the precursor for the butyl products. The decarboxylation is postulated to occur *via* two successive 1-equiv processes, in which the oxidation of the carboxylate moiety by silver(II) yields carbon dioxide and an alkyl radical followed by further oxidation of the alkyl radical to the cation by a second silver(II) species.

Silver(II) species are among the most powerful oxidants available for organic chemistry.[1-4] In aqueous solutions, Ag^{2+} is viable only in highly acidic media[5] in which it is in equilibrium with Ag^{3+}. Even under

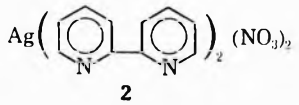
$$2Ag^{2+} \rightleftharpoons Ag^{+} + Ag^{3+} \quad (1)$$

these conditions Ag^{2+} is coordinated with such weakly complexing ions as perchlorate.[6] Aqueous solutions of Ag^{2+} are, moreover, relatively unstable and oxidize water to oxygen at room temperature.[7]

We found that silver(II) species were formed as metastable intermediates in the silver(I)-catalyzed reactions of peroxodisulfate ion and were highly effective in the oxidative decarboxylation of acids.[8] Several stable silver(II) complexes have been reported: silver(II) picolinate (**1**), bisbipyridinesilver(II) nitrate (**2**),



1



2

and silver oxide (AgO). In this paper we sought to determine the effectiveness of these silver(II) complexes in the direct oxidative decarboxylation of acids. The liberation of carbon dioxide and the formation of alkyl radicals are diagnostic of the transformation of silver(II) to silver(I) in common with the behavior of other 1-equiv oxidants.[9]

$$RCO_2H \xrightarrow{-e} R\cdot + CO_2 + H^{+} \quad (2)$$

All three silver(II) complexes listed above were employed in comparative studies of the oxidative decarboxylation of pivalic, isobutyric, butyric, and acetic acids, which served as representative examples.

Results

Studies of oxidative decarboxylation of acids by silver(II) complexes were all carried out using a common procedure. The silver(II) compound was weighed into a flask which was sealed with a rubber septum and degassed *in vacuo*. The carboxylic acid was added with a hypodermic syringe after thorough degassing to remove oxygen. The reaction mixture was stirred magnetically and decomposed thermally.

Oxidative Decarboxylation with Silver(II) Picolinate.—Decarboxylations with silver(II) picolinate were carried out in carboxylic acid as solvent to avoid complications from water. The reduction of silver(II) proceeded readily at 90° and could be followed visually by the disappearance of the orange silver(II) species to the colorless silver(I) picolinate. The reaction times listed on Table I were a qualitative yet reliable measure of the complete reduction of silver(II).

Carbon dioxide and alkene and alkyl esters were formed in excellent yields in most cases. Thus pivalic acid afforded carbon dioxide, isobutylene, and *t*-butyl pivalate according to the stoichiometry given in eq 3. Isobutyric, *n*-butyric, and even acetic acid under-

$$(CH_3)_3CCO_2H + 2Ag^{II} \longrightarrow [(CH_3)_3CO_2C(CH_3)_3 + (CH_3)_2C{=}CH_2] + CO_2 + 2H^{+} + 2Ag^{I} \quad (3)$$

went decarboxylation in an analogous manner. With the exception of isobutyric acid, alkanes were generally minor products. It should be noted that the principal product from the oxidative decarboxylation of *n*-butyric acid was the unrearranged *n*-propyl *n*-butyrate. The isopropyl isomer was only a minor constituent.

Oxidative decarboxylation by silver(II) picolinate was accelerated by trifluoroacetic acid and even more so by pyridine. Neither of these additives, however, significantly affected the stoichiometry of the decarboxylation (Table I). Copper(II) acetate, on the other hand, retarded the decarboxylation induced by silver(II) picolinate. The addition of as little as 1% copper(II) acetate [based on silver(II)] increased the reaction time from 1 hr to >20 hr. Under these conditions, *alkane* was the major product, although at higher copper(II) concentrations alkene predominated. In the latter cases, the extent of oxidative decarboxylation was minor. These reactions were not homogeneous and we are unable to draw any conclusions regarding the inhibitory effect of copper(II) on the decarboxylation. The inhomogeneity of the reaction may also reflect the otherwise inexplicable observation that the relative rates of decarboxylation (gross overall) by silver(II) picolinate appeared to

(1) For a review of the higher oxidation states of silver, see J. A. McMillan, *Chem. Rev.*, **62**, 65 (1962).

(2) J. B. Lee and T. G. Clarke, *Tetrahedron Lett.*, 415 (1967).

(3) L. Syper, *ibid.*, 4193 (1967).

(4) R. G. R. Bacon and D. J. Munro, *J. Chem. Soc.*, 1339 (1960); R. G. R. Bacon and W. J. W. Hanna, *ibid.*, 4692 (1965); R. G. R. Bacon and D. Stewart, *ibid.*, *C*, 1384 (1966).

(5) (a) A. A. Noyes, J. L. Hoard, and K. S. Pitzer, *J. Amer. Chem. Soc.*, **57**, 1221 (1935); *J. Chem. Phys.*, **59**, 1316 (1937); (b) G. A. Rechnitz and S. B. Zamochnick, *Talanta*, **11**, 713, 1645 (1964); **12**, 479 (1965).

(6) J. B. Kirwin, F. D. Peat, P. J. Proll, and L. H. Sutcliffe, *J. Phys. Chem.*, **67**, 1617 (1963).

(7) H. N. Po, J. H. Swinehart, and T. L. Allen, *Inorg. Chem.*, **7**, 244 (1968).

(8) J. M. Anderson and J. K. Kochi, to be published.

(9) (a) Pb^{IV}: J. K. Kochi, J. D. Bacha, and T. W. Bethea, *J. Amer. Chem. Soc.*, **89**, 6538 (1967). (b) Ce^{IV}: R. A. Sheldon and J. K. Kochi, *ibid.*, **90**, 6688 (1968). (c) Co^{III}: S. S. Lande and J. K. Kochi, *ibid.*, **90**, 5196 (1968).

TABLE I

DECARBOXYLATION OF ACIDS BY Ag(PICOLINATE)$_2$ AT 90°[a]

				Products, mmol [+ indicates traces (<0.01 mmol)]							
Acid	Additive	Additive/ Ag^{II}	Reacn time, min	CO_2	$2CO_2/Ag^{II}$	RH	R(−H)	Ester	Ester	R_{ox}[b]/ alkane	ΣR[c]/ CO_2
Pivalic	...	...	600	0.53	1.06	0[d]	0.34[e]	0.10[f]	0	>100	0.83
	TFA	5	120	0.51	1.02	0	0.31	+	0	>100	0.61
	C_5H_5N	5	30	0.48	0.96	+	0.28	+	0	>60	0.59
Isobutyric	...	...	120	0.60	1.20	0.19[g]	0.13[h]	0.09[i]	0	1.1	0.68
〃	...	...	420	0.50	1.00	0.16	0.12	0.10	0	1.4	0.75
	TFA	5	150	0.54	1.08	0.12	0.13	0.11	0	2.0	0.67
	C_5H_5N	5	15	0.52	1.04	0.10	0.14	0.13	0	2.7	0.71
〃	$Cu(OAc)_2$	1	1440	0.13	0.26	+	0.14	<0.03	0	>40	1.00
n-Butyric	...	...	60	0.52	1.04	0.05[g]	0.08[h]	0.02[k]	0.27[l]	7.4	0.81
〃	...	...	120	0.45	0.90	0.05	0.07	0.02	0.17	5.2	0.67
	TFA	5	30	0.46	0.92	0.05	0.07	0.02	0.13	4.4	0.59
	C_5H_5N	5	15	0.50	1.00	0.05	0.05	+	0.24	5.8	0.68
〃	$Cu(OAc)_2$	1	1440	0.26	0.52	+	0.16	<0.03	0	>33	0.70
Acetic	...	...	60	0.50	1.00	0.09[m]	...	0.43[n]	0	4.7	1.00
	...	...	30	0.47	0.94	+	...	0.32	0	80	0.68
	TFA	5	15	0.47	0.94	+	...	0.13	0	>26	0.28
	C_5H_5N	5	15	0.46	0.92	+	...	0.38	0	>78	0.83

[a] 1.0 mmol of Ag(picolinate)$_2$ in 10 ml of carboxylic acid. [b] R_{ox} includes alkene and esters. [c] $\Sigma R\cdot$ includes all products derived from alkyl moiety (alkene, alkane, and ester) and represents material balance. [d] Isobutane. [e] Isobutylene. [f] *t*-Butyl pivalate. [g] Propane. [h] Propylene. [i] Isopropyl isobutyrate. [j] 80°. [k] Isopropyl *n*-butyrate. [l] *n*-Propyl *n*-butyrate. [m] Methane. [n] Methyl acetate.

TABLE II

DECARBOXYLATION OF ACIDS BY $Ag(C_{10}H_8N_2)_2(NO_3)_2$ AT 60°[a]

		Products, mmol						
Acid	Reacn time, min	CO_2	$2CO_2/Ag^{II}$	RH	R(−H)	ROH	Ester	$\Sigma R\cdot$[b]/ CO_2
Pivalic[c]	20	0.24	0.75	0	0.08[d]	0.15[e]	0	0.96
Isobutyric	3	0.33	1.02	0	0.12[f]	0.10[g]	0.05[h]	0.82
n-Butyric	10	0.28	0.86	0	0.11[f]	+[g]	0.06[i]	0.63

[a] 0.65 mmol of $Ag(C_{10}H_8N_2)_2(NO_3)_2$ in 5 ml of 50% aqueous carboxylic acid. [b] $\Sigma R\cdot$ includes all products (alkene, alkane, ester, and alcohol) derived from alkyl moiety. [c] 0.65 mmol of $Ag(C_{10}H_8N_2)_2(NO_3)_2$ in 10 ml of pivalic acid–water–DMSO (33:33:33, v/v/v). [d] Isobutylene. [e] *t*-Butyl alcohol. [f] Propylene. [g] Isopropyl alcohol. [h] Isopropyl isobutyrate. [i] Isopropyl *n*-butyrate.

TABLE III

DECARBOXYLATION OF ACIDS BY AgO AT 90°[a]

				Products, mmol							
Acid	Additive	Additive/ AgO	Reacn time, hr	CO_2	$2CO_2/AgO$	RH	R(−H)	Ester	Ester	R_{ox}[b]/ alkane	$\Sigma R\cdot$[c]/ CO_2
Pivalic[d]	...	...	3	1.54	1.00	0	1.10[e]	0.22[f]	0.08[g]	>200	0.91
	AgOAc	1.0	3	1.55	1.01	0	1.08	0.23	0.08	>200	0.90
	TFA	1.0	1	1.43	0.92	0	0.35	0.51	0.10	>200	0.67
	TFA	2.0	1	1.46	0.96	0	0.31	0.52	0.08	>200	0.62
Isobutyric	...	...	24	0.72	0.48	+	0.08[h]	0.02[i]	+[j]	20	0.14
	TFA	1.0	1	0.78	0.52	+	0.10	0.08	+	36	0.24
n-Butyric	...	...	24	0.86	0.57	+	0.05[h]	+[k]	0	10	0.05
	AgOAc	1.0	14	0.34	0.23	+	0.06	+		10	0.18
	TFA	1.0	1	0.65	0.43	+	0.05	+	0	10	0.10
	TFA	2.0	3	0.85	0.57	+	0.10	+	0	10	0.12

[a] 3.0 mmol of AgO in 10 ml of carboxylic acid. [b] R_{ox} includes alkene and esters. [c] $\Sigma R\cdot$ includes all products (alkene, alkane, and esters) derived from alkyl moiety. [d] *t*-BuCOOH–HOAc (96:4, w/w). [e] Isobutylene. [f] *t*-Butyl pivalate. [g] *t*-Butyl acetate. [h] Propylene. [i] Isopropyl isobutyrate. [j] Isopropyl acetate. [k] Trace amounts of *n*-propyl *n*-butyrate, isopropyl *n*-butyrate, and isopropyl acetate.

decrease in the order acetic > *n*-butyric > isobutyric > pivalic acid.[10]

Oxidative Decarboxylation with Bis(α,α'-bipyridine)-silver(II) Nitrate.—Oxidative decarboxylation of acids with bis(α,α'-bipyridine)silver(II) was carried out in solutions containing 50% by volume aqueous carboxylic acid (Table II). Water was added as a cosolvent to provide an homogeneous medium. The reduction of silver(II) was complete within a few minutes at 60° under these conditions. Excellent yields of carbon dioxide, alkene, alcohol, and ester were obtained according to the stoichiometry given by eq 4.

$$RCO_2H + 2Ag^{II}(bipyridine)_2^{2+} \longrightarrow R_{ox}^{+} + CO_2 + H^{+} + 2Ag^{I}(bipyridine)_2^{1+} \quad (4)$$

R_{ox}^{+} = R(−H), ROH, RO_2CR

The yield of alkane was unimportant (<0.01 mmol). It is noteworthy that oxidative decarboxylation of *n*-butyric acid produced significant amounts of the rearranged isopropyl alcohol and isopropyl *n*-butyrate.

Oxidative Decarboxylation with Silver Oxide.—Carboxylic acids were decarboxylated with silver oxide by vigorous stirring in the neat acid at 90° (Table III). The silver(I) carboxylate products were not soluble under these conditions. On heating the reaction mixtures, the finely divided black suspension of silver oxide was gradually replaced by a flocculent white precipitate. Silver(I) carboxylates were readily iso-

(10) Competitive decarboxylations are not always reliable in heterogeneous systems.

TABLE IV

EFFECT OF ACETONITRILE ON OXIDATIVE DECARBOXYLATIONS WITH SILVER OXIDE[a]

Acid RCO_2H	CH_3CN, vol. %	Reacn time, min	Products, mmol CO_2	RH	R(−H)	RNHAc	Ester	$\Sigma R\cdot/CO_2$
Pivalic	10	15	0.98	0	0.62	0.11	0.12	0.87
Pivalic	25	15	1.01	0	0.54	0.19	0.10	0.82
Pivalic	50	15	0.95	0	0.36	0.31	0.08	0.79
Pivalic	50[b]	720	0.82	0	0.71	0	...	0.86
Isobutyric	25	3[c]	0.41	0	0.04	+[d]	+	0.10
n-Butyric	25	4[c]	0.42	0	0.03	+	+	0.07

[a] In solutions containing 2.0 mmol of AgO in 10 ml of solvent at 85°. [b] N,N-Dimethylacetamide. [c] 110°. [d] Trace, <0.01 mmol.

lated by filtration and the procedure could be conveniently employed to prepare these silver(I) salts.

The oxidation of pivalic acid (with 4% by volume acetic acid to facilitate handling) by silver oxide afforded high yields of carbon dioxide. Greater than 90% of the *t*-butyl moiety could be accounted for as isobutylene and *t*-butyl pivalate. A small amount of acetate ester was derived from the acetic acid.

$$(CH_3)_3CCO_2H + 2AgO \longrightarrow [(CH_3)_2C{=}CH_2 + (CH_3)_3CO_2CC(CH_3)_3] + CO_2 + 2Ag^{I}OH \quad (5)$$

$$Ag^{I}OH + (CH_3)_3CCO_2H \longrightarrow Ag^{I}O_2CC(CH_3)_3 + H_2O \quad (6)$$

Oxidative decarboxylations with silver oxide proceeded significantly faster when acetonitrile was employed as a cosolvent. The silver(I) carboxylates formed soluble complexes in acetonitrile and on complete reduction the reaction mixture consisted of a homogeneous solution. In the presence of acetonitrile an additional product, N-alkylacetamide, was also found in yields proportional to the concentration of

$$(CH_3)_3CCO_2H + 2AgO \xrightarrow{CH_3CN} (CH_3)_3CNHCOCH_3 + CO_2 + Ag^{I}{}_2O(CH_3CN)_n \quad (7)$$

acetonitrile (Table IV). The rate of reduction of silver oxide was also accelerated by trifluoroacetic acid. N,N-Dimethylacetamide had little effect and pyridine a retarding one.

The yields of carbon dioxide from the oxidation of isobutyric, *n*-butyric, and acetic acid by silver oxide were not as good as those from pivalic acid. Acids with available α hydrogens are also susceptible to side-chain oxidation which consumes oxidant but does not lead directly to decarboxylation.[11] These pro-

$$M^{n+} + \text{>CHCO}_2\text{H} \longrightarrow M^{(n-1)+} + \text{>}\dot{\text{C}}\text{CO}_2\text{H etc.} \quad (8)$$

cesses may also play a role in these oxidations. The use of silver oxide was further limited by the rather poor material balance between the carbon dioxide liberated and the alkyl products produced (Table IV, last column). Part of this problem may have been due to scavenging of alkyl radicals by the oxygen produced in the acid-catalyzed decomposition of silver oxide.[12]

$$4AgO + 4H^+ \longrightarrow 4Ag^+ + O_2 + 2H_2O \quad (9)$$

(11) *Cf.* the oxidation of acetic acid with Mn^{III}: R. E. Van der Ploeg and E. C. Kooyman, *J. Catal.*, **10**, 52 (1968); E. I. Heiba, R. E. Dessau, and W. J. Koehl, Jr., *J. Amer. Chem. Soc.*, **91**, 138 (1969); **90**, 5905 (1968); J. B. Bush, Jr., and H. Finkbeiner, *ibid.*, **90**, 5903 (1968).

Discussion

Silver picolinate, bis(bipyridine)silver nitrate, and silver oxide represent silver(II) complexes of three different structural types. Silver picolinate is a well-characterized silver(II) compound in which the silver atom exhibits *trans* square dsp^2 hybridization.[13] Burstall and Morgan[14] characterized the silver complex isolated from the oxidation of bis(α,α-bipyridine)-silver(I) nitrate with peroxodisulfate as the tris(bipyridine)silver(II) nitrate. Analysis of the compound which we isolated using their procedure indicates that it is the bis(bipyridine)silver(II) nitrate. The latter is in accord with the coordination number of 4 generally associated with the silver(II) species.[1] It is, moreover, consistent with the stoichiometry observed in oxidative decarboxylations (*cf.* Table II). In the crystal lattice of silver oxide, the silver atoms occupy two different sites[15] characteristic of silver(I) and silver(III) oxidation states. Silver oxide does produce silver(II) species, however, on dissolution in strong mineral acids, albeit in low yields.[16]

Despite the diversity of structural types, these silver(II) compounds exhibit common oxidizing properties in the decarboxylation of acids. Difficulties with solubility preclude a detailed comparison of their chemical properties and a quantitative kinetic examination at this time. Certain characteristic features of oxidative decarboxylation by these three silver(II) complexes are, however, clearly brought out with pivalic acid.

The essential stoichiometry of the oxidative decarboxylation of pivalic acid by all three silver(II) oxidants is given by eq 10. One mole of carbon dioxide is

$$(CH_3)_3CCO_2H + 2Ag^{II} \longrightarrow [(CH_3)_3C^+] + CO_2 + H^+ + 2Ag^{I} \quad (10)$$

formed from 2 mol of Ag^{II}. The fate of the *t*-butyl cation is dependent on the medium. It gives rise to isobutylene by proton loss and *t*-butyl alcohol or *t*-butyl ester by solvation in the protic solvents. Furthermore, in the presence of acetonitrile, the cation affords N-alkylacetamide.[17]

(12) (a) Oxygen was detected by gas chromatography after completion of the reduction; (b) T. P. Dirkse and B. Wiers, *J. Electrochem. Soc.*, **106**, 284 (1959).

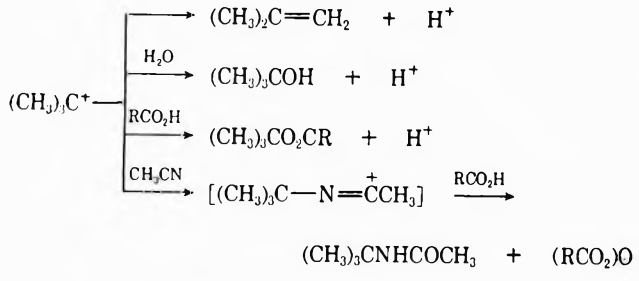
(13) E. G. Cox, W. Wardlow, and K. C. Webster, *J. Chem. Soc.*, 775 (1936).

(14) (a) G. T. Morgan and F. H. Burstall, *ibid.*, 2594 (1930); (b) see also S. Sugden, *ibid.*, 161 (1932).

(15) (a) J. A. McMillan, *J. Inorg. Nucl. Chem.*, **13**, 28 (1960); (b) V. Scatturin, P. L. Bellon, and R. Zannetti, *Ric. Sci.*, **30**, 1034 (1960); *J. Electrochem. Soc.*, **108**, 819 (1961).

(16) D. H. Huchital, N. Sutin, and B. Warnqvist, *Inorg. Chem.*, **6**, 839 (1967).

(17) *Cf.* J. K. Kochi and A. Bemis, *J. Amer. Chem. Soc.*, **90**, 4038 (1968).



We tentatively suggest[18] that oxidative decarboxylation by silver(II) proceeds by two discrete 1-equiv oxidations. First, oxidation of the carboxylate group by silver(II) occurs followed by further oxidation of the alkyl radical by a second silver(II) species (eq 11 and 13).

$$RCO_2H + Ag^{II} \rightleftharpoons H^+ + RCO_2Ag^{II} \longrightarrow RCO_2\cdot + Ag^I \quad (11)$$

$$RCO_2\cdot \longrightarrow R\cdot + CO_2 \quad (12)$$

$$R\cdot + Ag^{II} \longrightarrow [R^+] + Ag^I \quad (13)$$

The metastability of aquosilver(II) species in the presence of carboxylic acids and the formation of alkyl radicals has been described.[8] A similar role is ascribed to silver(II) complexes in these studies, but the rates are no doubt slower. The high efficiency with which silver oxide effects oxidative decarboxylation can be formulated in an analogous manner.

$$(CH_3)_3CCO_2H + AgO \longrightarrow (CH_3)_3CCO_2Ag^{II}OH \quad (14)$$

$$(CH_3)_3CCO_2Ag^{II}OH \longrightarrow (CH_3)_3CCO_2\cdot + Ag^IOH \text{ etc.} \quad (15)$$

The formation of alkanes represents indirect evidence for alkyl radicals as intermediates, although further work is necessary to establish this point. Yields of alkanes from the decarboxylation of pivalic, isobutyric, *n*-butyric, and acetic acid by silver(II) species are significantly lower than those obtained from decarboxylation induced by other metal oxidants such as cobalt(III), lead(IV), manganese(III), cerium(IV), and thallium(III).[9,19] Esters and alkenes predominate as products, and even acetic acid produces high yields of methyl acetate. We interpret this to indicate that silver(II) complexes carry out efficient oxidation[20] of alkyl radicals (eq 13) in a manner similar to the structurally related copper(II) species.[21]

Carbonium ions appear to be intermediates in the decarboxylation of pivalic acid by silver(II) species. Similarly, the products from the oxidation of isopropyl and *n*-propyl radicals are consistent with the formation of an isopropyl cation. However, the oxidation of *n*-butyric acid by silver(II) picolinate afforded *n*-propyl *n*-butyrate when carried out in the neat acid as solvent. The formation of this unrearranged ester in such relatively high yields is rather unique.[9] It may arise directly from solvolysis of an alkylsilver intermediate under these rather poorly ionizing conditions.[22]

$$R\cdot + Ag^{II} \longrightarrow [R\text{-}Ag]^{2+} \xrightarrow{RCO_2H} RO_2CR + Ag^I + H^+ \quad (16)$$

Experimental Section

Materials.—The carboxylic acids were redistilled before use. Pivalic acid was generously donated by the Enjay Chemical Co. Pyridine was distilled from barium oxide. Esters was obtained from commercial sources or prepared by esterification and redistilled before use.

Silver(II) picolinate was prepared by oxidation of silver(I) picolinate by peroxodisulfate in the presence of excess picolinic acid.[13,23] The total silver content was determined by reduction followed by Volhard determination of silver(I).

Anal. Calcd for $C_{12}H_{10}O_4N_2Ag$: Ag, 30.6. Found: Ag, 30.1.

Silver oxide was prepared by oxidation of silver nitrate with peroxodisulfate in an alkaline medium.[24] The silver(II) content was determined by reduction with an excess of a standard ferrous solution and back titration with standard ceric ammonium sulfate. The total silver content was also determined gravimetrically by electrodeposition.

Anal. Calcd for AgO: Ag, 87.1. Found: Ag, 87.1 (titration), 87.5 (electrodeposition).

Bis(α,α'-bipyridine)silver(II) nitrate was prepared in poor yields from the oxidation of bis(α,α'-bipyridine)silver(I) nitrate with ammonium peroxodisulfate.[14,25] The melting point (176°) and solubility characteristics paralleled those described by Morgan and Burstall. Elemental analysis, however, indicated that it was the bisbipyridine complex.

Anal. Calcd for $Ag(C_{10}H_8N_2)_2(NO_3)_2$: C, 44.11; H, 2.95; N, 15.44. Calcd for $Ag(C_{10}H_8N_2)_3(NO_3)_2$: C, 51.5; H, 3.4; N, 16.0. Found: C, 42.5; H, 2.86; N, 15.3. Further analysis of this complex is in progress.

Procedure.—The silver(II) compound was weighed into a long-neck, round-bottom flask and sealed with a gas-tight rubber septum. The flask was evacuated *in vacuo*. A degassed solution of the carboxylic acid was added with a hypodermic syringe and the mixture was stirred magnetically. Decarboxylations were carried out thermally in a thermostated bath.

The carbon dioxide was sampled directly from the reaction flask and analyzed by gas chromatography (Varian Aerograph, Porapak Q) using ethane as an internal standard. The gaseous hydrocarbons were analyzed in a similar manner to isomeric analogs as internal standards (15 ft, 30% Dowtherm on firebrick). Calibration curves were prepared by adding known amounts of gases to a system which simulated reaction conditions as closely as possible.

The reaction mixture was diluted with ether, washed with water, and extracted with sodium carbonate solution. The esters were analyzed by gas chromatography using isomeric esters as internal standards. Calibration curves were always constructed by subjecting known mixtures to the same work-up procedure. Reactions carried out in aqueous solution were analyzed directly without work-up. The following columns were used in the analyses: 8-ft diethylene glycol succinate at 85°, 6-ft Morflex at 85°, and 10-ft FFAP at 80° (Varian Aerograph Co.). Oxygen was analyzed on a 6-ft molecular-sieve 5A column at room temperature.

Registry No.—Silver(II) picolinate, 22721-95-5; bis(α,α'-bipyridine)silver(II) nitrate, 23467-69-8; silver oxide, 1301-96-8.

Acknowledgment.—We wish to thank the National Science Foundation for generous financial support of this work.

(18) Largely by analogy with other oxidants.[9]

(19) J. K. Kochi and T. W. Bethea, *J. Org. Chem.*, **33**, 75 (1968).

(20) Alternatively, the high yields of esters and alkenes can mean that a direct 2-equiv oxidation pertains. Such an oxidation can occur *via* a binuclear Ag^{II} species or a Ag^{III} species: $RCO_2H - 2e \longrightarrow R^+ + CO_2 + H^+$. (b) *Cf.* D. Sen, *J. Chem. Soc., A*, 1304 (1969).

(21) (a) J. K. Kochi and R. V. Subramanian, *J. Amer. Chem. Soc.*, **87**, 4855 (1965); (b) J. K. Kochi, C. L. Jenkins, and A. Bemis, *ibid.*, **90**, 4616 (1968); (c) *cf.* G. W. A. Fowles, R. W. Mathews, and R. A. Walton, *J. Chem. Soc., A*, 1108 (1968).

(22) Analogous alkylcopper species have been postulated in related oxidations with copper(II).[21b]

(23) R. G. R. Bacon and W. J. W. Hanna, *J. Chem. Soc.*, 4962 (1965).

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Electrophilic Properties of Benzoyloxy Radicals

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Received July 31, 1969

Free-radical aromatic substitution by oxy radicals of the type p-$XC_6H_4CO_2\cdot$, where X = NO_2, H, or CH_3, was carried out with a series of aromatics. The oxy radicals were generated by the copper-catalyzed decomposition of the corresponding peroxide, $(p\text{-}XC_6H_4CO_2)_2$, at 60°. Yields of aryl benzoates, p-$XC_6H_4CO_2Ar$, ranged from *ca.* 20% with chlorobenzene to *ca.* 80% with anisole. Isomer distributions and relative rates of reaction were determined. From this data, partial rate factors for substitution by these radicals on anisole, toluene, and chlorobenzene were calculated. A plot of these factors *vs.* σ^+ substituent constants gave ρ values of −2.52, −1.61, and −1.28 for aromatic substitution by p-$O_2NC_6H_4CO_2\cdot$, $C_6H_5CO_2\cdot$, and p-$CH_3C_6H_4CO_2\cdot$, respectively. The effect of the *para* substituents on the degree of electrophilic character of the benzoyloxy radicals is in keeping with their normal electronic influences. A comparison of this system is made to the effect of substituents on the polarity of phenyl radicals.

Aromatic substitution reactions have often proven useful in qualitative and quantitative studies of the polar characteristics of free radicals.[2,3] By their reactivities in ring substitution, carbon radicals have been shown to be electrophilic, nucleophilic, or neutral, depending on the nature of the groups attached to the odd electron-bearing carbon. For example, methyl[2a,4] and cyclohexyl[5] radicals are nucleophilic, whereas trichloromethyl,[6] triphenylmethyl,[3a] and appropriately substituted phenyl radicals[2b,7] display electrophilic tendencies to varying extents.

This same technique, as well as other evidence,[8] has been used to demonstrate that oxy radicals are generally electrophilic;[9,10] yet little systematic work on the effect of varying the group attached to the oxy-radical site has been done.

Recently, a smooth method of intermolecular free-radical oxygenation of the type shown in eq 1 was

$$(RCO_2)_2 + ArH \xrightarrow{CuX_2} RCO_2Ar + RCO_2H \qquad (1)$$
$$R = i\text{-}C_3H_7O \text{ or } C_6H_5$$

discovered.[11] The salient step of the reaction involved addition to the ring by the oxy radical[12] followed by rapid conversion into product by a metal salt oxidant

$$RCO_2\cdot + ArH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} RCO_2ArH\cdot \xrightarrow[k_2]{CuCl_2} RCO_2Ar + HCl + CuCl \qquad (2)$$

(eq 2). With cupric chloride, k_2 was shown to be much faster than k_{-1}, as evidenced by the complete lack of an isotope effect in the substitution process.[11c] Thus the aromatic ester product obtained gives a fairly reliable index of the reactivity pattern of the radical toward the aromatic compound, making this system appealing for further studies of oxy-radical behavior.

The purpose of this work was to quantitatively study the effects of substituents, X, on the electrophilic nature of benzoyloxy radicals, p-$XC_6H_4CO_2\cdot$, as gauged by their substitution reactions with a series of aromatic hydrocarbons.

Results

A series of substituted benzoyl peroxides, $(p\text{-}XC_6H_4CO_2)_2$, where X = NO_2, H, and CH_3, were synthesized and their cupric chloride catalyzed decomposition was carried out with toluene, chlorobenzene, and anisole in acetonitrile solution. p,p'-Dimethylbenzoyl peroxide was also allowed to react with acetophenone. The yields of the corresponding aryl benzoates as well as their isomer distributions are shown in Table I.

Other reaction products were analogous to those reported in an earlier study[11b] and are accounted for by decarboxylation of the benzoyloxy radical (eq 3) followed by the usual reactions of the resulting phenyl radical (eq 4–6).

$$p\text{-}XC_6H_4CO_2\cdot \longrightarrow p\text{-}XC_6H_4\cdot + CO_2 \qquad (3)$$

$$p\text{-}XC_6H_4\cdot \xrightarrow{ArH} p\text{-}XC_6H_4Ar \qquad (4)$$
$$p\text{-}XC_6H_4\cdot \xrightarrow{CuCl_2} p\text{-}XC_6H_4Cl \qquad (5)$$
$$p\text{-}XC_6H_4\cdot \xrightarrow{RH} C_6H_5X + R\cdot \qquad (6)$$

The decarboxylation reaction competed more strongly with oxygenation in the studies with the less reactive

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(11) (a) M. E. Kurz and P. Kovacic, *J. Amer. Chem. Soc.*, **89**, 4960 (1967); (b) M. E. Kurz and P. Kovacic, *J. Org. Chem.*, **33**, 1950 (1968); (c) M. E. Kurz, P. Kovacic, A. K. Bose, and I. Kugajevsky, *J. Amer. Chem. Soc.*, **90**, 1818 (1968).

(12) Complete scrambling of the labeled oxygen in the aryl benzoate obtained from the system p-xylene–copper chloride–benzoyl peroxide–carbonyl-^{18}O [C. G. Reid and P. Kovacic, *J. Org. Chem.*, **34**, 3308 (1969)] as well as orientation similarities for the ester from runs with and without added copper salt[11c] indicated that the free oxy radical and not a radical–metal complex was the most likely attacking entity.

TABLE I

OXYGENATION IN THE SYSTEM BENZOYL PEROXIDE–COPPER CHLORIDE–AROMATIC COMPOUND

$(p\text{-}XC_6H_4CO_2)_2$, X	Aromatic compd	Yield, %[b]	Aryl benzoates, isomer distribution: *ortho*	*meta*	*para*
NO_2	Toluene	47	58	18	24
NO_2	Anisole	89	66	<1	34
NO_2	Chlorobenzene	17	52	15	33
H	Toluene	41	56	19	25
H	Anisole	76	67	<1	33
H	Chlorobenzene	23	52	16	32
CH_3	Toluene	38	52	22	26
CH_3	Anisole	76	67	<1	33
CH_3	Chlorobenzene	25	47	21	32
CH_3	Acetophenone[c]	*d*	36	50	14

[a] Aromatic compound/benzoyl peroxide/$CuCl_2$ ratio = 30:1:0.3, trace of CuCl added, acetonitrile solvent, 60°. [b] Based on moles of product per mole of peroxide consumed. [c] Determined after hydrolysis to the phenols. [d] Not determined.

TABLE II

Relative Rates of Oxygenation with $p\text{-}XC_6H_4CO_2\cdot$

$(p\text{-}XC_6H_4CO_2)_2$, X	Aromatic compd	$k_{ArH}/k_{C_6H_6}$[a]: [ArH]/[C_6H_6] = 1.0	[ArH]/[C_6H_6] = 0.2	Avg
NO_2	Toluene	4.25	4.19	4.22
NO_2	Anisole	8.30	8.68	8.49
NO_2	Chlorobenzene	0.28	0.30	0.29
H	Toluene	2.54	2.40	2.47
H	Anisole	10.22	10.33	10.28
H	Chlorobenzene	0.49[b]	0.52	0.51
CH_3	Toluene	2.00	2.16	2.08
CH_3	Anisole	13.56	12.97	13.27
CH_3	Chlorobenzene	0.64[b]	0.58	0.61
CH_3	Acetophenone	0.27[b,c]	0.32[c]	0.30

[a] All values are the average of two runs corrected for concentration. The error involved ranged from ±0.03 to 0.08. [b] [ArH]/[C_6H_6] = 0.1. [c] Determined after hydrolysis to the phenols.

aromatics. Another process, hydrogen abstraction by the benzoyloxy radical, took place to a minor extent.[11b] In all cases these side reactions did not adversely affect the ring substitution process data.

To determine the relative rates of oxy-radical substitution, mixtures of aromatics were allowed to compete for a limited amount of peroxide. Table II summarizes these results with the same series of hydrocarbons compared with benzene.

Partial rate factors were determined for the effect of substituents upon ring substitution by the three oxy radicals (Table III).

TABLE III

PARTIAL RATE FACTORS (F) FOR $p\text{-}XC_6H_4CO_2\cdot$ ATTACK

Aromatic substituent	F for $p\text{-}XC_6H_4CO_2\cdot$: X = NO_2	X = H	X = CH_3
m-CH_3	2.28	1.41	1.37
p-CH_3	6.08	3.70	3.24
p-OCH_3	17.35	20.03	25.4
m-Cl	0.13	0.25	0.38
p-Cl	0.57	0.98	1.17
m-$COCH_3$	...	...	0.44
p-$COCH_3$	...	...	0.25

The logarithms of the partial rate factors were plotted against σ^+ values (both established[13] and recently revised[14] values were used). A computerized least-squares treatment was used to determine the ρ values (Table IV).

TABLE IV

CALCULATED ρ VALUES FOR RING SUBSTITUTION

Radical	Brown's[a] σ^+: ρ	Avg deviation in log F[c]	Swain's[b] σ^+: ρ	Avg deviation in log F[c]
$p\text{-}CH_3C_6H_4CO_2\cdot$	−1.28[d,e]	0.047	−1.32[d,f]	0.038
$C_6H_5CO\cdot$	−1.61	0.044	−1.88	0.025
$p\text{-}O_2NC_6H_4CO_2\cdot$	−2.52[d]	0.058	−2.71[d]	0.104

[a] Reference 13. [b] Reference 14. [c] Deviation from calculated slope. [d] Corrected values, disregarding log $F_{p\text{-}OCH_3}$. [e] Used $F_{m\text{-}COCH_3}$. [f] Used $F_{m\text{-}COCH_3}$ and $F_{p\text{-}COCH_3}$.

A poor fit to the best straight line was noted for the log $F_{p\text{-}OCH_3}$ value for both the *p*-nitro- and *p*-methylbenzoyloxy radicals; so this value was not used in these slope computations. We are unable to determine the reason for this anomalous behavior at this time. Both sets of σ^+ constants gave calculated slopes from which the average point deviation was quite small. Slightly higher negative ρ values were obtained using Swain's values.[14]

We obtained a much better correlation using σ^+ rather than σ substituent values, indicating that resonance stabilization of oxy radical–aromatic adduct plays an important role.

On the basis of the $\rho\sigma$ treatment, it can be seen that the electrophilicity of the oxy radicals lies in the order $p\text{-}O_2NC_6H_4CO_2\cdot > C_6H_5CO_2\cdot > p\text{-}CH_3C_6H_4CO_2\cdot$. These results are consistent with the normal polar effects attributed to the nitro and methyl groups.[13a]

(13) (a) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 87, 90; (b) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

(14) C. G. Swain and E. C. Lupton, Jr., *ibid.*, **90**, 4328 (1968).

As expected from structural considerations, all three radicals are appreciably more electron deficient than the hydroxyl radical ($\rho = -0.41$[10]).[15] Only the *p*-nitrobenzoyloxy radical is more polar than the isopropyl carbonate radical ($\rho = -2.30$[16]), however.

A comparison with the more thoroughly studied *t*-butoxy radical indicates that aroyloxy radicals are more effective in adding to unsaturated systems,[17] whereas *t*-butoxy radicals are more inclined toward hydrogen abstraction from donor molecules.[6] While there are basic differences in structure and in the cleavage reaction that each undergoes, it would appear the greater electrophilicity in the radical favors addition reactions compared with hydrogen abstraction. In light of the attraction of electrophiles to electron-rich π clouds, this is not unexpected. Thus differences in the polarity of radicals brought about by changes in structure can be very important in determining the mode of chain-transfer reactions of oxy radicals.

It is interesting to compare the effect of substituents in this system with their effect on the phenyl radical. The ρ values for aromatic substitution by the *p*-methylphenyl, phenyl, and *p*-nitrophenyl radicals, respectively, were 0.03, 0.05, and −0.81.[7] Comparable values were also found for abstraction from hydrogen donors by these same radicals.[17,18] Thus the corresponding oxy radicals are considerably more sensitive to substituent effects in the aromatic compound than are the phenyl radicals. This is in line with a recent report concerning polar effects in the addition to monomers by phenyl and benzoyloxy radicals.[19] The *p*-methyl substituent has more of an influence on the oxy radical than it does on the phenyl radical, while the *p*-nitro group has a fairly marked effect on both.

Experimental Section

Benzoyl peroxide (Lucidol) was recrystallized from chloroform–methanol before use. The substituted peroxides were prepared from sodium peroxide and the appropriate acid chloride[20] and analyzed for purity by standard procedures.[21] *p,p'*-Dinitrobenzoyl peroxide, mp 156° (lit.[20] mp 156°), was 99.6% pure, while *p,p'*-dimethylbenzoyl peroxide, mp 139–140° (lit.[22] mp 136°), was 98.6% pure.

The aromatic hydrocarbons were checked for purity by vpc and used directly.

General Reaction.—The procedure used was essentially the same as described earlier,[11a] except that the amount of solvent had to be expanded to allow for the lower solubility of the substituted peroxides. A larger scale reaction was carried out with each peroxide in the presence of each aromatic compound to allow for product isolation and identification upon work-up. Reactions were carried out with or without stirring (no difference) in a constant-temperature bath at 60 ± 0.5°. Aliquots were periodically removed for titration to determine peroxide content, against a salt-solution blank. The reaction was considered complete when all the peroxide was consumed. Total reaction time ranged from 18 hr for *p,p'*-dimethylbenzoyl peroxide to 23 hr for *p,p'*-dinitrobenzoyl peroxide. For reactions involving the latter peroxide a small amount of an insoluble cupric salt precipitated from solution; the other reactions were homogeneous throughout. Reaction work-up was carried out as before.

Products were separated and analyzed by vpc using Varian Aerograph Models 90-P and Hy-Fi with 20% SE-30 on 60–80 firebrick columns. The products were compared with authentic aryl benzoates (which were synthesized from the appropriate phenol and acid chloride in the presence of pyridine or sodium hydroxide) by ir spectra and vpc retention time. In a few cases where authentics were not available, the vpc traces were so similar to analogous reactions that identity of the particular products was assumed.

Smaller scale reactions were carried out for 24 hr for the determination of yields, isomer distributions, and relative rates. A known amount of the appropriate authentic phenyl benzoate was added as an internal marker just before reaction work-up to determine yields. Quantitative determinations of isomer distributions, relative rates, and product yields were carried out after calibration for peak areas with three mixtures containing varying amounts of authentic ester products. Competition runs were done in duplicate as well as at two different ratios of benzene to substituted benzene substrate using a large excess of both.

The aryl esters from acetophenone could not be analyzed directly by vpc, but were hydrolyzed to the hydroxyacetophenones. Quantitative analysis of the phenols was done on a Beckman GC-2A using an SE-30 on firebrick column. Control runs done on mixture of the authentic esters indicated that the hydrolysis method was quantitative.

Registry No.—*p*-$O_2NC_6H_4CO_2\cdot$, 14337-48-5; $C_6H_5CO_2\cdot$, 1854-28-0; *p*-$CH_3C_6H_4CO_2\cdot$, 23074-26-2.

Acknowledgment.—We are grateful to the National Science Foundation Summer Research Program for partial support of this work, and to Professor Cheves Walling for his advice and the use of his facilities. We wish to thank Dr. Max Taylor for his assistance with the computerized least-squares treatment.

(15) The low selectivity of the hydroxyl radical may be due more to the very high rate and low activation energy of the reaction (which is almost diffusion controlled) than to a lower electron deficiency (our thanks to Professor Cheves Walling for this suggestion).

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Abstraction of Methyl Hydrogen of Substituted Anisoles by *t*-Butoxy Radicals[1a]

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Received June 2, 1969

Relative reactivities of the methyl hydrogens of eight ring-substituted anisoles toward *t*-butoxy radicals were determined in 1,1,2-trichlorotrifluoroethane at 45.0°. Di-*t*-butyl peroxyoxalate was used as a source of *t*-butoxy radicals. One methyl hydrogen of anisole was slightly less reactive than that of toluene. The logarithms of the relative reactivities of anisoles show a good $\rho\sigma$ correlation, the ρ value being -0.41. This figure indicates that the transmitting efficiency of polar effects of anisoles toward hydrogen abstraction is rather unexpectedly high compared with that of toluene. An attempt to correlate the reactivities of anisoles and toluenes in various reactions was made in terms of transmission of polar effects.

In a previous paper,[2] we have indicated that abstraction of benzylic hydrogen atoms of substituted toluenes by *t*-butoxy radicals gives rise to rate data better correlated with σ^+ parameters than with σ. It follows, therefore, that rates of abstraction of benzylic[3] and phenolic[4] hydrogens by electron-seeking radicals are generally correlated with σ^+ parameters. It is very interesting to compare these results with the facts that ionization potentials of substituted benzyl[5] and phenoxy[6] radicals as well as solvolytic rates in benzylic systems follow the $\rho\sigma^+$ relationship.

We now report relative reactivities of methyl hydrogens of substituted anisoles toward *t*-butoxy radicals in the same reaction conditions for substituted toluenes.[2] These data are discussed in terms of transmission of polar effects and comparison of other pertinent data.

Results and Discussion

The relative reactivities of the *t*-butoxy radical toward hydrogen donors can be measured by the following competition.

$$(CH_3)_3CO\cdot + RH \xrightarrow{k_a} (CH_3)_3COH + R\cdot$$

$$(CH_3)_3CO\cdot \xrightarrow{k_d} (CH_3)_2CO + CH_3\cdot$$

Thus the ratio of the rate constant, k_a/k_d, can be calculated from the *t*-butyl alcohol/acetone ratio by the equation[7]

$$[(CH_3)_3COH]/[CH_3COCH_3] = (k_a/k_d)[RH]$$

By comparing the ratios of k_a/k_d for substituted anisoles, the relative reactivities of these compounds may be obtained.

As pointed out by Walling and Wagner[8] and by us in the previous paper,[2] the effects of solvents (or reactants in the case of neat states) on these competitions could be quite significant. However, in a common solvent at high dilution, k_d must be kept constant no matter how large the solvent effect may be. Thus, if the rate expression is valid, the experimental points of the plot of the resulting *t*-butyl alcohol/acetone ratios against the initial concentration of each substrate should lie on a straight line with a slope equal to k_a/k_d. Experiments indicate that this is true. The *t*-butyl alcohol/acetone ratios do not depend on the substrate/peroxide ratio but on the concentration of the substrate.

The relative reactivities of substrates toward *t*-butoxy radicals may be determined by competitive chlorination with *t*-butyl hypochlorite.

$$(CH_3)_3COCl \longrightarrow (CH_3)_3CO\cdot + Cl\cdot$$

$$(CH_3)_3CO\cdot + R^1H \longrightarrow (CH_3)_3COH + R^1\cdot$$

$$(CH_3)_3CO\cdot + R^2H \longrightarrow (CH_3)_3COH + R^2\cdot$$

$$R^1\cdot + (CH_3)_3COCl \longrightarrow (CH_3)_3CO\cdot + R^1Cl$$

$$R^2\cdot + (CH_3)_3COCl \longrightarrow (CH_3)_3CO\cdot + R^2Cl$$

Relative rates of abstraction for R^1H and R^2H may be measured directly from the R^1Cl/R^2Cl ratio. This method has been accepted widely. However, as pointed out earlier,[2] chlorination by *t*-butyl hypochlorite can involve chlorine atoms instead of *t*-butoxy radicals as the chain carrier. This view has been once rejected,[9] but quite recently, Walling and McGuinness[10] have recognized properly that *t*-butyl hypochlorite chlorinations actually involve chlorine-atom chains in certain substrates, especially in compounds having benzylic hydrogens. Therefore, the present method seems at this time to be most reliable to estimate reactivities toward the *t*-butoxy radicals.

The relative reactivities of substituted anisoles for hydrogen abstraction are determined in 1,1,2-trichlorotrifluoroethane (Freon-113) at 45.0° using di-*t*-butyl peroxyoxalate[11] as the source of *t*-butoxy radicals. Di-*t*-butyl peroxyoxalate was decomposed in excess of substituted anisole of varying concentrations, and *t*-butyl alcohol/acetone ratios were determined by gas chromatography. The plots of *t*-butyl alcohol/acetone *vs.* concentration of the substrates gave excellent straight lines, as shown in Figure 1. The ratios of k_a/k_d were calculated by the method of least squares, the results being listed in Table I. Figure 2 represents the relationship between log (k_a/k_d) and Hammett's σ values.[12]

(1) (a) Presented in part at the 8th Symposium on Free-Radical Reactions, Nagoya Japan, Oct 1967, Preprints, p 14. (b) To whom correspondence should be addressed: Department of Chemistry, Faculty of Science, Tohoku University, Katahira-cho, Sendai, Japan.

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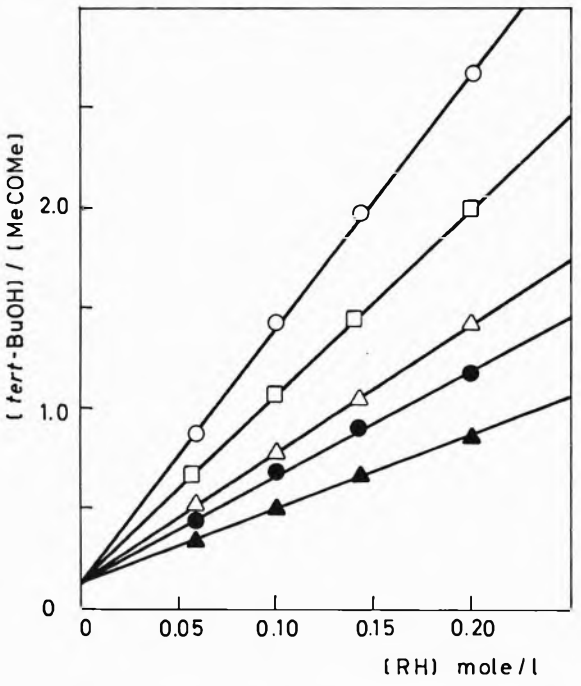

Figure 1.—Typical examples of *t*-butyl alcohol/acetone ratios in hydrogen abstraction from anisoles in Freon-113 at 45.0°: —○—○—, *m*-methoxy; —□—□—, *p*-phenoxy; —△—△—, unsubstituted; —●—●—, *m*-chloro; —▲—▲—, *p*-cyano.

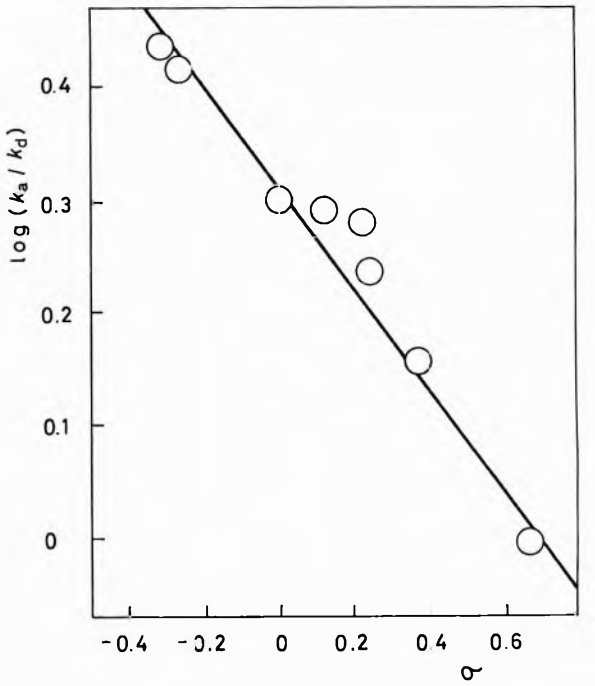

Figure 2.—Correlation of log (k_a/k_d) + 1 and σ for abstraction of methyl hydrogen of substituted anisoles by the *t*-butoxy radical in Freon-113 at 45.0°.

TABLE I

RELATIVE REACTIVITIES OF ONE METHYL HYDROGEN (k_a/k_d) OF SUBSTITUTED ANISOLES TOWARD *t*-BUTOXY RADICALS IN FREON-113 AT 45.0°

Substituent	k_a/k_d[a]
p-C_6H_5O	2.65 ± 0.02[b]
p-CH_3O	2.59 ± 0.01
H	1.99 ± 0.05
m-CH_3O	1.98 ± 0.01
p-Cl	1.94 ± 0.07
m-C_6H_5O	1.74 ± 0.04
m-Cl	1.44 ± 0.04
p-CN	0.99 ± 0.01

[a] The k_a/k_d value for one aromatic ring hydrogen was estimated as 0.14–0.16 in Freon-113 using $C_6H_5OC_6H_5$ or C_6H_5Cl as model substrates. Results in this table are corrected for the reactivities of ring hydrogens. [b] Deviation listed for two or three runs.

As anticipated, the relative reactivities are correlated with σ. These results clearly demonstrate that electron availability plays an important role in determining the relative rates in reactions of this type.[3]

Recently, Mulcahy, Tucker, Williams, and Wilmshurst[13] have observed that a phenoxymethyl radical produced in the gas phase gave benzaldehyde, presumably by a mechanism involving simultaneous phenyl migration and hydrogen-atom ejection.

$$PhOCH_2\cdot \longrightarrow O{=}CHPh + H\cdot$$

However, the main fate of phenoxymethyl radicals in solution was revealed to be dimerization to give 1,2-diphenoxyethane.

$$2PhOCH_2\cdot \longrightarrow PhOCH_2CH_2OPh$$

The latter compound has been characterized by comparison of its physical properties with those of an authentic sample. This observation is in accord with the fact that chlorination of anisole by *t*-butyl hypochlorite gave chloromethyl phenyl ether.[14]

The k_a/k_d value of anisole, 1.99, indicates that one methyl hydrogen of unsubstituted anisole is slightly less reactive than that of unsubstituted toluene (k_a/k_d = 2.19 in Freon-113).[2] However, the transmitting efficiency of polar effects of anisole toward hydrogen abstraction appears unexpectedly high. Thus the ρ value of anisoles (−0.41) is rather large in absolute magnitude compared with those of toluenes (−0.35 with σ^+ or −0.40 with σ)[2] in spite of the circumstance that the substituent-carrying benzene ring of the former is separated by one more atom, oxygen, from the reaction center. It is well established that the interposition of a methylene group decreases the ρ value by a factor of *ca.* 2.3. Such "superconducting effect" of oxygen was observed also in nmr data.[15]

Now it appears of interest to compare ρ values of appropriate reactions in which stabilization of the benzylic carbonium ions plays a crucial role with that of the corresponding reaction of the phenoxymethyl systems under the same reaction conditions. Table II lists some data, including the present study, and contains also the Hammett correlations observed on nmr chemical shifts for anisoles[16] and toluenes.[15]

For *t*-butyl phenoxyperacetates, only half-lives of unimolecular decomposition were reported;[17] however, the data fit satisfactorily with the $\rho\sigma$ relationship and the ρ value is calculated by the method of least squares. Although the mechanism of the decomposition of *t*-butyl phenoxyperacetates have not been fully elucidated, the fact that α-alkoxyperalkanoic esters decomposed by

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TABLE II

COMPARISON OF ρ VALUES FOR ANISOLES AND TOLUENES IN SOME REACTIONS

No.	Reactant	Reaction	ρ (σ or σ^+)	$\rho_{anisole}/\rho_{toluene}$	Ref
1	4-X-$C_6H_4OCH_3$	*a*	16.2 (cps/σ)		*b*
				1.27	
	4-X-$C_6H_4CH_3$	*a*	12.8 (cps/σ)		*c*
2	X-$C_6H_4OCH_3$	*d*	0.41 (σ)		*e, f*
				1.17	
	X-$C_6H_4CH_3$	*d*	0.35 (σ^-)		*g*
3	X-$C_6H_4OCH_2CO_3C(CH_3)_3$	*h*	1.18 (σ)		*i*
				1.08	
	X-$C_6H_4CH_2CO_3C(CH_3)_3$	*j*	1.09 (σ^+)		*k*
4	X-$C_6H_4OCH{=}CH_2$	*l*	1.7 (σ)		*m*
				0.84	
	X-$C_6H_4CH{=}CH_2$	*l*	2.03 (σ^+)		*n*
5	X-$C_6H_4OCH{=}CH_2$	*o*	2.2 (σ)		*p*
				0.65	
	X-$C_6H_4CH{=}CH_2$	*q*	3.42 (σ^+)		*r*

[a] Chemical shifts of methyl protons in CCl_4 at 60 MHz. [b] C. Heathcock, *Can. J. Chem.*, **40**, 1865 (1962). [c] Reference 15. [d] Hydrogen abstraction by *t*-butoxy radicals at 45.0° in Freon-113. [e] This study. [f] K. Uneyama, H. Namba, and S. Oae have reported $\rho = -0.38$ in the reaction of six anisoles with di-*t*-butyl peroxide at 130° in chlorobenzene: Preprints, 8th Symposium on Free-Radical Reactions, Nagoya, Japan, Oct 1967, p 15. [g] Reference 2. [h] Spontaneous decomposition at 70.5° in ethylbenzene. [i] C. Rüchardt, H. Bock, and I. Rüchardt, *Angew. Chem.*, **78**, 267 (1966). [j] Spontaneous decomposition at 90.7° in chlorobenzene. [k] P. D. Bartlett and C. Rüchardt, *J. Amer. Chem. Soc.*, **82**, 1756 (1960). [l] Cationic copolymerization. [m] T. Okuyama, I. Matsumura, T. Fueno, and J. Furukawa, Preprints, 19th Annual Meeting of the Chemical Society of Japan, Tokyo, April 1966, IV, p 107. [n] C. G. Overberger, L. H. Arond, D. Tanner, J. J. Taylor, and T. Alfrey, Jr., *J. Amer. Chem. Soc.*, **74**, 4848 (1952); J. P. Kennedy in "Copolymerization," G. E. Ham, Ed., Interscience Publishers, New York, N. Y., 1964, p 308. [o] Hydrolysis at 35.0° in 0.2 *N* HCl–dioxane (80)–water (20). [p] T. Fueno, I. Matsumura, T. Okuyama, and J. Furukawa, Preprints, 17th Symposium on Organic Reaction Mechamisms, Tokyo, Oct 1966, p 121. [q] Hydration at 25.0° in 3.83 *M* $HClO_4$. [r] W. M. Schubert, B. Lam, and J. Reefe, *J. Amer. Chem. Soc.*, **86**, 4727 (1964).

a concerted mechanism[18] indicates that phenoxyperacetates also decompose in a concerted fashion like phenylperacetates.[19]

$$PhCH_2CO_3(CH_3)_3 \longrightarrow [PhCH_2\cdots\cdots CO_2\cdots OC(CH_3)_3] \longrightarrow \text{products}$$

$$PhOCH_2CO_3C(CH_3)_3 \longrightarrow [PhOCH_2\cdots\cdots CO_2\cdots OC(CH_3)_3] \longrightarrow \text{products}$$

These results demonstrate a marked similarity in the polar substituent effects between homolytic processes, such as hydrogen abstraction and unimolecular bond breaking, and a cationic process, such as hydration of olefins. The gradual change of ρ values seen in Table II originates naturally in the difference of capability to transmit the polar effects.

The difference in the capability to transmit the polar effects between benzyl systems (I) and phenoxymethyl systems (II) results in such a gradual change of relative

I II

ρ values according to increasing ionic characters of the transition state. Thus, the greater the electron demand at the transition state, the smaller should be the $\rho_{anisole}/\rho_{toluene}$ ($\equiv \rho_{II}/\rho_I$), since the interposition of an oxygen atom leads to suppression of direct conjugation between the benzene ring and the electron-deficient reaction center. The data in Table II now serve to draw a comparison of efficiency to transmit the polar effects between I and II.

A plot of (ρ_{II}/ρ_I) *vs.* $|\rho_I|$ is shown in Figure 3. Very remarkably, a good linear relationship was obtained. It is interesting to note that the nmr data

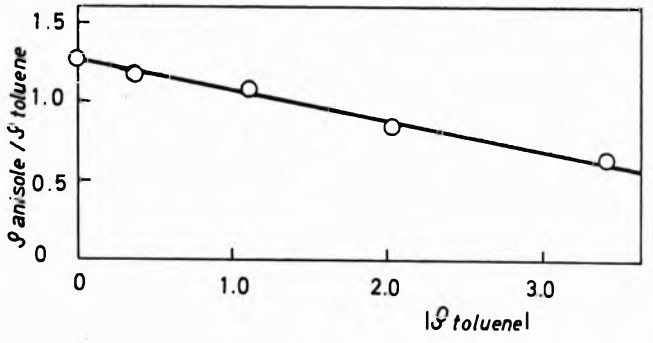

Figure 3.—Correlation of $\rho_{anisole}/\rho_{toluene}$ with $\rho_{toluene}$ of some homolytic and cationic reactions.

coincide very closely to the value corresponding to $\rho_I = 0$, indicative of the nmr data to be concerned with the characters of the ground states.

Several conclusions may be obtained from the relation; *e.g.*, (a) hydrogen abstaction by *t*-butoxy radicals leads to less polar transition states, (b) the ionic characters of the transition states of decomposition of peresters develop more than those of hydrogen abstractions, and (c) the carbonium-ion character of cationic polymerizations is less than that of hydration of olefins.

The results now demonstrate a marked parallelism in reactivities of homolytic with cationic processes on the polar substituent effects. For structural changes of the substrates in these reactions, for which the Hammett equation is applicable, differences in the bond dissociation energies of R–X bonds in question are less important[20] than those of ionization potentials of R· radicals. It should be emphasized that the $\rho\sigma^+$ rela-

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tionship observed in hydrogen abstraction reactions is concerned with the polar effects of substituents in stabilization of the benzylic carbonium ions and not with the resonance stabilization of the benzylic radicals.[21] No extra-delocalization effect of substituents is therefore required to express the reactivities of hydrogen abstraction in benzylic systems.

Experimental Section

Materials.—Di-*t*-butyl peroxyoxalate was prepared by the method of Bartlett, *et al.*[11] Freon-113 was commercially available and was used after distillation. Anisole and three derivatives, *p*-methoxy-, *p*-chloro-, and *p*-cyanoanisole, were commercial samples and were used after purification by usual way.

***p*-Phenoxyanisole.**—This compound was prepared from the potassium salt of *p*-methoxyphenol and bromobenzene by refluxing in the presence of copper powder: bp 136° (6 mm) [lit.[22] bp 186° (32 mm)]; n^{20}D 1.5781; d^{20} 1.1201.

***m*-Phenoxyanisole and *m*-Dimethoxybenzene.**—To the ethanol solution of resorcinol (220 g, 2.0 mol) and dimethyl sulfate (260 g, 2.06 mol) was added aqueous potassium hydroxide (112 g, 2.0 mol) with cooling by ice bath. By distillation, *m*-methoxyphenol (126 g, 1.02 mol, 51.0% yield) was obtained: bp 138° (27 mm) (lit.[23] bp 240–242°); n^{20}D 1.5492; d^{20}_4 1.1490. In addition, *m*-dimethoxybenzene (38 g, 0.275 mol, 13.8% yield) was obtained: bp 107° (27 mm) [lit.[24] bp 213–213.6° (753 mm)]; n^{20}D 1.5252; d_4^{20} 1.0721. *m*-Phenoxyanisole (23 g, 0.115 mol) was then prepared from *m*-methoxyphenol (50 g, 0.403 mol), bromobenzene (62 g, 0.395 mol), and potassium hydroxide (22 g, 0.393 mol) in the presence of a catalytic amount of copper powder in 28.5% yield: bp 134° (15 mm) [lit.[22] bp 175° (20 mm)]; n^{20}D 1.5798; d^{20}_4 1.1164.

***m*-Chloroanisole.**—This was prepared from the sodium salt of *m*-chlorophenol (25 g, 0.194 mol) by treating it with dimethyl sulfate (31.5 g, 0.25 mol) in water: yield 23.5 g (0.165 mol, 85.1% yield); bp 85° (27 mm) (lit.[25] bp 193–194°); n^{20}D 1.5359; d^{20}_4 1.1737.

Procedure for Kinetic Runs.—The reaction mixtures of varying concentrations (0.05–0.20 *M*) were made of samples of substituted anisole and di-*t*-butyl peroxyoxalate in Freon-113 which were accurately weighed. A reactant ratio of substituted anisole to di-*t*-butyl peroxyoxalate of 5:1 was employed. The reaction mixtures were then placed in a glass tube and were degassed by repeated freezing and melting under vacuum. The tubes were then sealed under vacuum and were immersed in a constant-temperature bath kept at 45.0 ± 0.1° for 7.5 hr. After being cooled in a Dry Ice–methanol bath, the tubes were opened and the *t*-butyl alcohol/acetone ratios were determined by glpc on a column packed with polyethylene glycol 1500 using helium as a carrier gas. The ratios of the rate constant k_a/k_d were calculated from the plots of *t*-butyl alcohol/acetone *vs.* concentration of the substrates by the method of least squares.

Registry No.—*p*-Phenoxyanisole, 1655-69-2; *p*-methoxyanisole, 150-78-7; anisole, 100-66-3; *m*-methoxyanisole, 151-10-0; *p*-chloroanisole, 623-12-1; *m*-phenoxyanisole, 1655-68-1; *m*-chloroanisole, 2845-89-8; *p*-cyanoanisole, 874-90-8.

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Nuclear Magnetic Resonance Spectroscopy. ^{13}C Spectra of Indole and Methylindoles[1]

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Received September 8, 1969

The natural-abundance ^{13}C nmr spectra of indole, the seven monomethylindoles, and some di- and trimethylindoles have been determined at 15.1 MHz. The chemical shifts of the ring carbons in these compounds were found to range over 50 ppm, and with the aid of complete proton decoupling it was possible to resolve all of the carbon resonances. Single-frequency and off-resonance proton-decoupling techniques were employed to assign the resonances to specific carbons.

Instrumentation is now available for relatively routine determination of high-resolution ^{13}C nmr (cmr) spectra in natural abundance in organic compounds.[2-5] Noise-modulated proton decoupling[6] is of special utility for organic structural analysis because it permits measurement of fully proton-decoupled spectra consisting of sharp singlets when other nuclei with nonzero spin are either absent or undergo rapid quadrupole relaxation.

No reports on the ^{13}C nmr spectra of indoles have appeared in the literature. As a part of our continuing efforts to measure and interpret the ^{13}C spectra of organic aromatic heterocyclic compounds,[4a] the chemical shifts of the carbons of indole and its seven monomethyl derivatives have been measured and assigned (Table I). From these data, it was found possible to compile a table of additivity parameters (Table II) for use in predicting the chemical shifts of some di- and trimethyl derivatives which were available for comparison.

Carbon spectra in which the protons were not at least partially decoupled were found to be unsatisfactory in this work because of their complexity and the long scanning times required.[5a] Off-resonance, single-frequency decoupled spectra, in which the sample is irradiated strongly at a frequency several hundred hertz from the region of proton resonance frequencies were found to be very helpful.[7] No long-range couplings

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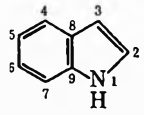
Table I

The Chemical Shifts[a] and Assignments for the ^{13}C Spectra of Indoles



Compd	C-2	C-3	C-4	C-5	C-6	C-7	C-9	C-9	Methyl
Indole	67.63	90.16	71.54	70.49	72.54	80.95	64.04	56.65	
1-Methyl-	63.48	91.48	71.51	70.91	73.03	83.02	63.39	55.27	160.71
2-Methyl-	57.10	92.40	72.75	71.70	72.93	81.90	62.90	55.70	179.40
3-Methyl-	70.07	81.36	73.39	70.54	73.20	81.06	63.61	55.49	182.95
4-Methyl-	68.62	91.73	62.58	70.61	72.67	83.51	64.11	56.26	171.19
5-Methyl-	67.81	90.69	69.06	64.00	72.01	81.50	63.65	57.57	171.31
6-Methyl-	68.49	90.48	72.07	70.94	61.30	81.20	66.15	55.49	171.08
7-Methyl-	68.03	89.81	73.92	70.08	72.48	71.93	64.38	56.42	176.15
1,2-Dimethyl-	54.74	92.78	72.80	72.08	73.19	83.58	63.94	55.75	164.13
									180.55
2,3-Dimethyl-	61.44	85.97	74.41	71.66	73.51	82.07	62.54	56.55	181.67
									184.32
2,7-Dimethyl-	57.65	91.83	75.14	71.13	72.95	72.87	63.34	56.28	176.16
									179.40
2,3,5-Trimethyl-	61.58	86.48	70.31	65.01	74.67	82.60	62.35	58.21	171.25
									181.66
									184.40

[a] In parts per million upfield from carbon disulfide.

Table II

The Incremental Changes in Chemical Shift of the Ring Carbons in Indoles upon Methyl Substitution

Compd	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9
Indole[a]	67.63	90.16	71.54	70.49	72.54	80.95	64.04	56.65
1-Methyl-	−4.15	+1.32	−0.03	+0.42	+0.49	+2.07	−0.65	−1.38
2-Methyl-	−10.53	+2.24	+1.21	+1.21	+0.39	+0.95	−1.14	−0.95
3-Methyl-	+2.44	−8.80	+1.85	+0.05	+0.66	+0.11	−0.43	−1.16
4-Methyl-	+0.99	+1.57	−8.96	+0.12	+0.13	+2.56	+0.07	−0.39
5-Methyl-	+0.18	+0.53	−2.48	−6.49	−0.53	+0.55	−0.49	+0.92
6-Methyl-	+0.86	+0.32	+0.53	+0.45	−11.24	+0.25	+2.11	−1.16
7-Methyl-	+0.40	−0.35	+2.38	−0.41	−0.06	−9.02	+0.34	−0.23

[a] Relative to carbon disulfide.

are observed in such spectra and direct ^{13}C–H couplings are reduced to 20–40 Hz while still providing favorable Overhauser enhancement[3,8] of the signal intensity. In the indoles we have studied, off-resonance proton decoupling yielded fairly clean doublets for the ring carbons bearing a proton and singlets for the quaternary carbons. An additional aid in assigning the quaternary carbons was the observation that the quaternary carbons bearing a methyl group appeared to be slightly more intense (about 10%) than the carbons at the ring junction (C-8 and C-9).

Exact proton-decoupling frequencies for each carbon were also an aid in making the chemical-shift assignments. Because the protons at C-2, C-3, and C-4 can be easily assigned in the proton spectra of these indoles,[9] this technique was used exclusively where applicable.

Discussion of Spectra. A. Indole.—The fully-proton-decoupled cmr spectrum of indole (Figure 1) consists of eight nearly equally intense peaks which, with narrower sweeps, become six sharp, equally intense, singlets and two smaller, broader singlets. The off-resonance decoupled spectrum showed the broad

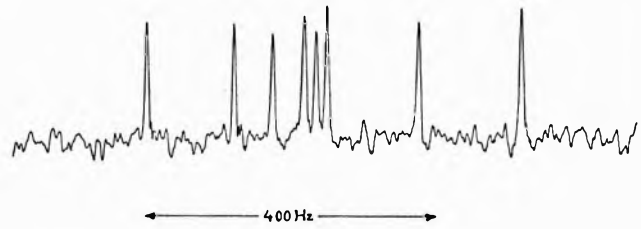


Figure 1.—Noise-decoupled, natural-abundance cmr spectrum of indole at 15.1 MHz. The field increases to the right and the farthest right-hand peak (C-3) is 90.16 ppm upfield from CS_2.

singlets to be the quaternary carbons, C-8 and C-9. The low-field singlet at 56.65 ppm was assigned to C-9 since carbons adjacent to nitrogen in pyrroles[10] and pyridines[11] have been shown to appear at lower field than those in a β position. The singlet at 64.04 ppm is then assigned to C-8.

Because the protons at C-2, C-3, and C-4 can be readily assigned in the proton spectrum, single-frequency decoupling was employed to assign C-2 at 67.63 ppm, C-3 at 90.16 ppm, and C-4 at 71.54 ppm. Three singlets, 70.49, 72.54, and 80.95 ppm, then remained unassigned. The identities of the unassigned singlets were established by comparison with the spec-

(8) K. F. Kuhlman and D. M. Grant, *J. Amer. Chem. Soc.*, **90**, 7355 (1968).

(9) (a) M. G. Reinecke, H. W. Johnson, Jr., and J. F. Sebastian, *ibid.*, **91**, 3817 (1969); (b) P. J. Black and M. L. Heffernan, *Aust. J. Chem.*, **18**, 353 (1965).

(10) T. F. Page, J. T. Alger, and D. M. Grant, *J. Amer. Chem. Soc.*, **87**, 5333 (1965).

(11) P. C. Lauterbur, *Ann. N. Y. Acad. Sci.*, **70**, 841 (1958).

tra of 5-, 6-, and 7-methylindole. Thus, C-5 appears at 70.49 ppm in indole, C-6 at 72.54 ppm, and C-7 at 80.95 ppm.

B. 1-Methylindole.—In the spectrum of 1-methylindole, C-2 and C-9 both undergo downfield shifts of 4.15 and 1.38 ppm, respectively, compared with the corresponding carbons of indole, presumably owing to a slight difference in polarization of the C–N σ bonding electrons. The chemical shifts of the other carbons remain essentially unchanged with the exception of C-7 which is shifted 2.07 ppm upfield. This shift may be the result of a steric interaction between the C-7H and 1-methyl group which could cause some steric compression at C-7.[12] An electron-releasing effect from the five-membered ring into the six-membered ring on N-methyl substitution seems to be small because there is very little change at the other carbons in the six-membered ring as is observed on methylation of anilines.

C. 2-Methylindole.—Substitution of a methyl group at C-2 causes two large changes in the spectrum, relative to indole. C-2 undergoes a large downfield shift of 10.53 ppm while C-3 shifts upfield by 2.24 ppm. Both of these changes are about the same as those found for methyl substitution in alkanes[3a] and pyrrole, furan, and thiophene.[4a] The changes in the chemical shifts of C-4, C-5, C-6, and C-7 are in the upfield direction indicating some electron release into the six-membered ring upon methyl substitution at carbon in the five-membered ring. Both C-8 and C-9 shift slightly downfield.

D. 3-Methylindole.—The spectrum of 3-methylindole is very similar to that of 2-methylindole with the changes in shifts of C-2 and C-3 reversed. C-3 undergoes an 8.80-ppm downfield shift relative to indole, while C-2 is shifted upfield 2.44 ppm. The upfield shifts at C-5, C-6, and C-7 are smaller than in the case of 2-methylindole, while C-4 is shifted to even higher field, perhaps owing to a steric interaction between the hydrogen at C-4 and the methyl group.

E. 4-Methylindole.—The major changes in the spectrum of 4-methylindole, relative to indole, are at C-4 and C-7. C-4, as expected, is shifted downfield by 8.96 ppm upon methyl substitution. The change in chemical shift at C-7 is almost identical with that observed between benzene and the *para* position of toluene, 2.56 ppm upfield.[12] On this basis, it appears that a *para* effect is operative in the six-membered ring and a large upfield shift should generally be expected at the carbon "*para*" to the one bearing the methyl group.

F. 5-Methylindole.—The indole which deviates most from the general pattern is 5-methylindole. The downfield shift of the resonance of C-5 is only 6.49 ppm and there is a large, unexplained downfield shift of C-4 (but not C-6) by 2.48 ppm. The effect at C-5 may be the result of some sort of an electron saturation effect because C-5 is "*para*" to the nitrogen. A similar effect is evident at C-9 where there is an upfield shift of 0.9 ppm instead of the expected 2 ppm.

G. 6-Methylindole.—Introduction of a methyl group at C-6 causes reasonably expected changes. The downfield shift of C-6 is somewhat larger than expected, 11.24 ppm, and there is a sizable upfield shift of 2.11 ppm at C-8 which corresponds to the *para*-methyl effect.

H. 7-Methylindole.—The only significant changes in the chemical shifts in 7-methylindole, relative to indole, occur at C-7, whose resonance is shifted downfield by 9.02 ppm, and at C-4, which is upfield by 2.38 ppm as the result of the *para* effect.

Methyl Groups.—The chemical shifts of the methyl groups appear to be typical for their particular environment. Those attached to the five-membered ring, with the exception of the N-methyl group, are at slightly higher field than those in the six-membered ring and are in agreement with the values found in methylpyrroles.[10] The methyls attached to the six-membered ring appear at the same position as those in toluene, the xylenes, etc.[13]

Additive Effects.—If the chemical shifts of the carbons at each position in the seven monomethylindoles are compared with the chemical shifts of the corresponding carbons in indole, the incremental change in chemical shift at each carbon for each type of methyl substitution can be calculated (Table II) and used to predict by simple additivity the chemical shifts of indoles containing more than one methyl group. The predicted and observed chemical shifts for three dimethylindoles and 2,3,5-trimethylindole are shown in Table III. The

TABLE III
OBSERVED AND PREDICTED CHEMICAL SHIFTS FOR SOME METHYL-SUBSTITUTED INDOLES

Carbon	Obsvd	Predicted	Difference[a]
	1,2-Dimethylindole		
2	54.74	52.95	+1.79
3	92.78	93.72	−0.94
4	72.80	72.72	+0.08
5	72.08	72.12	−0.04
6	73.19	73.42	−0.23
7	83.58	83.97	−0.39
8	63.95	62.25	+1.70
9	55.75	54.32	+1.43
	2,3-Dimethylindole		
2	61.44	59.54	+1.90
3	85.97	83.60	+2.37
4	74.40	74.60	−0.20
5	71.66	71.75	−0.09
6	73.51	73.59	−0.08
7	82.07	82.01	+0.07
8	62.54	62.47	+0.07
9	56.55	54.54	+2.01
	2,7-Dimethylindole		
2	57.65	57.50	+0.15
3	91.83	92.05	−0.22
4	75.14	75.13	+0.01
5	71.13	71.29	−0.16
6	72.95	72.87	+0.08
7	72.87	72.88	−0.01
8	63.34	63.24	+0.10
9	56.28	55.47	+0.81
	2,3,5-Trimethylindole		
2	61.58	59.72	+1.86
3	86.48	84.13	+2.35
4	70.31	72.12	−1.81
5	65.01	65.26	−0.25
6	74.67	73.06	+1.61
7	82.60	82.56	+0.04
8	62.35	61.98	+0.37
9	58.21	55.46	+2.75

[a] Observed chemical shift minus that predicted.

(12) H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 722, 731 (1961).

(13) P. C. Lauterbur, *J. Amer. Chem. Soc.*, **83**, 1838 (1961).

chemical shifts of these four indoles were assigned using techniques described earlier in this paper.

The quality of the predictions appear to be good to excellent. For 2,7-dimethylindole, the difference between the predicted and observed values is only about 0.1 ppm, except at C-9 where the difference is somewhat greater but still less than 1.0 ppm. This could be expected to provide a favorable case because the two methyl groups are not close to one another and their mutual interactions should be small.

With the 1,2- and 2,3-dimethylindoles, the 1,2-methyl interactions should be roughly the same and as a result the deviations from the predicted shifts should be about the same. This is apparent from the resonance of C-2 which is upfield for both compounds by 2.0 ppm from what is predicted. The C-2 shift may be the result of methyl–methyl repulsions causing slight lengthening of the 1,2-ring bond in 1,2-dimethylindole and the 2,3-ring bond in 2,3-dimethylindole.[7] There is also an upfield shift at C-9 for both compounds, possibly because the methyl–methyl repulsions deform the five-membered ring with resultant lengthening of the 1,9 bond.

The worst agreement between prediction and experiment is seen for 2,3,5-trimethylindole. The previously discussed effects at C-2, C-3, and C-9 are present in about the same magnitude but the resonances at C-4 and C-6 show rather large unexplained deviations from prediction. These may be connected with the abnormalities of 5-methylindole itself as discussed above.

Experimental Section

The indoles used in this study were commercial materials and were used without further purification.

The chemical shifts were measured using the digital frequency sweep spectrometer[6a] with pseudo-random, noise-modulated, proton decoupling[6a] as previously described. The samples were dissolved in dioxane, usually at concentrations of 1.0 g/1.5 ml at which it was usually only necessary to average 10 to 15 scans to obtain adequate signal-to-noise ratios. Sweep rates of 2- or 4-Hz/sec at 50- or 100-Hz sweep widths were generally employed. The peak widths were usually on the order of from 1 to 3 Hz. The off-resonance, proton-decoupled spectra usually required 30 to 40 time-averaged scans although it was possible in most cases to identify the quaternary carbons after 10 to 15 scans.

Registry No.—Indole, 120-72-9; 1-methylindole, 603-76-9; 2-methylindole, 95-20-5; 3-methylindole, 83-34-1; 4-methylindole, 16096-32-5; 5-methylindole, 614-96-0; 6-methylindole, 3420-02-8; 7-methylindole, 933-67-5; 1,2-dimethylindole, 875-79-6; 2,3-dimethylindole, 91-55-4; 2,7-dimethylindole, 5621-13-6; 2,3,5-trimethylindole, 21296-92-4.

Diazo Alkane Adducts of Thiete Sulfone (Thiacyclobutene 1,1-Dioxide) in Synthesis of Thiabicyclopentane Dioxides, Pyrazoles, and Tetrahydrothiophene Sulfones[1-3]

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Received August 18, 1969

Diazoalkanes have been added to the double bond of thiete sulfone (thiacyclobutene 1,1-dioxide) to yield 1- or 2-pyrazolines. Adducts of diphenyldiazomethane or methylphenyldiazomethane lose nitrogen on heating or on irradiation with ultraviolet light to give 2-thiabicyclo[2.1.0]pentane 2,2-dioxides. In contrast, the adducts of phenyldiazomethane and *p*-methoxyphenyldiazomethane lose sulfur dioxide to give pyrazoles. A route to thiophane (tetrahydrothiophene) sulfones from the thiabicyclopentane sulfones is shown.

Thiete sulfone has a reactive double bond; it and substituted thiete sulfones add anions readily and are dienophiles in the Diels–Alder reaction.[4] 1,3-Cycloadditions of diazo alkanes with acyclic[5a] and cyclic[5b] α,β-unsaturated sulfones are known. Adducts of diazo alkanes with thiete sulfone may be potentially useful intermediates in the synthesis of highly strained systems (such as bicyclobutanes) if the simultaneous or stepwise loss of both nitrogen and sulfur dioxide can be effected from the adducts. Cyclopropanes are formed by loss of nitrogen from 1-pyrazolines[6] and by loss of sulfur dioxide from certain four-membered cyclic sulfones (thietane sulfones).[7]

Addition of Diazo Alkanes to Thiete Sulfone.—Thiete sulfone yields crystalline adducts with various diazo alkanes. All of the adducts are 1-pyrazolines[8] with the exception of the adduct obtained from ethyl diazoacetate which forms a 2-pyrazoline. Table I lists the pyrazolines prepared. Where R and R′ are different groups, the stereochemistry (*syn,anti*) of the adducts was not determined although it is reasonable to assume

(1) This work was aided by Grant 5R01 CA 08250 of the National Institutes of Health, for which we are grateful.

(2) Reported at the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, Abstracts of Papers, Division of Organic Chemistry, No. 178.

(3) For further details, see R. Glassman, Ph.D. Thesis, Syracuse University, 1969.

(4) (a) D. C. Dittmer and M. E. Christy, *J. Amer. Chem. Soc.*, **84**, 399 (1962); R. H. Hasek, P. G. Gott, R. H. Meen, and J. C. Martin, *J. Org. Chem.*, **28**, 2496 (1963); D. C. Dittmer and N. Takashina, *Tetrahedron Lett.*, 3809 (1964); R. Hasek, R. H. Meen, and J. C. Martin, *J. Org. Chem.*, **30**, 1495 (1965); L. A. Paquette and T. R. Phillips, *ibid.*, 3883 (1965); G. Opitz and H. Schempp, *Ann.*, **684**, 103 (1965); J. N. Wells and F. S. Abbott, *J. Med. Chem.*, **9**, 489 (1966); N. Takashina, unpublished observations. (b) D. C. Dittmer and F. A. Davis, *J. Org. Chem.*, **32**, 3872 (1967).

(5) (a) W. E. Parham, F. D. Blake, and D. R. Theissen, *ibid.*, **27**, 2415 (1962); L. I. Smith and H. R. Davis, Jr., *ibid.*, **15**, 824 (1950). (b) H. J. Backer, N. Dost, and J. Knotnerus, *Rec. Trav. Chim.*, **68**, 237 (1949).

(6) Reviewd by B. Eistert, M. Regitz, G. Heck, and H. Schwall, Houben-Weyl, "Methoden der Organischen Chemie, Stickstoffverbindungen I," Vol. X, part 4, G. Thieme Verlag, Stuttgart, 1968, p 810 ff, and by B. P. Stark and A. J. Duke, "Extrusion Reactions," Pergamon Press, New York, N. Y., 1967, p 118 ff.

(7) R. M. Dodson and G. Klose, *Chem. Ind.*, (London), 450 (1963); W. E. Truce and J. R. Norell, *J. Amer. Chem. Soc.*, **85**, 3236 (1963). Sulfur dioxide and a proton are lost readily from benzothiete sulfone giving possibly a benzocyclopropenium ion as indicated by mass spectrometry.[4b]

(8) Infrared absorption at 1540 cm^{-1} and ultraviolet absorption at 335 nm for –N=N–; no absorption for N—H in the infrared.

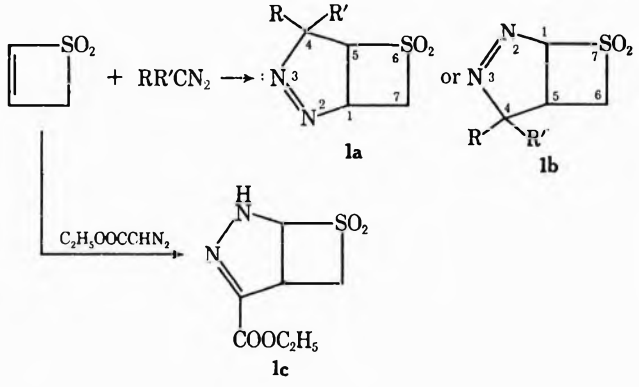
TABLE I
PYRAZOLINES DERIVED FROM THIETE SULFONE AND DIAZO ALKANES

R	R′	Structure
H	H	1b[a]
C_6H_5	H	1a
p-$CH_3OC_6H_4$	H	1a
CH_3	H	1a
C_6H_5	D	1a
C_6H_5	C_6H_5	1a
C_6H_5	CH_3	1a
CH_3	CH_3	1b[a]
C_2H_5OCO	H	1c

[a] Some **1a** also is formed.

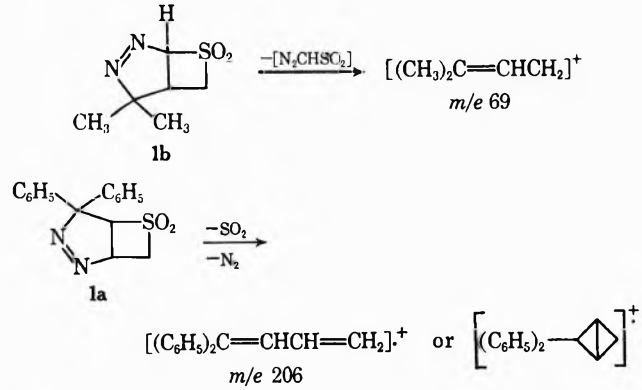
that the more bulky group would prefer to be *anti* to the sulfone group.

Structure **1a** is favored for most of the adducts but a mixture of both **1a** and **1b** is formed from diazomethane and dimethyldiazomethane. The major adducts (**1b**)



from the addition of diazomethane or dimethyldiazomethane show very intense peaks in their mass spectra corresponding to the loss of $[N_2CHSO_2]$. Adducts of structure **1a**, on the other hand, exhibit intense ions in their mass spectra corresponding to the loss of sulfur dioxide plus nitrogen. Since the plan for the synthesis of bicyclobutanes from the adducts calls for extrusion of sulfur dioxide and nitrogen from the 1-pyrazolines, the mass spectral data are promising. Scheme I illustrates the difference in fragmentation for adducts **1a** and **1b**.

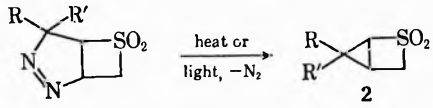
SCHEME I



The adduct **1b** of dimethyldiazomethane shows absorption at δ 7.18 (complex) in the nmr spectrum which is absent in adducts to which structure **1a** is assigned. This low field absorption is attributed to a proton situated on a carbon flanked by the azo group and the sulfone group and further supports structure **1b** for this particular adduct.

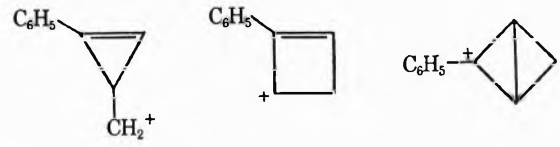
The initial adduct of ethyl diazoacetate presumably tautomerizes to the 2-pyrazoline (**1c**) because of the reactivity of the proton adjacent to the carbethoxy group in the 1-pyrazoline.

Loss of Nitrogen from Adducts.—When the pyrazoline obtained from thiete sulfone and diphenyldiazomethane or phenylmethyldiazomethane is heated at 130° or irradiated in the presence of benzophenone with light from a low pressure mercury lamp at room temperature,[9] nitrogen is lost to give the corresponding [2.1.0]thiabicyclopentane dioxide (**2**) in about 50% yield. These appear to be the first known thiabicyclopentane derivatives, but heterocyclic bicyclopentanes containing oxygen or nitrogen are known or have been proposed.[10]



R = R′ = C_6H_5–
R = C_6H_5; R′ = CH_3–

These thiabicyclopentane sulfones show absorption in the infrared at 1295–1300 and 1125–1150 cm^{-1} attributed to the sulfone group and at 1025–1028 and 855–867 cm^{-1} attributed to the cyclopropane ring.[11] The mass spectrum of the diphenyl derivative shows the formation of ions derived from the phenyl groups and ions attributed to $(C_6H_5)_2C^+$ and to the parent ion minus sulfur dioxide. The mass spectrum of the methyl phenyl derivative shows ions corresponding to a loss of sulfur dioxide and sulfur dioxide plus a methyl group from the parent ion. The abundant ions at m/e 129 may be cyclopropenylmethyl, cyclobutenonium, or bicyclobutane cations, or each may be some hybrid of the structures shown. The proton nmr spectrum of the



diphenyl adduct is complex: absorption occurs at δ 7.30 (10 aromatic protons), 4.10 (complex multiplet $-CH_2SO_2-$), 3.55 (two doublets, cyclopropane proton nearest sulfone group), and 2.75 (triplet of doublets, other cyclopropane proton). In the methyl phenyl compound there is absorption at δ 7.34 (five phenyl protons), 4.10 ($-CH_2SO_2-$), 3.92 (cyclopropyl proton adjacent to $-SO_2-$), 2.60 (remaining cyclopropyl proton), and 1.74 (CH_3).

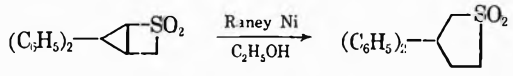
The diphenylthiabicyclopentane dioxide loses sulfur dioxide at high temperatures as well as in the mass spectrometer, but products have not been identified. Whether the thiabicyclopentane derivatives can be made to yield bicyclobutanes or whether they isomerize

(9) Irradiation was done only with the diphenyldiazomethane adduct.

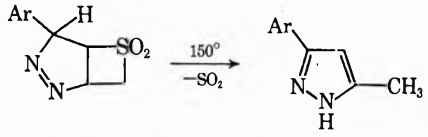
(10) C. D. Hurd and R. E. Christ, *J. Org. Chem.*, **1**, 142 (1936); G. A. R. Kon, L. F. Smith, and J. F. Thorpe, *J. Chem. Soc.*, **127**, 569 (1925); J. Bastus and J. Castells, *Proc. Chem. Soc.*, 216 (1962); M. Busch and J. Becker, *Ber.*, **29**, 1689 (1896); F. P. Woerner, H. Reimlinger, and D. R. Arnold, *Angew. Chem., Int. Ed. Engl.*, **7**, 130 (1968).

(11) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 2nd ed, 1958, p 29.

analogously to bicyclopentanes[12] remains to be determined. When the diphenylthiabicyclopentane dioxide was treated with Raney nickel, the cyclopropane ring was opened.



Loss of Sulfur Dioxide.—The adduct of thiete sulfone and phenyldiazomethane decomposes at 150° with loss of sulfur dioxide (but not nitrogen) to yield pyrazole **3** (52% Ar = C_6H_5), whose physical properties are identical with the physical properties of 3(5)-methyl-5(3)-phenylpyrazole which has been prepared previously from benzoylacetone and semicarbazide, hydrazine, or aminoguanidine.[13] If the adduct had

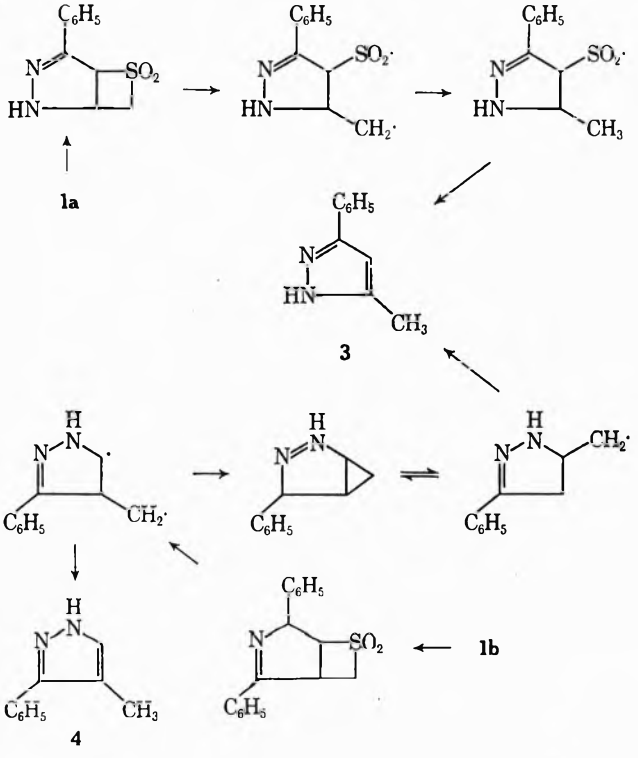


3

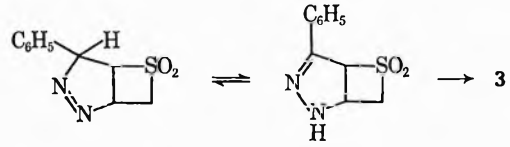
Ar = C_6H_5 or p-$CH_3OC_6H_4$–

structure **1b**, an isomeric pyrazole, 4-methyl-3(5)-phenylpyrazole (**4**), might have been formed (Scheme II), although isomerization of **1b** to **3** by way of a cyclopropane intermediate cannot be ruled out. None of **4** is observed. The adduct of thiete sulfone and p-methoxyphenyldiazomethane decomposes also to a pyrazole.

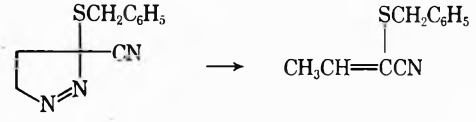
SCHEME II



The formation of **3** from **1a** may proceed *via* a diradical as shown or *via* a zwitterion. Tautomerization to the 2-pyrazoline stabilizes the molecule to loss of nitrogen. The hydrogen transfer, which is shown from



a diradical intermediate, is analogous to that observed in the loss of nitrogen from the 1-pyrazolines obtained from diazomethane and 1-benzylmercaptocrotonic acid nitrile or α-cyanoacrylic acids.[14]



Experimental Section[15]

Formation of 1-Pyrazolines. Addition of Diazomethane to Thiete Sulfone.—Thiete sulfone[16] (3.1 g, 0.030 mol) in 400 ml of ether was added to 150 ml of an ether solution of diazomethane,[17] prepared from Diazald (p-toluenesulfonylmethylnitrosamide, Aldrich, 21.5 g, 0.10 mol). The yellow solution was let stand at 0–5° for 4 days. Filtration gave 7-thia-2,3-diazabicyclo[3.2.0]hept-2-ene 7,7-dioxide (3.2 g, 0.0219 mol, 73%), mp 105–112°. Three recrystallizations from chloroform produced an analytical sample, mp 113–114°.

Anal. Calcd for $C_4H_6N_2O_2S$: C, 32.88; H, 4.14; N, 19.17; S, 21.91. Found: C, 32.79; H, 4.18; H, 19.04; S, 21.87.

Ultraviolet spectrum ($CHCl_3$): 328 nm (ϵ 277). Infrared spectrum (KBr): 3000 (w), 2950 (w), 1540 (w), 1430 (m), 1410 (w), 1325 (s, doublet), 1290 (m), 1235 (m), 1220 (m), 1200 (m), 1180 (s), 1135 (s), 1100 (w), 1090 (m), 1035 (w), 980 (s), 940 (m), 915 (w), 890 (w), 845 (w), 820 (m), 770 (w), 745 (w) cm^{-1}. The 60-MHz proton nmr spectrum was run in dimethyl sulfoxide-d_6: δ 7.16 (complex, 1 H, N=NCHSO$_2$), 4.85 (complex, 2 H), 4.40 (complex, 1 H), 3.85 (quartet, 1 H), 2.87 (complex, 1 H, H β to both N=N and SO$_2$). Mass spectrum:[18] m/e 28 (3.72), 29 (10.0), 39 (100), 40 (6.48), 41 (61.8), 42 (16.7), 43 (5.30), 44 (2.84), 45 (3.23), 48 (2.45), 52 (4.12), 53 (51.5), 54 (56.0), 55 (17.6), 61 (4.41), 62 (2.50), 63 (4.12), 64 (7.95), 69 (11.2), 70 (9.43), 71 (2.35), 72 (5.60), 73 (7.36), 76 (2.11), 82 (3.23), 146 (2.06).

Evaporation of the original filtrate produced more adduct (0.90 g, 0.00616 mol, 20.5%), mp 90°. Three recrystallizations from chloroform gave a mixture (mp 88–92°) of **1b** (R = R′ = H) and 6-thia-2,3-diazabicyclo[3.2.0]hept-2-ene 6,6-dioxide (**1a**, R = R′ = H). The 60-MHz proton nmr spectrum of the mixture was taken in dimethyl sulfoxide-d_6 (all absorptions are complex): δ 7.16 (1.0 H, **1b**, N=NCHSO$_2$), 5.40 (1.6 H, **1a**, tertiary H α to N=N), 4.95 (6.7 H, **1a** + **1b**), 4.40 (2.8 H, **1a** +

(12) M. J. Jorgenson and T. J. Clark, *J. Amer. Chem. Soc.*, **90**, 2188 (1968), and references cited therein.

(13) (a) C. Runti and L. Sindellari, *Ann. Chim.* (Rome), **49**, 877 (1959); *Chem. Abstr.*, **54**, 4482 (1960). (b) G. N. Pershin, N. A. Novitskaya, A. N. Kost, and I. I. Grandberg, *Dokl. Akad. Nauk SSSR*, **123**, 200 (1958); *Chem. Abstr.*, **53**, 3490 (1959). (c) S. C. De and P. C. Rakshit, *J. Indian Chem. Soc.*, **13**, 509 (1936); *Chem. Abstr*, **31**, 1403 (1937).

(14) K.-D. Gundermann and R. Thomas, *Chem. Ber.*, **93**, 883 (1960); F. D. Popp and A. Catala, *J. Org. Chem.*, **26**, 2738 (1961); J. Hamelin, D. Vandevin, and R. Carrié, *Compt. Rend.*, **260**, 3102 (1965).

(15) Melting points are uncorrected and were obtained on a Fisher-Johns melting block. Infrared spectra were taken on a Perkin-Elmer Model 137 infrared spectrophotometer or on a Perkin-Elmer Model 521 grating spectrophotometer. The infrared absorptions are reported as weak (w), medium (m), strong (s); sh stands for shoulder. Ultraviolet spectra were obtained on a Perkin-Elmer Model 202 ultraviolet spectrophotometer. The absorptions are reported in nanometers and the intensity (ϵ) of the absorptions in liter/mole-centimeter. Proton nuclear magnetic resonance (nmr) spectra were obtained on a Varian Model A-60 nmr spectrometer. Nmr absorptions are reported in parts per million (ppm) downfield from tetramethylsilane. Microanalyses were performed at Galbraith Laboratories, Knoxville, Tenn. Molecular weight determinations were done by vapor pressure osmometry in an appropriate solvent. Mass spectra were run at the Department of Chemistry, Syracuse University, Syracuse, N. Y., on a Perkin-Elmer Hitachi Model RMU-6E single-focusing spectrometer at an ionizing voltage of 20 V using direct inlet, unless otherwise noted. The internal ovens were kept at 250°, and each sample was heated at the lowest temperature which produced a spectrum.

(16) D. C. Dittmer and M. E. Christy, *J. Org. Chem.*, **26**, 1324 (1961).

(17) T. J. DeBoer and J. Backer, *Org. Syn.*, **36**, 16 (1956).

(18) Per cent of base peak is given in parentheses.

1b), 3.85 (1.5 H, **1a** + **1b**), 2.87 (1.0 H, **1b**, H β to both N=N and SO_2).

Addition of Phenyldiazomethane to Thiete Sulfone.—Thiete sulfone (1.0 g, 0.010 mol) in 200 ml of ether was added to 250 ml of an ether solution of phenyldiazomethane,[19] prepared from 10.0 g (0.045 mol) of azibenzil,[19] and the solution was allowed to stand at 0–5° for 1 day. A white solid was removed by filtration and recrystallized four times from chloroform to give 4-phenyl-6-thia-2,3-diazabicyclo[3.2.0]hept-2-ene 6,6-dioxide (**1a**, R = C_6H_5; R′ = H) (1.2 g, 0.0055 mol, 55%), mp 161–162° dec.

Anal. Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.06; H, 4.54; N, 12.61; S, 14.40; mol wt, 222. Found: C, 53.89; H, 4.45; N, 12.59; S, 14.14; mol wt (chloroform), 245.

Ultraviolet spectrum: 331 nm (ϵ 315) (C_6H_6); 331 nm (ϵ 260) ($CHCl_3$). Infrared spectrum (KBr): 3000 (m), 2950 (w), 1540 (m), 1490 (m), 1450 (m), 1385 (m), 1340 (m, sh), 1310 (s), 1300 (m, sh), 1260 (m), 1250 (m), 1230 (m), 1190 (s), 1170 (s), 1120 (s), 1080 (m), 1070 (m), 1030 (w), 1020 (w), 1000 (w), 985 (w), 945 (w), 925 (w), 912 (w), 880 (w), 850 (m), 840 (w), 820 (w), 795 (w), 750 (m), 740 (s), 715 (m), 695 (s) cm^{-1}. The 60-MHz proton nmr spectrum was taken in dimethyl sulfoxide-d_6: δ 7.35 (complex, 5 H, C_6H_5), 6.47 (triplet, 1 H, $C_6H_5CHN{=}N-$), 5.85 (complex, 1 H), 5.00 (doublet, 1 H), 4.84 (quartet, 1 H), 4.39 (complex, 1 H). Mass spectrum:[18] *m/e* 55 (5.71), 83 (1.47), 91 (2.05), 102 (1.47), 103 (2.45), 104 (2.41), 115 (7.49), 116 (2.85), 127 (1.43), 128 (4.95), 129 (51.0), 130 (100) 131 (11.0), 158 (1.69), 194 (0.110).

Addition of *p*-Methoxyphenyldiazomethane to Thiete Sulfone.—A solution of *p*-methoxyphenyldiazomethane[20] in 100 ml of ether and thiete sulfone (1.0 g, 0.010 mol) in 250 ml of ether was let stand at 0–5° for 2 days. A solid was removed by filtration and recrystallized three times from methanol to produce an analytical sample of 4-*p*-methoxyphenyl-6-thia-2,3-diazabicyclo-[3.2.0]hept-2-ene 6,6-dioxide (**1a**, R = *p*-$CH_3OC_6H_4$; R′ = H) (1.5 g, 0.0060 mol, 60%) as white crystals, mp 131–133° dec.

Anal. Calcd for $C_{11}H_{12}N_2O_3S$: C, 52.38; H, 4.80; N, 11.11; S, 12.71; mol wt, 252.2. Found: C, 52.18; H, 4.68; N, 11.14; S, 12.65; mol wt (benzene), 268.

Ultraviolet spectrum: 328 nm (ϵ 348); ($CHCl_3$) 330 nm (ϵ 327) (CH_3SOCH_3). Infrared spectrum (KBr): 3030 (w), 2950 (w), 2870 (w), 1625 (m), 1600 (w), 1550 (w, sh) ,1525 (m), 1465 (w), 1450 (w), 1400 (w), 1340 (m), 1320 (s), 1295 (m, sh), 1255 (s), 1230 (m), 1200 (m), 1180 (s), 1140 (m), 1110 (m), 1075 (w), 1030 (m), 960 (w), 943 (w), 860 (m), 840 (m), 812 (m), 800 (w), 785 (w), 775 (m), 745 (m), 730 (w) cm^{-1}. The 60-MHz proton nmr spectrum was taken in dimethyl sulfoxide-d_6: δ 7.10 (complex, 4 H, C_6H_4), 6.45 (complex, 1 H, *p*-$CH_3OC_6H_4CHN{=}$ N), 5.98 (complex, 1 H, H α to $-N{=}N-$), 4.85 (complex, 1 H, H α to $-SO_2-$), 4.35 (complex, 1 H, H α to $-SO_2-$), 3.77 (singlet, 3 H, *p*-$CH_3OC_6H_4-$), 3.32 (complex, 1 H, H α to $-SO_2-$). Mass spectrum:[18] *m/e* 45 (20.7), 55 (2.11), 64 (16.5), 115 (2.11), 117 (11.8), 128 (4.01), 129 (21.1), 130 (5.07), 131 (2.11), 132 (2.11), 144 (6.34), 145 (17.3), 146 (2.74), 147 (4.85), 158 (2.11), 159 (43.1), 160 (100), 161 (12.7), 175 (2.11), 188 (5.49), 224 (1.49).

Addition of Methyldiazomethane to Thiete Sulfone.—A solution of methyldiazomethane[21] in 250 ml of ether and thiete sulfone (3.1 g, 0.030 mol) in 400 ml of ether was let stand at 0-5° for 3 days. Filtration provided 4-methyl-6-thia-2,3-diazabicyclo-[3.2.0]hept-2-ene 6,6-dioxide (**1a**, R = CH_3; R′ = H) (3.2 g, 0.020 mol, 67%), mp 108-118°. Three recrystallizations from methanol produced an analytical sample of long white needles, mp 135°.

Anal. Calcd for $C_5H_8N_2O_2S$: C, 37.50; H, 5.04; N, 17.49; S, 19.99; mol wt, 160.1. Found: C, 37.54; H, 5.10; N, 17.61; S, 19.74; mol wt (acetone), 162.

Ultraviolet spectrum ($CHCl_3$): 323 nm (ϵ 233). Infrared spectrum (KBr): 2990 (m), 2950 (m), 1550 (w), 1480 (w. sh), 1450 (w), 1400 (m), 1380 (w), 1330 (s), 1310 (s), 1220 (m), 1200 (s), 1125 (s), 1105 (m, sh), 1090 (m), 1070 (m), 1025 (w), 990 (w), 940 (w), 915 (w), 860 (w), 830 (w), 785 (m), 765 (w, sh), 735 (m) cm^{-1}. The 60-MHz proton nmr spectrum was run in dimethyl sulfoxide-d_6: δ 5.45 (complex, 2 H, CHN=NCH), 4.75 (complex, 2 H), 4.15 (2 quartets, 1 H), 1.28 [doublet (J = 8.0 cps), 3 H, CH_3]. Mass spectrum (70 V, indirect inlet):[18] *m/e* 50 (5.50), 51 (9.26), 52 (7.89), 53 (81.6), 54 (10.9), 55 (15.4), 56 (2.38), 57 (2.57), 61 (2.02), 62 (4.40), 63 (4.95), 64 (49.5), 65 (10.2), 66 (9.90), 67 (100), 68 (89.0), 69 (6.05), 81 (6.97), 95 (27.8), 96 (33.0), 97 (22.9).

Addition of Phenyldiazomethane-α-*d* to Thiete Sulfone.—A solution of thiete sulfone (1.0 g, 0.01 mol) in 400 ml of ether and phenyldiazomethane-α-d[22] in 125 ml of ether, prepared from 5.6 g (0.025 mol) of azibenzil,[19] was let stand at 0–5° for 2 days. Filtration and recrystallization from ether gave 4-deuterio-4-phenyl-6-thia-2,3-diazabicyclo[3.2.0]hept-2-ene 6,6-dioxide (**1a**, R = C_6H_5; R′ = D) (1.2 g, 0.0054 mol, 54%) as a white solid, mp 136–138° dec. A second recrystallization from ether produced an analytical sample, mp 141–142° dec.

Anal. Calcd for $C_{10}H_9DN_2O_2S$: C, 53.90; H, 4.97; N, 12.58; S, 14.40; mol wt, 223.2. Found: C, 53.78; H, 4.88; N, 12.51; S, 14.56; mol wt (chloroform), 226.

Ultraviolet spectrum (C_6H_6): 329 nm (ϵ 300). Infrared spectrum (KBr): 3000 (w), 1540 (w), 1490 (w), 1450 (w), 1410 (w), 1400 (w), 1325 (s, doublet), 1250 (w), 1220 (m), 1210 (m), 1180 (s), 1140 (s), 1120 (m), 1100 (m), 1080 (w), 1050 (w), 1010 (w), 935 (w), 895 (w), 825 (w), 805 (w), 785 (w), 755 (m), 735 (m), 700 (m) cm^{-1}. The 60-MHz proton nmr was taken in dimethyl sulfoxide-d_6: δ 7.35 (complex, 5 H, C_6H_5), 5.85 (complex, 1 H), 4.91 (complex, 1 H), 4.55 (complex, 1 H), 4.25 (complex, 1 H). Mass spectrum (70 V, direct inlet):[18] *m/e* 74 (7.54), 75 (7.53), 76 (11.8), 77 (29.4), 78 (20.9), 79 (12.4), 81 (7.20), 89 (7.20), 90 (8.84), 91 (39.2), 92 (33.3), 102 (9.80), 103 (12.7), 104 (9.16), 105 (8.50), 115 (25.5), 116 (56.9), 117 (11.1), 118 (8.50), 124 (8.50), 127 (8.19), 128 (26.4), 129 (50.0), 130 (99.0), 131 (100), 132 (13.1), 157 (20.9), 158 (36.3), 159 (16.3), 195 (2.29).

Addition of Diphenyldiazomethane to Thiete Sulfone.—Diphenyldiazomethane[23] (3.9 g, 0.020 mol), prepared from benzophenone hydrazone (4.9 g, 0.025 mol), was added to thiete sulfone (1.0 g, 0.010 mol) in 400 ml of ether. The deep red solution was allowed to stand at 0–5° for 10 days. Evaporation of solvent produced a solid which was washed with cold ether and recrystallized twice from ether to give 4,4-diphenyl-6-thia-2,3-diazabicyclo-[3.2.0]hept-2-ene 6,6-dioxide (**1a**, R = R′ = C_6H_5) (1.5 g, 0.0050 mol, 50%), as long white needles, mp 151–152° dec.

Anal. Calcd for $C_{15}H_{14}N_2O_2S$: C, 64.42; H, 4.73; N, 9.39; S, 10.73; mol wt 298. Found: C, 64.35; H, 4.51; N, 9.50; S, 10.84; mol wt (chloroform), 292.

Ultraviolet spectrum (95% C_2H_5OH): 341 nm (ϵ 310). Infrared spectrum (KBr): 3000 (w), 2930 (w), 1598 (w), 1540 (w), 1485 (m), 1440 (m), 1398 (w), 1320 (s), 1220 (s), 1200 (s), 1170 (s), 1130 (s), 1110 (m), 1090 (w), 1080 (w), 1050 (w), 1030 (w), 1000 (w), 990 (w), 980 (w), 930 (m), 920 (w), 900 (w), 892 (m), 840 (w), 760 (s), 745 (s), 690 (s) cm^{-1}. The 60-MHz proton nmr spectrum was run in dimethyl sulfoxide-d_6: δ 7.50 (complex, 5 H, C_6H_5), 7.35 (complex, 5 H, C_6H_5), 4.18 (complex, 2 H), 3.25 (complex, 2 H). Mass spectrum:[18] *m/e* 64 (24.6), 74 (5.10), 91 (16.7), 115 (1.85), 128 (8.80), 129 (4.54), 165 (1.85), 191 (18.1), 192 (4.17), 204 (3.24), 205 (15.3), 206 (100), 207 (19.0), 208 (2.78).

Addition of 1-Phenyldiazoethane to Thiete Sulfone.—Thiete sulfone (2.1 g, 0.020 mol) in 400 ml of ether was added to 100 ml of an ether solution of 1-phenyldiazoethane,[24] prepared from acetophenone hydrazone[25] (15.0 g, 0.11 mol). The red solution was let stand at 0–5° for 1 day, and a white solid was removed by filtration. Two recrystallizations from methanol produced an analytical sample of 4-methyl-4-phenyl-6-thia-2,3-diazabicyclo-

(19) P. Yates and B. L. Shapiro, *J. Org. Chem.*, **23**, 759 (1958).

(20) *p*-Methoxyphenyldiazomethane was prepared from anisaldazine (10.0 g, 0.0373 mol, Aldrich) and anhydrous hydrazine (7.5 g, 0.23 mol, Matheson Coleman and Bell) according to the procedure of C. G. Overberger, N. Weinshenker, and J.-P. Anselme, *J. Amer. Chem. Soc.*, **87**, 4123 (1967).

(21) Methyldiazomethane was prepared from N-ethyl-N′-nitro-N-nitrosoguanidine (16.1 g, 0.10 mol) and potassium hydroxide (22.4 g, 0.40 mol) according to the procedure of A. F. McKay, W. L. Ott, G. W. Taylor, M. N. Buchanan, and J. F. Crooker, *Can. J. Res.*, **28B**, 683 (1950); *Chem. Abstr.*, **45**, 4646 (1951).

(22) Phenyldiazomethane-α-d was prepared according to the same procedure for the preparation of phenyldiazomethane[19] by use of sodium deuteroxide (40% solution in D_2O) and methanol-d_6 (Diaprep, Inc., Atlanta, Ga.) in place of sodium hydroxide and methanol, respectively.

(23) Diphenyldiazomethane was prepared in (a) 6 hr according to the procedure of L. I. Smith and K. L. Howard, "Organic Syntheses," Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p 351, or (b) 75 min according to the procedure of J. B. Miller, *J. Org. Chem.*, **24**, 560 (1959).

(24) H. Staudinger and A. Gaule, *Ber.*, **49**, 1897 (1916).

(25) A. Schönberg, A. E. K. Fateen, and A. E. M. A. Sammour, *J. Amer. Chem. Soc.*, **79**, 6020 (1957).

[3.2.0]hept-2-ene 6,6-dioxide (1a, R = C_6H_5; R′ = CH_3) (3.9 g, 0.17 mol, 83%), mp 170° dec.

Anal. Calcd for $C_{11}H_{12}N_2O_2S$: C, 55.93; H, 5.12; N, 11.86; S, 13.55; mol wt, 236. Found: C, 56.14; H, 5.13; N, 11.97; S, 13.81; mol wt (chloroform), 225.

Ultraviolet spectrum ($CHCl_3$): 251 nm (ε 350), 336 (190). Infrared spectrum (KBr): 3000 (w), 1540 (w), 1500 (w), 1465 (w), 1445 (w), 1410 (w), 1375 (w), 1325 (s, doublet), 1250 (w), 1225 (m), 1210 (m), 1190 (s), 1140 (s), 1125 (m), 1115 (m), 1100 (w), 1090 (m), 1070 (w), 1055 (w), 1040 (w), 1030 (w), 1005 (w), 950 (m), 930 (w), 920 (w), 905 (w), 865 (w), 810 (w), 797 (w), 764 (s), 741 (w), 695 (s) cm^{-1}. The 60-MHz proton nmr spectrum was run in dimethyl sulfoxide-d_6: δ 7.45 (complex, 5 H, C_6H_5), 4.18 (complex, 1 H, N=NCH), 3.18 (complex, 3 H, $CHSO_2CH_2$), 1.50 (singlet, 3 H, CH_3–). Mass spectrum:[18] *m/e* 91 (4.94), 103 (0.988), 104 (1.11), 105 (5.68), 115 (2.10), 116 (2.06), 117 (3.46), 118 (1.07), 127 (2.35), 128 (8.40), 129 (100), 130 (14.0), 131 (35.0), 132 (5.18), 141 (1.69), 142 (3.21), 143 (17.3), 144 (51.8), 145 (8.89), 146 (1.15), 147 (0.823), 157 (3.34), 158 (0.989), 159 (2.47), 160 (1.98), 161 (2.84), 162 (1.81), 172 (0.949), 208 (2.18).

Addition of Dimethyldiazomethane to Thiete Sulfone.—Dimethyldiazomethane,[24] prepred from acetone hydrazone[26] (29 g, 0.4 mol) and yellow mercuric oxide (102 g, 0.47 mol) in 87 g of xylene (distilled), was added to thiete sulfone (1.0 g, 0.010 mol) in 300 ml of ether. The red color disappeared immediately and a white solid precipitated after a few minutes. The mixture was let stand at 0–5° for 7 days. Evaporation of solvent produced 4,4-dimethyl-7-thia-2,3-diazabicyclo[3.2.0]hept-2-ene 7,7-dioxide (1b, R = R′ = CH_3) (1.05 g, 0.0060 mol, 60%). Three recrystallizations from ether produced an analytical sample, mp 199° dec.

Anal. Calcd for $C_6H_{10}N_2O_2S$: C, 41.38; H, 5.79; N, 16.09; S, 18.38; mol wt, 174.2. Found: C, 41.14; H, 5.79; N, 15.91; S, 18.43; mol wt (methanol), 184.

Ultraviolet spectrum (CH_3OH): 330 nm (ε 140). Infrared spectrum (KBr): 3000 (w), 2950 (w), 2880 (w), 1530 (w), 1470 (w), 1450 (w), 1405 (m), 1360 (m), 1330 (s), 1255 (w), 1220 (m), 1195 (s), 1150 (s), 1130 (s), 1055 (m), 1020 (w), 995 (w), 967 (w), 952 (w), 915 (m), 900 (w), 870 (w), 810 (w), 785 (m), 740 (w), 720 (w) cm^{-1}. The 60-MHz proton nmr spectrum was run in dimethyl sulfoxide-d_6: δ 7.18 (complex, 1 H, N=NCHSO$_2$), 4.10 (complex, 2 H, $-SO_2CH_2$), 2.68 (complex, 1 H, H β to –N=N– and $-SO_2-$), 1.55 (singlet, 3 H, CH_3–), 1.21 (singlet, 3 H, CH_3–). Mass spectrum:[18] *m/e* 41 (21.9), 42 (10.7), 43 (8.15), 53 (5.20), 67 (45.6), 68 (10.7), 69 (100), 70 (10.4), 76 (15.9), 81 (4.08), 82 (21.9), 83 (9.26), 95 (20.9), 97 (9.64), 100 (8.90), 110 (11.1).

Addition of Ethyl Diazoacetate to Thiete Sulfone.—A solution of thiete sulfone (0.52 g, 0.0050 mol) and ethyl diazoacetate[27] (1.7 g, 0.015 mol) was let stand in 30 ml of benzene (distilled) at room temperature for 4 days. Filtration and concentration of the filtrate yielded 4-ethoxycarbonyl-7-thia-2,3-diazabicyclo [3.2.0]hept-3-ene 7,7-dioxide (1c, 0.70 g, 0.0032 mol, 64%), mp 130–135°. Two recrystallizations from acetone produced an analytical sample, mp 149–151°.

Anal. Calcd for $C_7H_{10}N_2O_4S$: C, 38.54; H, 4.62; N, 12.84; S, 14.67; mol wt, 218.2. Found: C, 38.32; H, 4.75; N, 12.62; S, 14.36; mol wt (ethanol), 217.

Ultraviolet spectrum (95% C_2H_5OH): 229 nm (ε 5000). Infrared spectrum (KBr): 3220 (s), 2970 (m), 2900 (m), 2500 (w), 2380 (w), 1700 (s), 1480 (w), 1440 (m), 1390 (w), 1365 (m), 1290 (s), 1230 (w), 1180 (s), 1150 (m), 1100 (m), 1080 (s), 1060 (m), 1040 (s), 1010 (m), 945 (w), 885 (w), 875 (w), 845 (s), 805 (m), 795 (m), 750 (w) cm^{-1}. The 60-MHz proton nmr spectrum was run in dimethyl sulfoxide-d_6: δ 8.95 (singlet, broad, 1 H, NH), 7.74 (singlet, 1 H, –NCHSO$_2$), 4.25 (quartet, 2 H, $-OCH_2CH_3$), 4.02 (broad, 3 H, SO_2CH_2 and N=CCH), 1.30 (triplet, 3 H, $-OCH_2CH_3$). Mass spectrum:[18] *m/e* 64 (71.8), 80 (10.1), 81 (17.6), 107 (41.5), 108 (26.4), 109 (35.2), 123 (14.5), 125 (100), 126 (15.7), 139 (20.8), 141 (16.4), 153 (28.9), 154 (47.2), 155 (12.0).

Thiabicyclopentanes. 5,5-Diphenyl-2-thiabicyclo[2.1.0]pentane 2,2-dioxide. Pyrolysis of 4,4-Diphenyl-6-thia-2,3-diazabicyclo[3.2.0]hept-2-ene 6,6-Dioxide.—4,4-Diphenyl-6-thia-2,3-diazabicyclo[3.2.0]hept-2-ene 6,6-dioxide (1a, R = R′ = C_6H_5) (0.23 g, 0.00077 mol) was refluxed in 20 ml of commercial xylene (mixture of isomers, distilled) for 2.5 hr. Evaporation of xylene on a rotary evaporator left a brown solid, which was washed with cold ether and recrystallized from benzene–ether[28] to give 5,5-diphenyl-2-thiabicyclo[2.1.0]pentane 2,2-dioxide (2, R = R′ = C_6H_5) (0.10 g, 0.00039 mol, 50%) as white crystals, mp 198°.

Photolysis of 4,4-Diphenyl-6-thia-2,3-diazabicyclo[3.2.0]hept-2-ene 6,6-Dioxide.—A solution of 4,4-diphenyl-6-thia-2,3-diazabicyclo[3.2.0]hept-2-ene 6,6-dioxide (1a, R = R′ = C_6H_5) 0.0745 g, 0.000250 mol) and benzophenone (0.0455 g, 0.000250 mol) in 250 ml of benzene (distilled from calcium hydride) was irradiated (low pressure mercury lamp) for 3 hr at room temperature. Evaporation of benzene left a white oil, which was recrystallized from ether, and then from benzene–ether to yield 5,5-diphenyl-2-thiabicyclo[2.1.0]pentane 2,2-dioxide (2, R = R′ = C_6H_5) (0.0300 g, 0.000111 mol, 45.0%), mp 198°.

When the thiabicyclopentane sulfone was heated at 260° (under nitrogen in a flask with a cold finger or in a sealed tube), a tar was formed. Sulfur dioxide was detected by odor and by an acidic reaction to wet pH test paper.

Anal. Calcd for $C_{16}H_{14}O_2S$: C, 71.10; H, 5.22; S, 11.84; mol wt, 270. Found: C, 71.25; H, 5.28; S, 11.69; mol wt (chloroform), 262.

Ultraviolet spectrum ($CHCl_3$): 268.5 nm (ε 380). Infrared spectrum (KBr, Perkin-Elmer 521): 3050 (w), 3010 (w), 2940 (w), 1600 (w), 1585 (w), 1495 (w), 1450 (m), 1405 (w), 1310 (s), 1265 (w), 1220 (s), 1165 (w), 1150 (s), 1105 (w), 1080 (w), 1035 (w), 1028 (w), 1000 (w), 956 (w), 934 (w), 912 (w), 867 (w), 846 (w), 817 (m), 775 (m), 760 (w), 750 (s), 740 (w), 705 (s), 690 (m) cm^{-1}. The 60-MHz proton nmr spectrum was run in deuteriochloroform: δ 7.40 (complex, 5 H, C_6H_5), 7.20 (singlet, 5 H, C_6H_5), 4.10 (complex, 2 H, $-SO_2CH_2-$), 3.55 (quartet, 1 H, cyclopropyl H α to $-SO_2-$), 2.75 (sextet, 1 H, cyclopropyl H β to $-SO_2-$). Mass spectrum (70 V, direct inlet): *m/e* 51 (23.1), 63 (12.8), 69 (25.6), 76 (12.8), 77 (23.1), 78 (15.4), 85 (64.1), 87 (28.2), 89 (15.4), 91 (61.5), 101 (43.6), 102 (15.4), 103 (25.6), 115 (20.5), 116 (15.4), 127 (18.0), 128 (35.9), 129 (25.6), 131 (33.3), 135 (28.2), 137 (12.8), 147 (18.0), 151 (28.2), 152 (12.8), 153 (18.0), 163 (15.4), 165 (28.2), 178 (20.5), 179 (12.8), 189 (15.4), 190 (15.4), 191 (33.3), 201 (18.0), 202 (18.0), 203 (28.2), 204 (25.6), 205 (53.9), 206 (100), 207 (20.5).

5-Methyl-5-phenyl-2-thiabicyclo[2.1.0]pentane 2,2-Dioxide.—4-Methyl-4-phenyl-6-thia-2,3-diazabicyclo[3.2.0]hept-2-ene 6,6-dioxide (1a, R = C_6H_5; R′ = CH_3) (0.472 g, 0.002 mol) was heated in 20 ml of benzene (distilled) in a sealed tube at 150° for 3 hr. An ultraviolet spectrum of the benzene solution contained no absorption at 335 nm. Evaporation of benzene left a white oil, which was recrystallized from ether to give 5-methyl-5-phenyl-2-thiabicyclo[2.1.0]pentane 2,2-dioxide (2, R = C_6H_5; R′ = CH_3) (0.235 g, 0.00113 mol, 56.7%), mp 95–105°. A second recrystallization from ether produced an analytical sample, mp 110–111°. Alternatively, the pyrolysis was performed in refluxing xylene (distilled) overnight.

Anal. Calcd for $C_{11}H_{12}O_2S$: C, 63.45; H, 5.81; S, 15.37; mol wt, 208.2. Found: C, 63.35; H, 5.59; S, 15.31; mol wt (benzene), 216.

Ultraviolet spectrum ($CHCl_3$): 253 nm (ε 167), 259 (210), and 265 (170). Infrared spectrum (KBr, Perkin-Elmer 521): 3070 (w), 3005 (w), 2990 (w), 2950 (w), 2920 (w), 1595 (w), 1575 (w), 1490 (m), 1435 (m), 1405 (w), 1375 (w), 1345 (w), 1335 (w), 1295 (s), 1265 (m), 1205 (s), 1155 (m), 1125 (s), 1105 (w), 1055 (w), 1025 (w), 1005 (w), 990 (w), 935 (w), 910 (w), 890 (w), 855 (w), 845 (w), 795 (w), 785 (w), 760 (s), 695 (s) cm^{-1}. The 60-MHz proton nmr spectrum was run in dimethyl sulfoxide-d_6: δ 7.34 (singlet, 5 H, C_6H_5), 4.10 (complex, 2 H, $CHSO_2CH_2$), 3.92 (complex, 1 H, $-CHSO_2CH_2-$), 2.60 (complex, 1 H, cyclopropyl H β to $-SO_2-$), 1.74 (singlet, 3 H, CH_3). Mass spectrum:[18] *m/e* 64 (6.07), 76 (5.54), 78 (2.50), 91 (3.03), 102 (1.78), 103 (1.78), 104 (1.78), 105 (11.1), 115 (5.00), 116 (2.32), 117 (2.14), 127 (5.00) 128 (19.8), 129 (100), 130 (13.6), 131 (3.57), 141 (4.29), 142 (4.11), 143 (18.2), 144 (36.4), 145 (6.80), 208 (2.50).

Formation of Pyrazoles. Pyrolysis of 4-Phenyl-6-thia-2,3-diazabicyclo[3.2.0]hept-2-ene 6,6-Dioxide.—4-Phenyl-6-thia-2,3-diazabicyclo[3.2.0]hept-2-ene 6,6-dioxide (1a, R = C_6H_5; R′ = H) (0.087 g, 0.00039 mol) was heated in a sublimator at 150° (3 mm) for 10 min. A white solid sublimed, mp 121–123°; three more sublimations produced an analytical sample of 3(5)-methyl-5(3)-phenylpyrazole (3, Ar = C_6H_5) (0.032 g,

(26) T. Curtius and L. Pflug, *J. Prakt. Chem.*, **44**, (2) 543 (1891).

(27) N. E. Searle, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 424.

(28) A solution was obtained by stirring the solid in refluxing ether and adding hot benzene dropwise until all the solid dissolved.

0.00020 mol, 52%), mp 124° (lit.[13] mp 128, 127, 125–126, and 127–128°). A picrate was obtained, mp 158° (lit.[29] mp 158°).

Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71; mol wt, 158.2. Found: C, 75.96; H, 6.22; N, 17.81; mol wt (benzene), 165.

Ultraviolet spectrum: 251 nm (ε 15,600) (CH_3OH); 248 nm (ε 9200) ($CHCl_3$). Infrared spectrum (KBr): 3170 (m), 3120 (m), 3075 (m), 3000 (m), 2920 (m), 2840 (m), 1595 (m), 1580 (m), 1520 (m), 1500 (m, doublet), 1465 (m), 1410 (w), 1380 (w), 1320 (m), 1295 (m), 1275 (m), 1205 (m), 1155 (w), 1130 (w), 1100 (w), 1080 (m), 1060 (w), 1030 (m), 1015 (w), 965 (m), 915 (w), 870 (m), 840 (w), 795 (w), 760 (s), 715 (m), 690 (s) cm^{-1}. The 60MHz proton nmr spectrum was run in deuteriochloroform and in carbon tetrachloride: δ 12.66 ($CDCl_3$), 13.50 (CCl_4) [singlet ($CDCl_3$), broad (CCl_4), 1 H, –NH–]; 7.43 ($CDCl_3$), 7.40 (CCl_4) (complex, 5 H, C_6H_5); 6.24 ($CDCl_3$), 6.15 (CCl_4) (singlet, 1 H, –C=CH–); 2.12 ($CDCl_3$), 2.15 (CCl_4) (singlet, 3 H, CH_3). Mass spectrum:[18] *m/e* 55 (1.37), 77 (0.99), 78 (0.76), 81 (0.76), 90 (1.52), 91 (0.46), 102 (0.38), 103 (1.75), 104 (0.91), 115 (0.91), 116 (0.61), 117 (2.81), 118 (0.61), 127 (0.38), 128 (1.37), 129 (1.60), 130 (2.81), 131 (0.53), 143 (2.05), 157 (16.4), 158 (100), 159 (11.6), 160 (0.76).

Pyrolysis of 4-*p*-Methoxyphenyl-6-thia-2,3-diazabicyclo[3.2.0]-hept-2-ene 6,6-Dioxide.—4-*p*-Methoxyphenyl-6-thia-2,3-diazabicyclo[3.2.0]hept-2-ene 6,6-dioxide (**1a**, R = *p*-$CH_3OC_6H_4$–; R′ = H) (0.22 g, 0.00089 mol) was heated in a sublimator at 125° (5 mm) for 30 min. A white solid sublimed, mp 108°; two more sublimations produced an analytical sample of 3(5)-methyl-5-(3)-*p*-methoxyphenylpyrazole (**3**, Ar = *p*-CH_3O-C_6H_5) 0.060 g, 0.00032 mol, 36%), mp 111°.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88; mol wt, 188.2. Found: C, 70.40; H, 6.62; N, 14.87; mol wt (chloroform), 206.

Ultraviolet spectrum ($CHCl_3$): 261 nm (ε 18,600). Infrared spectrum (KBr): 3100 (m), 3000 (m), 2850 (m), 1620 (w), 1580 (w), 1525 (m), 1460 (m), 1440 (m), 1300 (w, sh), 1275 (m), 1250 (s), 1210 (w, sh), 1180 (m), 1160 (m), 1115 (w), 1070 (w), 1025 (m), 1010 (m), 960 (w), 840 (m, sh), 830 (m), 810 (w), 790 (m, sh), 780 (m), 685 (w) cm^{-1}. The 60-MHz proton nmr spectrum was run in deuteriochloroform: δ 12.07 (singlet, 1 H, NH), 7.18 (quartet, 4 H, C_6H_4), 6.20 (singlet, 1 H, –C=CH), 3.76 (singlet, 3 H, CH_3O), 2.20 (singlet, 3 H, CH_3C=C). Mass spectrum (70 V, indirect inlet): *m/e* 90 (4.17), 91 (14.9), 92 (3.57), 94 (8.63), 102 (4.75), 103 (3.57), 104 (3.57), 115 (19.1), 116 (8.64), 117 (6.55), 145 (39.2), 146 (5.06), 159 (4.76), 173 (66.0), 174 (8.94), 188 (100), 189 (13.4).

5,5-Diphenyl-2-thiabicyclo[2.1.0]pentane 2,2-Dioxide. Reduction with Raney Nickel.—A solution of 5,5-diphenyl-2-thiabicyclo[2.1.0]pentane 2,2-dioxide (**2**, R = R′ = C_6H_5) (0.108 g, 0.00040 mol) in 40 ml of warm ethanol was added to a suspension of W-4 Raney nickel,[30] prepared from 10 g of nickel–aluminum alloy (K & K Laboratories, Jamaica, N. Y.) in 75 ml of 95% ethanol. The mixture was refluxed for 16 hr and the metal was removed by filtration from the hot solvent. Evaporation of ethanol left 3,3-diphenyltetrahydrothiophene 1,1-dioxide (0.052 g, 0.00019 mol, 47%) as a white solid, mp 135°. Two recrystallizations from ether produced an analytical sample of colorless crystals, mp 144–145°.

Anal. Calcd for $C_{16}H_{16}O_2S$: C, 70.58; H, 5.92; S, 11.75; mol wt, 272.3. Found: C, 70.78; H, 5.92; S, 11.69; mol wt (chloroform), 269.

Ultraviolet spectrum ($CHCl_3$): 253 nm (ε 208), 260 (238), 270 (ε 168). Infrared spectrum (KBr): 3010 (w), 2950 (w), 1600 (w), 1490 (m), 1450 (m), 1410 (w), 1400 (w), 1300 (s), 1240 (w), 1220 (s), 1180 (w), 1125 (s), 1090 (w), 1070 (w), 1030 (w), 1005 (w), 980 (w), 955 (w), 915 (w), 910 (w), 875 (w), 860 (w), 805 (w), 795 (w), 775 (m), 745 (s), and 700 (s), cm^{-1}. The 60 MHz proton nmr spectrum was run in dimethyl sulfoxide-d_6: δ 7.35 [complex, 10 H, $(C_6H_5)_2C$–], 3.89 (complex, 4 H, $CH_2SO_2CH_2$), 3.05 (triplet, 2 H, $-CH_2CH_2SO_2-$). Mass spectrum (20 V, indirect inlet):[18] *m/e* 91 (9.10), 117 (8.44), 129 (16.7), 165 (10.4), 167 (48.9), 168 (6.75), 179 (8.60), 180 (100), 181 (15.8), 193 (42.1), 194 (6.85), 207 (25.2), 208 (6.24), 272 (9.70).

Registry No.—Thiete sulfone, 7285-32-7; 7-thia-2,3-diazobicyclo[3.2.0]hept-2-ene 7,7-dioxide, 23263-85-6; 3,3-diphenyltetrahydrothiophene 1,1-dioxide, 23263-97-0; **1a** (R = C_6H_5; R′ = H), 23263-86-7; **1a** (R = *p*-$CH_3OC_6H_4$; R′ = H), 23263-87-8; **1a** (R = CH_3; R′ = H), 23263-88-9; **1a** (R = C_6H_5; R′ = D), 23263-89-0; **1a** (R = R′ = C_6H_5), 23282-27-1; **1a** (R = C_6H_5; R′ = CH_3), 23263-90-3; **1b** (R = R′ = CH_3), 23263-91-4; **1c**, 23263-92-5; **2** (R = R′ = C_6H_5), 23263-93-6; **2** (R = C_6H_5; R′ = CH_3), 23263-94-7; **3** (Ar = C_6H_5), 3440-06-0; **3** (Ar = *p*-$CH_3OC_6H_4$), 23263-96-9.

(29) I. I. Grandberg and A. N. Kost, *Zh, Obshch. Khim.*, **28**, 3071 (1958); *Chem. Abstr.*, **53**, 10188 (1959).

(30) A. A. Pavlic and H. Adkins, *J. Amer. Chem. Soc.*, **68**, 1471 (1946).

The Thermal Decomposition of Benzenediazo Sulfones. I. Methyl Benzenediazo Sulfone[1]

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Received September 2, 1969

The thermal decomposition of methyl benzenediazo sulfone (**1c**) has been investigated in four different solvents. In three nonpolar solvents, benzene, cumene, and diphenylmethane, the principal identifiable decomposition products (Table I) are all ones that can be most easily interpreted as arising *via* a mechanism involving initial homolytic dissociation of **1c** and free-radical intermediates. The involvement of radical intermediates in the decomposition under these conditions is also shown by the results of experiments using a stable free radical (**2**) to scavenge the radicals formed by decomposition of **1c**. In the polar, aprotic solvent acetonitrile, on the other hand, the principal decomposition product, acetanilide, is thought to arise *via* an initial heterolytic dissociation of **1c** into a sulfinate and a benzenediazonium ion and reaction of the latter with the solvent in the manner shown in eq 10.

Benzenediazo sulfones (**1**) are an intriguing and little studied class of compounds which can be easily prepared by the reaction of a benzenediazonium salt with the salt of a sulfinic acid (eq 1). Although one reference work[2]

$$C_6H_5N_2^+ + RSO_2^- \longrightarrow C_6H_5N{=}N{-}\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}{-}R \qquad (1)$$

1

claims that their thermal decomposition in nonpolar solvents leads to the formation of the sulfone $C_6H_5SO_2R$ and nitrogen, a study of the decomposition of phenyl

(1) This research was supported by National Science Foundation Grant GP-1975.

(2) Houben-Weyl, "Methoden der Organischen Chemie," 4th ed, Vol. 9, Georg Thieme Verlag, Stuttgart, 1955, p 334.

TABLE I

THERMAL DECOMPOSITION PRODUCTS OF METHYL BENZENEDIAZO SULFONE IN NONPOLAR SOLVENTS[a]

Products, mol/mol of 1c	Benzene	Benzene + suspended CaO	Cumene	Ph_2CH_2
SO_2	0.14	0.14	0.03	0.11
Biphenyl	0.26	0.32	...	...
Azobenzene	0.14	0.03	...	...
Benzene	(Solvent)	(Solvent)	0.24	0.23
$CH_3SO_3C_6H_5$	0.07	0.00	0.07	0.00
Bis(methanesulfonyl)-phenylhydrazine (4a or 4b)	0.05	...	...	...
p-Phenylazobenzene	0.00	0.02	...	...
Benzhydryl methyl sulfone	...	...	...	0.11
sym-Tetraphenylethane	...	....	...	0.065
o- and *p*-Phenyldiphenyl methane	...	...	...	0.08
Bicumyl	...	...	0.12	...

[a] All data for 80°, initial concentration of 1c, 0.10–0.13 *M*.

benzenediazo sulfone (1a, R = C_6H_5) by Overberger and Rosenthal[3] has shown that this is certainly not true for this diazo sulfone at least. In benzene as solvent they found that the principal products of the thermal decomposition of 1a were biphenyl, nitrogen, and benzenesulfinic acid, only 5% of diphenyl sulfone being formed.

Our own interest in the thermal decomposition of benzenediazo sulfones was first aroused when we happened to prepare benzyl benzenediazo sulfone (1b, R = $C_6H_5CH_2$) and discovered[4] that its decomposition in benzene gave products entirely different from those given by 1a. We felt that our efforts to understand the complex behavior of the benzyl compound might be materially improved if we had available knowledge about the thermal decomposition of a simpler alkyl benzenediazo sulfone (1c, R = CH_3). Such information, for example, would tell us whether all alkyl benzenediazo sulfones behave very differently on thermal decomposition than their aryl counterparts, or whether, alternatively, there is something special about the decomposition of 1b.

The present paper describes the results of our investigation of the thermal decomposition of 1c. These show that its behavior is basically similar to that of the aryl compound[3] 1a and that it is the decomposition of the benzyl compound 1b which behaves in an unusual manner.

Results

Products of the Thermal Decomposition of 1c in Nonpolar Solvents.—Samples of methyl benzenediazo sulfone (1c) were decomposed at 80° in three different nonpolar solvents—benzene, cumene, and diphenylmethane. The decompositions were carried out under a nitrogen atmosphere, and a slow stream of nitrogen was passed through the solution during the decomposition in order to remove any sulfur dioxide which might be liberated in the decomposition as rapidly as it was formed.

In studying the kinetics of the decomposition of 1a, Overberger and Rosenthal[3] observed that the rate tended to accelerate with time, and that this acceleration was apparently due to autocatalysis by an acidic material formed in the decomposition, since the acceleration could be eliminated by suspending a small amount of calcium oxide in the solvent. We have also observed (*vide infra*) a similar but much less pronounced phenomenon in the decomposition of 1c. Because of this we determined the nature of the decomposition products of 1c in benzene for runs both in the presence and absence of suspended calcium oxide. The results of these and the runs in the other two solvents (no calcium oxide was added here) are summarized in Table I. Besides the reaction products listed, there was formed in all runs a large amount of intractable, tarry material, which, in our hands at least, did not prove amenable to chromatographic separation into identifiable components. Infrared spectra of the tarry material indicated that it contained NH, sulfonyl, and phenyl groups.

In benzene we see that the principal identifiable product is biphenyl and that a significant amount of sulfur dioxide is also formed. In the absence of suspended calcium oxide a good bit of azobenzene is formed, but the yield of this product drops to almost nothing when CaO is present. In cumene and diphenylmethane we find quite large amounts of benzene and significant amounts of the coupling products from solvent-derived radicals—bicumyl and *sym*-tetraphenylethane. In diphenylmethane we also find a significant amount of benzhydryl methyl sulfone, a product which could arise from coupling of a $CH_3SO_2\cdot$ radical with a solvent-derived diphenylmethyl radical, and small amounts of both *o*- and *p*-$C_6H_5C_6H_4CH_2C_6H_5$, products that would result from attack of phenyl radicals on the aromatic rings of diphenylmethane.

One curious product which was isolated in significant yield from the decompositions of 1c in both benzene and cumene, although not from the decomposition in benzene in the presence of calcium oxide, is phenyl methanesulfonate. Another, bis(methanesulfonyl)-phenylhydrazine, isolated from the decomposition of 1c in benzene, presumably results from the addition of the elements of methanesulfinic acid across the nitrogen–nitrogen double bond of 1c.

Products of Thermal Decomposition of 1c in Acetonitrile.—We also investigated the decomposition of 1c in the polar, aprotic solvent acetonitrile at 80°. On chromatographic work-up, only one organic product, acetanilide (0.71 mol/mol of 1c), was isolated. Only

(3) C. G. Overberger and A. J. Rosenthal, *J. Amer. Chem. Soc.*, **82**, 108, 117 (1960).

(4) J. L. Kice and R. S. Gabrielsen, *J. Org. Chem.*, **35**, 1010 (1970).

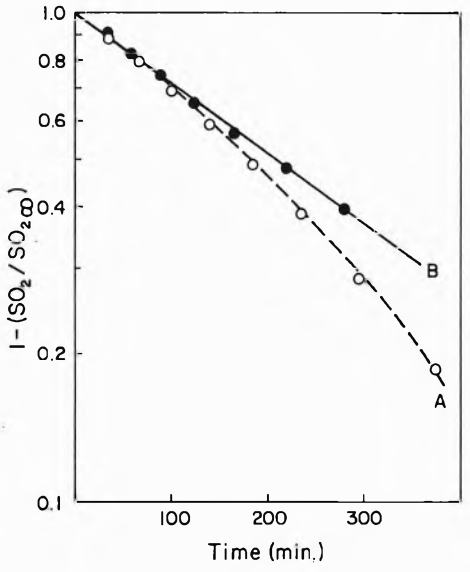


Figure 1.—Plot of log $(1 - SO_2/SO_{2\infty})$ *vs.* time for the decomposition of 0.10 *M* **1c** in benzene at 80°: curve A, ○, absence of suspended CaO; curve B, ●, presence of CaO.

0.03 mol of SO_2 was evolved. Clearly, in polar, aprotic solvents the decomposition of **1c** takes a very different course than it does in nonpolar solvents like benzene.

Rate of Decomposition of 1c in Benzene.—Because alkyl benzenediazo sulfones have a weak, but well-defined, absorption maximum in the visible region of the spectrum, we originally hoped to follow the disappearance of **1c** by observing the change in the visible absorption of the solution with time. However, because the solution turns from yellow-orange to a deep red during the course of the decomposition, apparently owing mainly to the formation of some of the products later isolated as intractable, tarry material, this turns out not to be feasible. An alternate approach was accordingly used.

We have seen that some sulfur dioxide (0.14 mol/mol of **1c**) is evolved in the decomposition of **1c** in benzene. The rate at which this gas is evolved can be followed by sweeping it out of the reaction vessel as it is formed and observing the time required for the reduction of an aliquot of standard iodine solution in a trap attached to the reaction vessel. Figure 1 shows a plot of log $(1 - SO_2/SO_{2\infty})$ *vs.* time for the decomposition of a 0.01 *M* solution of **1c** in benzene at 80° both in the absence (curve A) and the presence (curve B) of suspended calcium oxide. One sees that suspending CaO in the solution stops the gradual acceleration of the rate otherwise observed during the decomposition. This acceleration is similar to, although considerably less pronounced than, that observed in the decomposition of **1a**.[3] The first-order rate constant, k_d, for the disappearance of **1c** at 80° in benzene, as estimated from the slope of curve B, is 5.5×10^{-5} sec^{-1}.

Rate of Free-Radical Production in the Decomposition of 1c.—A common procedure for measuring the rate at which free radicals are produced in a given system is to add a known quantity of some reagent which is known to be extremely effective at scavenging free radicals and then to measure the rate at which this radical scavenger is consumed.[5,6] If the initial concentrations are chosen such that the concentration of the scavenger is much smaller than that of the radical

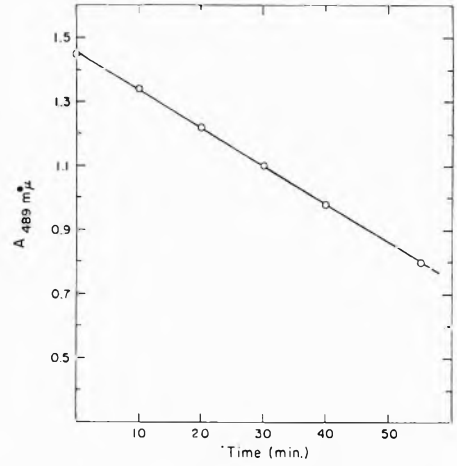


Figure 2.—Plot of optical density at 489 mμ *vs.* time for the decomposition at **1c** (5.3×10^{-4} *M*) in the presence of **2** (5×10^{-5} *M*) in benzene at 70°.

source, and if the scavenger is highly effective at capturing all radical intermediates produced before they can undergo bimolecular radical termination, then the disappearance of the scavenger will follow zero-order kinetics and the experimental zero-order rate constant will be equal to the rate of radical production.[5] We have employed this type of technique to measure the rate of radical production during the decomposition of **1c**.

The radical scavenger used in the present work was the stable free radical α,γ-bis(biphenylene)-β-phenylallyl[7] (**2**), the so-called Koelsch radical. This has been used successfully on several occasions in the past for this purpose.[6] Experiments were carried out in benzene as solvent at temperatures of 55–80° using initial concentrations of **1c** and **2** of 5×10^{-4} *M* and 5×10^{-5} *M*, respectively. As can be seen from Figure 2, the disappearance of the Koelsch radical follows good zero-order kinetics under these conditions. The results of these runs are summarized in Table II.

TABLE II
DECOMPOSITION OF METHYL BENZENEDIAZO SULFONE IN THE PRESENCE OF **2** IN BENZENE

[1c] × 10⁴, *M*	[2] × 10⁴, *M*	Temp, °C	$k_0 \times 10^5$, *M* sec^{-1} [a]	$k_i \times 10^5$, sec^{-1} [b]
5.0	0.51	80.0	19	1.9
		70.0	7.3	0.73
		59.9	1.9	0.19
		54.8	0.86	0.086

[a] k_0 is the zero-order rate constant for disappearance of **2**. [b] k_i is the first-order rate constant for dissociation of **1c** into radicals estimated by assuming $k_0 = 2k_i$[1c].

The first-order rate constant for dissociation of **1c** into pairs of scavengable free radicals, k_i, is calculated from the zero-order rate constant for disappearance of **2**, k_0, by assuming[5,6] that $k_0 = 2k_i$[1c]. Comparing k_i at 80° with k_d, the overall rate of disappearance of **1c** at this temperature, as measured by the rate of evolu-

(5) (a) G. S. Hammond, J. N. Sen, and C. E. Boozer, *J. Amer. Chem. Soc.*, **77**, 3244 (1955); (b) C. E. H. Bawn and D. Verdin, *Trans. Faraday Soc.*, **56**, 815 (1960); (c) P. D. Bartlett and T. Funahashi, *J. Amer. Chem. Soc.*, **84**, 2596 (1962); (d) W. G. Bentrude and J. C. Martin, *ibid.*, **84**, 1561 (1962).

(6) (a) R. C. Lamb, J. G. Pacifici, and P. W. Ayres, *ibid.*, **87**, 3928 (1965); (b) R. C. Lamb and J. G. Pacifici, *ibid.*, **86**, 914 (1964).

(7) C. F. Koelsch, *ibid.*, **79**, 4439 (1957).

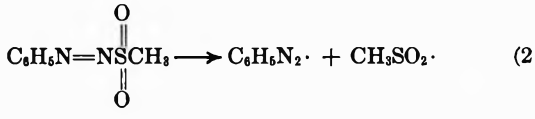
tion of sulfur dioxide, one sees that k_i/k_d = 0.35 (at 80° in benzene).

Discussion

Decomposition of Methyl Benzenediazo Sulfone (1c) in Nonpolar Solvents. Evidence for Radical Intermediates.—The experiments using the stable free radical 2 as a radical scavenger show that the decomposition of **1c** in nonpolar solvents leads to the production of free-radical intermediates, although the rate of radical production, k_i, as measured by these experiments, seems to be only about 35% of k_d, the overall rate of decomposition of **1c** under these conditions.

Deferring for the moment discussion of possible reasons for this difference between k_i and k_d, we will first point out that the principal identifiable decomposition products in such solvents are all ones that seem most easily accounted for in terms of reactions involving free-radical intermediates, and we will indicate the manner in which we believe they are formed.

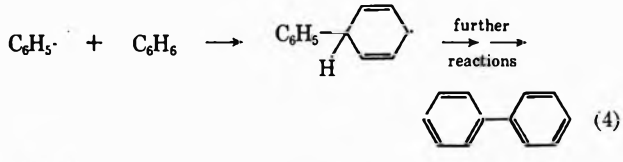
Homolytic dissociation of **1c** would presumably lead initially to the formation of a $CH_3SO_2\cdot$ radical and a $C_6H_5N_2\cdot$ radical (eq 2). Loss of nitrogen from the latter yields a phenyl radical (eq 3).



$$C_6H_5N{=}NSCH_3 \longrightarrow C_6H_5N_2\cdot + CH_3SO_2\cdot \qquad (2)$$

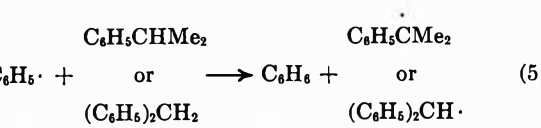
$$C_6H_5N_2\cdot \longrightarrow C_6H_5\cdot + N_2 \qquad (3)$$

Phenyl radicals are known[8] to react with benzene to give biphenyl (eq 4) *via* a reaction sequence which is initiated by addition of the phenyl radical to the aromatic ring. The yield of biphenyl (0.32 mol/mol of **1c**) from the decomposition of **1c** in benzene is *ca.* 70% of the amount (0.45 mol/mol of **1a**) formed in the decomposition of **1a** under the same conditions.

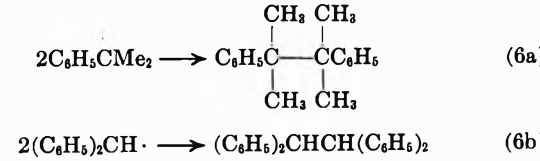


(4)

Both cumene and diphenylmethane possess hydrogen atoms that can be easily abstracted by phenyl radicals (eq 5). This presumably accounts for the considerable yield of benzene (0.25 mol/mol of **1c**) from the decomposition in these two solvents. Coupling (eq 6) of the cumyl (or diphenylmethyl) radicals produced in eq 5 accounts for the bicumyl (or *sym*-tetraphenylethane) isolated. In diphenylmethane we also apparently have some radical coupling between the solvent-derived radical and $CH_3SO_2\cdot$ (eq 7), since an appreciable amount of benzhydryl methyl sulfone (**3**), 0.11 mol/mol **1c**, was found to be one of the products in that solvent.

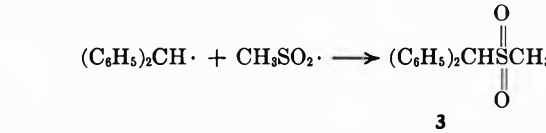


$$C_6H_5CHMe_2 \text{ or } (C_6H_5)_2CH_2 + C_6H_5\cdot \longrightarrow C_6H_6 + C_6H_5CMe_2 \text{ or } (C_6H_5)_2CH\cdot \qquad (5)$$



$$2C_6H_5CMe_2 \longrightarrow C_6H_5C(CH_3)_2{-}(CH_3)_2CC_6H_5 \qquad (6a)$$

$$2(C_6H_5)_2CH\cdot \longrightarrow (C_6H_5)_2CHCH(C_6H_5)_2 \qquad (6b)$$



$$(C_6H_5)_2CH\cdot + CH_3SO_2\cdot \longrightarrow (C_6H_5)_2CHS(O)_2CH_3 \qquad (7)$$

3

The fate of most of the $CH_3SO_2\cdot$ radicals formed in the initial homolysis of **1c** shown in eq 2 is not obvious. Some presumably desulfonylate (eq 8), thereby accounting for the sulfur dioxide evolved in the decomposition. In diphenylmethane others obviously react

$$CH_3SO_2\cdot \longrightarrow CH_3\cdot + SO_2 \qquad (8)$$

as shown in eq 7. Others probably abstract hydrogen atoms from one source or another, thereby being converted into methanesulfinic acid, CH_3SO_2H. We noted in the Results section that the bis(methanesulfonyl)-phenylhydrazine formed in the decomposition in benzene is a product which could well result from the addition of CH_3SO_2H across the nitrogen–nitrogen double bond of **1c**. However, what happens to any CH_3SO_2H formed under other conditions is not clear. Alkanesulfinic acids are generally considered[9] to be less stable than their aryl counterparts, and it could be that CH_3SO_2H once formed would itself decompose under the reaction conditions employed. (We did not, however, find any methyl methanethiolsulfonate, $CH_3SO_2SCH_3$, a product frequently formed on decomposition of the sulfinic acid.) Perhaps any CH_3SO_2H formed is simply lost during the chromatographic work-up procedure normally employed. However, according to the experience of Overberger and Rosenthal[3] it should have been isolable from the calcium salts recovered from the decomposition in the presence of suspended CaO if any had been there.

From the infrared spectra of the intractable, tarry residues always found as one of the major components of the decomposition products of **1c** it is clear that at least some of the original CH_3SO_2 groups of **1c** are contained therein, although in what form we do not know. In general, the large amount and the as yet unknown structures of the compounds in the intractable, tarry residue makes it unwarranted to conduct any further discussion of the origin of the products of the decomposition of **1c** in nonpolar solvents.

Possible Origins of the Difference between k_d and k_i.—We noted earlier that the apparent rate of radical production, k_i, as measured by scavenging experiments with **2**, was only about 35% of k_d, the overall rate of disappearance of **1c** under the same conditions. *A priori*, one can suggest three possible causes for this behavior for further consideration: (1) cage recombination of some of the initial radical pairs to give products before the radicals can diffuse away and be scavenged by **2**; (2) induced decomposition of some **1c** by attack of radicals on it, resulting in more than one molecule of **1c** disappearing for each initial homolytic act represented by eq 2; (3) a competing nonradical decomposition pathway.

Of these three, cage recombination is not apparently an important source of the difference between k_d and k_i, since no appreciable yield of any plausible cage recom-

(8) D. F. DeTar and R. A. J. Long, *J. Amer. Chem. Soc.*, **80**, 4742 (1958).

(9) See ref 2, pp 289–298.

bination product is found among the products. Although it is possible that the phenyl methanesulfonate isolated under certain conditions could arise from oxidation of initially formed phenyl methanesulfinate, and that the latter compound could be the product of a cage recombination reaction, *i.e.*

$$\mathbf{1c} \longrightarrow [C_6H_5N_2\cdot + CH_3SO_2\cdot] \xrightarrow{-N_2} [C_6H_5\cdot + CH_3SO_2\cdot] \longrightarrow C_6H_5OSCH_3 \quad (O)$$

this could only account for a small part of the difference between k_d and k_i.

On the other hand, if attack of different radicals on **1c** can lead to that complex product mixture which we have isolated only as an intractable, tarry residue, then clearly induced decomposition of **1c** remains a strong possibility for the source of the difference in rate between k_d and k_i.

However, the fact (*vide infra*) that decomposition of **1c** in polar aprotic solvents like acetonitrile obviously occurs by a nonradical route and the evidence that, in the absence of suspended calcium oxide, part of the decomposition in benzene apparently occurs by an acid-catalyzed, and presumably nonradical, pathway mean that one also cannot rule out the third alternative—a competing nonhomolytic pathway—as a potentially important source of a significant part of the difference between k_d and k_i.

The evidence presently at hand is simply not adequate to allow one to decide whether induced decomposition or the competing nonradical decomposition of **1c** is principally responsible for the fact that k_i/k_d is only 0.35, and for this reason any further speculation on this point is unjustified.

The important point to stress is that, whatever the origin of the difference between k_d and k_i, the decomposition of **1c** in nonpolar solvents *does occur to* at least *a sizeable extent via a radical mechanism* and that the products and other aspects of the reaction bear a considerable resemblance to the behavior[3] of the aryl benzenediazo sulfone **1a** under the same conditions. As will be seen in the accompanying paper,[4] the behavior of the aralkyl benzenediazo sulfone $C_6H_5CH_2SO_2N{=}NPh$ is different from that of either **1a** or **1c**.

Decomposition of Methyl Benzenediazo Sulfone (1c) in a Polar, Aprotic Solvent, Acetonitrile.—In acetonitrile the decomposition of **1c** takes an entirely different course than it does in nonpolar solvents, and the only organic product which was isolated on chromatographic work-up on alumina was acetanilide (0.71 moles/mole of **1c**).

Ritchie, Saltiel, and Lewis[10] have demonstrated that in the polar solvent methanol aryl benzenediazo sulfones are in equilibrium with the corresponding sulfinate and diazonium ions (eq 9). Since Makarova and Nesmeyanov[11] have found that decomposition of benzenediazonium fluoroborate in acetonitrile also results in the formation of acetanilide, it seems reasonable to suggest the mechanism shown in eq 9–12 for the decomposition of **1c** in acetonitrile. (No specific mechanism is implied for eq 10.)

$$C_6H_5N{=}NSCH_3 \rightleftharpoons C_6H_5N_2^+ + CH_3SO_2^- \quad (9)$$

$$C_6H_5N_2^+ + CH_3C{\equiv}N \longrightarrow C_6H_5\overset{+}{N}{\equiv}CCH_3 + N_2 \quad (10)$$

$$C_6H_5\overset{+}{N}{\equiv}CCH_3 + CH_3SO_2^- \longrightarrow C_6H_5N{=}C(OSCH_3){-}CH_3 \quad (11)$$

$$C_6H_5N{=}C(OSCH_3){-}CH_3 \xrightarrow[\text{on treatment with MeOH during work-up}]{\text{traces of moisture or}} C_6H_5N(H){-}CCH_3 \quad (12)$$

Table I shows that decomposition of **1c** in the absence of suspended CaO in benzene, conditions where presumably part of the decomposition involves an acid-catalyzed pathway, gave an appreciable amount of azobenzene, while practically no azobenzene was formed in the presence of suspended calcium oxide in that solvent. Given the results in acetonitrile, we speculate that the acid-catalyzed decomposition in benzene may also lead to the formation of the benzenediazonium ion from **1c**, and that this then reacts with the solvent to give azobenzene, *i.e.*

$$\mathbf{1c} \xrightarrow[\text{benzene}]{H^+} C_6H_5N_2^+ \xrightarrow{C_6H_6} C_6H_5{-}N{=}N{-}C_6H_5 + H^+$$

Experimental Section

Synthesis of 1c.—Benzenediazonium fluoroborate (3.64 g, 19.1 mmol) in 50 ml of water was added dropwise to a stirred cold solution of sodium methanesulfinate (2.42 g, 19.1 mmol) in 40 ml of water. The solution was stirred in the ice bath for an additional 15 min. The crystals which had formed were filtered off and washed with 100 ml of cold water. The yellow crystals of the diazo sulfone were dissolved in 30 ml of warm benzene, and the solution was filtered through anhydrous magnesium sulfate. Two volumes of hexane were added slowly to the benzene solution, and the solution was placed in the refrigerator overnight. The yellow needles of the diazo sulfone were filtered off, washed with cold hexane, and dried, giving 1.60 g (46%) of methyl benzenediazo sulfone (1c), mp 73–74.5° (lit.[12] mp 70–71°).

Purification of Solvents.—Reagent-grade benzene and cumene were refluxed over lithium aluminum hydride and then fractionally distilled through a 60-cm, glass helices packed column. Diphenylmethane was fractionally distilled twice under vacuum through a 40-cm Nester–Faust spinning-band column. Reagent grade acetonitrile was refluxed over calcium oxide for 24 hr, then fractionally distilled through a 60-cm, glass helices packed column. The distillate was then refluxed over and distilled from phosphorus pentoxide through the same column.

Thermal Decomposition of 1c. Product Studies.—The decompositions were carried out in an apparatus of the type previously described by Kice, Parham, and Simons.[13] The desired amount of diazo sulfone was placed in the decomposition flask, the solvent was pipetted in, and the vessel was covered with aluminum foil to prevent any photodecomposition of the diazo sulfone. The solution was then deaerated by passing a stream of nitrogen through it for 1 hr at room temperature, after which the vessel was immersed in a bath kept at 80° and left there until decomposition was complete. A slow stream of nitrogen was passed through the solution during the decomposi-

(10) C. D. Ritchie, J. D. Saltiel, and E. S. Lewis, *J. Amer. Chem. Soc.*, **83**, 4601 (1961).

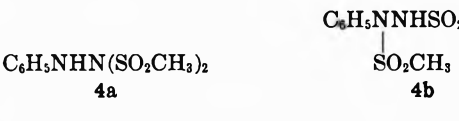
(11) L. G. Makarova and A. N. Nesmeyanov, *Izv. Akad. Nauk. SSSR, Otd. Khim. Nauk*, 1019 (1954); *Chem. Abstr.*, **50**, 241*a* (1965).

(12) P. K. Dutt, *J. Chem. Soc.*, **125**, 1463 (1924).

(13) J. L. Kice, F. M. Parham, and R. M. Simons, *J. Amer. Chem. Soc.*, **82**, 834 (1960).

tion in order to remove sulfur dioxide as it was formed and the nitrogen stream was subsequently passed through a trap containing standard iodine solution where the sulfur dioxide was absorbed.

Decomposition in Benzene.—To the final solution from the decomposition was added 1.5 times its volume of hexane, the mixture was cooled, and the crystals which formed were filtered off. The crystals were dissolved in benzene, treated with decolorizing charcoal, and filtered hot, and the benzene was removed under reduced pressure. Recrystallization of the residue from benzene–hexane gave light tan crystals, mp 155–156°. The spectral properties of the substance are consistent with either of the two possible bis(methanesulfonyl)phenylhydrazines (**4a** and **4b**).



$C_6H_5NHN(SO_2CH_3)_2$ (4a)

(4b)

Anal. Calcd for $C_8H_{12}N_2O_4S_2$: C, 36.35; H, 4.58; N, 10.60; mol wt, 264. Found: C, 36.57; H, 4.49; N, 10.68; mol wt, 267 ± 3.

The hexane–benzene filtrate was evaporated down under reduced pressure and the tarry residue was chromatographed on alumina. Elution with pure hexane gave a mixture of biphenyl and azobenzene. The amount of azobenzene was determined by dissolving this mixture in 95% ethanol, measuring the optical density at 315 mμ, and calculating the amount of azobenzene present from the known extinction coefficient of azobenzene at this wavelength.[14] The rest of the fraction was assumed to consist of biphenyl. Recrystallization of a portion of the fraction gave a pure sample of biphenyl, mp 69–71°, mixture melting point undepressed on admixture with a known sample.

Elution with 2:1 ether–methanol gave phenyl methanesulfonate, identified by its melting point, 60–61°, and its mixture melting point with a known sample.[15] The infrared spectra of the material isolated from the decomposition and the known sample were also identical.

Decomposition in Benzene with Suspended Calcium Oxide.—In the decomposition of **1c** in the presence of suspended calcium oxide (1.8 mol/mol **1c**) the final solution after the decomposition was complete was filtered, and the calcium salts on the filter were washed with small portions of benzene until colorless. After being dried overnight at room temperature, the calcium salts were dissolved in the minimum amount of dilute hydrochloric acid, and the pH of the solution was adjusted to 6 by the addition of sodium bicarbonate solution. The solution was then cooled in an ice bath and aqueous benzenediazonium fluoroborate was added. A yellow solution resulted, but there was no precipitate of **1c**, indicating that there could not have been very much calcium methanesulfinate in the recovered calcium salts.

The benzene filtrate was evaporated down and the residue was chromatographed on alumina. Elution with hexane gave biphenyl, this time free from any azobenzene, the latter being eluted with 80:20 hexane–benzene. Elution with 50:50 hexane–benzene gave a small amount of a product tentatively identified as *p*-phenylazobenzene on the basis of its infrared spectrum and melting point, 148–150° (lit.[16] mp 154–155°). No phenyl methanesulfonate was found on elution of the column with ether–methanol.

Decomposition in Cumene.—After the decomposition was complete, an aliquot of the reaction mixture was withdrawn and subjected to glpc on a 15-ft XF-1150 (15% on firebrick) column. The chromatogram showed two peaks with retention times identical with the retention times of known samples of benzene and cumene.

The remainder of the final solution was carefully fractionally distilled under vacuum to remove cumene and other volatiles. The tarry residue was chromatographed on alumina. Elution with hexane gave white crystals, whose infrared spectrum indicated that they were bicumyl (2,3-dimethyl-2,3-diphenylbutane), mp 117–118° (lit.[17] mp 119–120°). Elution with 2:1 ether–methanol gave some phenyl methanesulfonate.

Decomposition in Diphenylmethane.—At the end of the decomposition an aliquot was withdrawn and subjected to glpc in the same manner as for the decomposition in cumene. The chromatogram showed two peaks with retention times identical with those of known samples of benzene and diphenylmethane.

The remaining solution was carefully fractionally distilled under reduced pressure to remove the solvent and other volatiles and the tarry residue was chromatographed on alumina. Elution with hexane gave *o*-phenyldiphenylmethane, mp 55–56° (lit.[18] mp 54–56°). Elution with 95:5 hexane–benzene gave *p*-phenyldiphenylmethane, mp 85–86°, identified by infrared and mixture melting point comparison with a known sample.[19] Elution with 80:20 hexane–benzene gave *sym*-tetraphenylethane, mp 210–212°, identical in all respects with a known sample.[13] Elution with 80:20 benzene–ether afforded benzhydryl methyl sulfone (**3**), mp 129–133°, identical in all respects with a synthetic sample.[20]

Decomposition in Acetonitrile.—After decomposition was complete an aliquot of the solution was removed and subjected to glpc. No benzene was present.

The remaining solution was evaporated under reduced pressure to remove the acetonitrile and the residue was dissolved in a small amount of methanol. Alumina was added to the methanol solution, and the methanol was then evaporated. The coated alumina was placed on the top of a regular alumina chromatographic column and then the column was eluted with various solvents and solvent mixtures. Elution with 80:20 benzene–ether afforded acetanilide, mp 112–113°, identified by spectral and mixture melting point comparison with a known sample.

Kinetic Study of the Decomposition of 1c.—The same apparatus and procedure used for the product studies was employed. The rate of evolution of sulfur dioxide was followed in the manner described by Kice, Parham, and Simons.[13]

Rate of Free-Radical Production in the Decomposition of 1c.—The Koelsch radical **2** was prepared by the method used by Koelsch,[7] with two slight modifications: (1) 9-benzylidenefluorene was prepared by the improved procedure described by Kice,[21] and (2) α,γ-bis(diphenylene)-β-phenylallyl alcohol was prepared by the method used by Nelsen and Bartlett.[22] The crude radical was recrystallized from 95% ethanol, giving lustrous green plates, mp 186–188°. The visible spectrum in benzene showed a λ_{max} at 489 mμ (ϵ 2.71 × 10^4).

The rate at which **1c** decomposed to give radicals scavenged by **2** was measured by the method of Bartlett and Funahashi[6c] in a self-contained reaction cell of the type described by Kice and Pawlowski.[23] In a typical run 2.0 ml of a solution of **2** in benzene was placed in compartment B of the apparatus, and 2.0 ml of a solution of **1c** in benzene was placed in compartment A. The apparatus was connected to the vacuum line through D. The solutions in the two compartments were frozen, and the system was degassed in the usual way three times. After the third freeze–pump–thaw cycle, *ca* 400 mm of nitrogen pressure was introduced into the cell and the system was closed and disconnected from the vacuum system. The solutions in A and B were then mixed together and the resulting final solution was poured into cell C. The absorbance of the solution in C was then measured at 489 mμ. Cell C was then immersed in a thermostated oil bath and withdrawn after a suitable period of time. It was quickly cooled to room temperature, any bath oil was carefully rinsed off the outside of the cell, and the absorbance at 489 mμ was remeasured. Care was taken to ensure that cell C was always at the same temperature when the absorbance measurements were made. The process was repeated a number of times until the Koelsch radical had been consumed. In the absence of **1c** the Koelsch radical is indefinitely stable in benzene under the conditions employed.

Registry No.—**1c**, 23265-32-9.

(14) R. M. Silverstein and G. C. Bassler, "Spectrophotometric Identification of Organic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1963, p 177.

(15) B. Helferich and P. Papalambrou, *Justus Liebigs Ann. Chem.*, **551**, 235 (1942).

(16) W. F. Little and A. K. Clark, *J. Org. Chem.*, **25**, 1979 (1960).

(17) A. Klages, *Chem. Ber.*, **35**, 2633 (1902).

(18) J. P. Freeman, *J. Amer. Chem. Soc.*, **80**, 1926 (1958).

(19) V. S. Etlis and G. A. Razuvaev, *Zh. Obshch. Khim.*, **28**, 1225 (1958).

(20) M. M. Klenk, C. M. Suter, and S. Archer, *J. Amer. Chem. Soc.*, **70**, 3846 (1948).

(21) J. L. Kice, *ibid.*, **80**, 348 (1958).

(22) S. F. Nelsen and P. D. Bartlett, *ibid.*, **88**, 143 (1966).

(23) J. L. Kice and N. E. Pawlowski, *ibid.*, **86**, 4898 (1964).

The Thermal Decomposition of Benzenediazo Sulfones. II. Benzyl Benzenediazo Sulfone[1]

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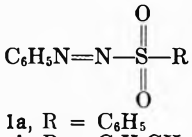
Received September 2, 1969

The thermal decomposition of benzyl benzenediazo sulfone (**1b**) has been examined in benzene, cumene, and diphenylmethane. In all three solvents the principal final products are sulfur dioxide, benzaldehyde phenylhydrazone, and N-benzyl benzaldehyde phenylhydrazone (**2**). The yield of **2** relative to the unsubstituted phenylhydrazone is largest in diphenylmethane and much smaller in benzene. Nmr experiments reveal that an intermediate is formed during the decomposition in benzene, and examination of the other spectral properties of this intermediate compound suggests that it is $PhCH_2N{=}NPh$. It subsequently isomerizes to benzaldehyde phenylhydrazone. Experiments using the Koelsch radical (**3**) as a radical scavenger suggest that in benzene the decomposition of **1b** involves a chain reaction. Two possible mechanisms for such a process, eq 1 and 2, are suggested, but no decision between them is possible at this time. In diphenylmethane the chain length appears to be considerably smaller, as suggested by the slower rate of disappearance of **1b** and the increased yields of **2**, which is thought to be a chain-termination product.

In the course of some other work the interesting compound benzyl benzenediazo sulfone (**1b**) was prepared. Some preliminary studies[2] revealed that its thermal decomposition in nonpolar solvents took a quite different course from that which had been observed by Overberger and Rosenthal[3] for the decomposition of the analogous phenyl compound **1a**. Since subsequent work[4] has shown that the decomposition of methyl benzenediazo sulfone (**1c**) behaves in a manner similar



1a, R = C_6H_5
b, R = $C_6H_5CH_2$
c, R = CH_3

to that of **1a**, the decomposition of the benzyl compound **1b** obviously also follows a different pattern than the thermal decomposition of simple alkyl benzenediazo sulfones like **1c**. Indeed the study of the decomposition of **1b** which we report in the present paper suggests that the reaction is a rather complex process which appears to possess a number of most unusual features.

Unfortunately, even after fairly extensive study of the decomposition of **1b**, we still cannot say that we fully understand all the facets of the process. However, since some important parts of the overall picture seem to be fairly well established, and since we plan no further work on the decomposition of **1b** or other diazo sulfones in the forseeable future, it seems worthwhile to report our results at this time, in the hope that they may stimulate others to unravel some of the remaining complexities of this most intriguing system.

Results

Products of Decomposition of 1b in Nonpolar Solvents.—Samples of benzyl benzenediazo sulfone (**1b**) were decomposed in three different nonpolar solvents—benzene, cumene, and diphenylmethane. The decompositions in cumene and diphenylmethane were carried out at 80°, that in benzene at 55°. In every case the reaction was done under a nitrogen atmosphere and a slow stream of nitrogen was passed through the solution during the decomposition to remove sulfur dioxide as it was formed. The nitrogen stream was subsequently passed through a trap containing a known amount of standard iodine, and the amount of sulfur dioxide being produced was determined quantitatively in this way. After decomposition was complete the other products were separated and purified by various chromatographic procedures (see Experimental Section), and their identity was established by appropriate comparisons with known samples. The results of the various product studies on the decomposition of **1b** are shown in Table I. Besides the reaction products shown, each decomposition also produced some intractable, tarry material that we were unable to separate chromatographically into identifiable compounds. The amount of such tarry material was, however, significantly less than the amount formed in the decomposition of **1c** under the same conditions.[4]

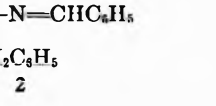
TABLE I

THERMAL DECOMPOSITION PRODUCTS OF BENZYL BENZENEDIAZO SULFONE IN NONPOLAR SOLVENTS[a]

Products, (mol/mol of **1b**)	Benzene, 55°	Cumene, 80°	Diphenylmethane, 80°
Sulfur dioxide	0.66	0.57	0.80
Benzaldehyde phenylhydrazone	0.55	0.46	0.34
N-Benzyl benzaldehyde phenylhydrazone	0.06	0.12	0.16
Biphenyl	0.02	...	...
Azobenzene	<0.01	...	...
Toluene	0.00	0.01	0.05
Benzene	(solvent)	0.11	0.15

[a] Initial concentration of **1b**, 0.08–0.10 *M*.

In all three solvents the principal products of the decomposition of **1b** are the same, sulfur dioxide and benzaldehyde phenylhydrazone ($C_6H_5{=}NNHC_6H_5$). Another product formed in every case is N-benzyl benzaldehyde phenylhydrazone (**2**), its yield being smallest



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in the solvent where the yield of benzaldehyde phenylhydrazone is largest and largest in the solvent where

(1) This research supported by National Science Foundation Grant GP-1975.

(2) R. H. Engebrecht, Ph.D. Thesis, Oregon State University, 1964.

(3) C. A. Overberger and A. J. Rosenthal, *J. Amer. Chem. Soc.*, **82**, 108, 117 (1960).

(4) J. L. Kice and R. S. Gabrielsen, *J. Org. Chem.*, **35**, 1004 (1970).

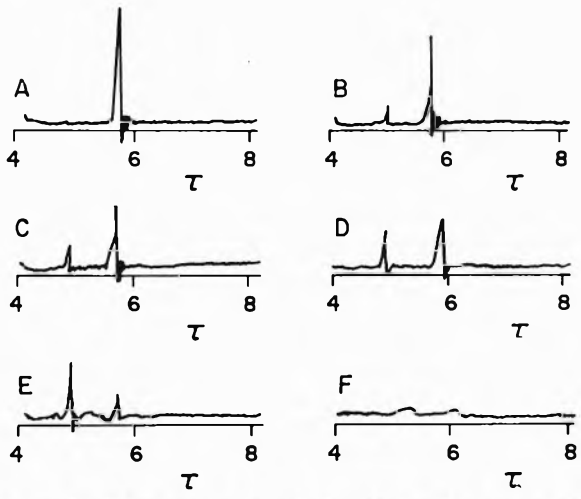

Figure 1.—Nmr spectra of solution during the course of the decomposition of **1b** (0.20 *M*) in benzene at 55°: curve A, initial solution; curve B, 2 hr; curve C, 3 hr; curve D, 4 hr; curve E, 5 hr; curve F, 8 hr.

the yield of the hydrazone is smallest. In cumene and diphenylmethane significant amounts of benzene (0.11–0.15 mol/mol **1b**) are formed. Whether this also happens in benzene as solvent one of course cannot tell. Some toluene is formed in the decomposition in diphenylmethane, much less in the one in cumene, and none that could be detected in the one in benzene. One of the most interesting facts is that no bicumyl or *sym*-tetraphenylethane were isolated from the decompositions in cumene and diphenylmethane, respectively. This is, of course, in striking contrast to the situation in the decomposition of the methyl diazo sulfone **1c**.[4]

Formation of an Intermediate During the Decomposition of 1b in Benzene.—The nmr spectrum of **1b** possesses a sharp singlet at τ 5.75 owing to the CH_2 protons of the benzyl group. During the decomposition of the diazo sulfone in benzene this peak decreases steadily in intensity and eventually disappears completely. As it decreases in intensity another sharp singlet begins to be seen at τ 4.92. This new peak increases in intensity up until the time when the original peak at τ 5.75 has almost vanished and then rapidly disappears itself. Figure 1 shows the appearance of the region from τ 4.0–6.0 with time for a typical decomposition of a 0.20 *M* solution of **1b** in benzene at 55°. Comparison of the integrated intensity of the signal at τ 4.92 at its maximum with that of a known amount of an internal standard (cyclohexane) suggests that at its peak the concentration of the intermediate responsible for the singlet at τ 4.92 is quite appreciable (0.40 mol/mol of **1b** originally present, if the signal at τ 4.92 is due to a CH_2 group).

In a second experiment another 0.20 *M* solution of **1b** in benzene was heated at 55° until nmr measurements showed that there was essentially no **1b** remaining (as indicated by the disappearance of the singlet at τ 5.75) and a maximum amount of the intermediate responsible for the singlet at τ 4.92. The solution was then frozen, and the benzene was pumped off under vacuum. Infrared, visible, and ultraviolet spectra were then taken on the residue. (That the intermediate was still present in the residue was shown by redissolving a portion of it and examining its nmr spectrum.) The infrared spectrum (in $CHCl_3$) showed no important absorption bands

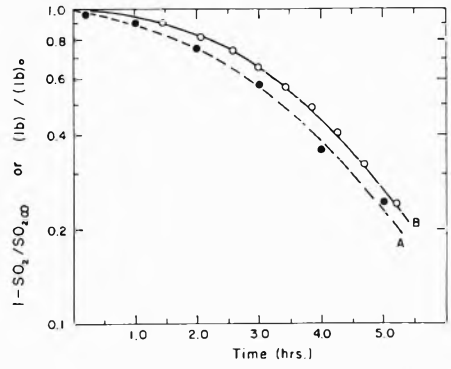

Figure 2.—Decomposition of **1b** (0.20 *M*) in benzene at 55°: curve A, ●, $[1b]/[1b]_0$ determined by following the intensity of the nmr singlet at τ 5.75; curve B, ○, log $(1 - SO_2/SO_{2\infty})$ as followed by SO_2 evolution.

other than those present in benzaldehyde phenylhydrazone. In particular, there were no bands present that could be attributed to either a sulfonyl (>SO_2) or a sulfinyl (>SO) group. The ultraviolet spectrum showed an absorption maximum at 335 mμ, but this is not particularly informative, since samples removed from the decomposition after the intermediate has disappeared show a maximum at 337 mμ, and benzaldehyde phenylhydrazone also is reported[5] to have a maximum close to this wavelength. The most significant spectral finding regarding the intermediate came from the visible spectrum of the residue. This showed a weak maximum at 405 mμ which was *not* present in the spectrum of samples removed from the decomposition after the intermediate had disappeared. O'Connor[6] has shown that compounds of the type $RN{=}NC_6H_5$ have low-intensity (ϵ 128–156) absorption maxima in the 400–407-mμ region.

Rate of Decomposition of 1b under Various Conditions.—The rate of the decomposition can be followed by two different procedures: (1) measurement of the decrease with time in the intensity of the nmr peak at τ 5.75 owing to the methylene protons of the benzyl group of **1b**; (2) measurement of the rate at which sulfur dioxide is evolved from the decomposition.

The nmr method could be applied only to decompositions of fairly concentrated (0.20 *M*) solutions of **1b**. In benzene at 55° under such conditions, the data for both nmr and sulfur dioxide evolution experiments when plotted in a first-order fashion give curved plots of the type shown in Figure 2. Although the results are not as reproducible from run to run as one would like, it appears that the rate of disappearance of **1b** as measured by nmr and the rate of formation of sulfur dioxide are the same. This is consistent with the fact that infrared spectra of the intermediate that forms under such conditions (*vide supra*) showed that it did not apparently contain either a sulfonyl or a sulfinyl group.

The decomposition of much more dilute (*ca.* 0.01 *M*) solutions of **1b** in benzene at 55° was followed by the sulfur dioxide evolution method. Under these conditions there is a pronounced "induction period" of *ca.* 2 hr, during which time sulfur dioxide is evolved at only a very slow rate. This is then followed by a relatively rapid evolution of the gas, which follows reasonably good first-order kinetics (Figure 3, curve A).

(5) H. R. Stevens and F. W. Ward, *J. Chem. Soc.*, **125**, 1324 (1924).
(6) R. O'Connor, *J. Org. Chem.*, **26**, 4375 (1961).

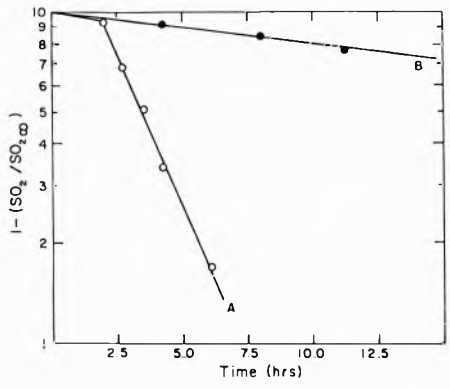

Figure 3.—Plot of log $(1 - SO_2/SO_{2\infty})$ *vs.* time for the decomposition of **1b** (0.01 *M*) in benzene at 55°: curve A, O, no added **3**: curve B, ●, 4×10^{-3} *M* added **3**.

We also measured the rate of evolution of sulfur dioxide from a 0.01 *M* solution of **1b** in benzene to which had been added 0.004 *M* α,γ-bis(biphenylene)-β-phenylallyl[7] (**3**). This stable free radical is known to be a very good reagent for scavenging reactive free radicals.[8,9] In the presence of **3** (curve B, Figure 3), one sees that the "induction period" prior to rapid evolution of sulfur dioxide is dramatically prolonged. We assume that the induction period observed in the absence of **3** is the result of the presence of a small amount of an impurity in either **1b** or the solvent which is also an effective inhibitor of a radical chain reaction.

We also determined the rate of decomposition of **1b** (0.08–0.10 *M*) in cumene and diphenylmethane at 80° by the sulfur dioxide evolution method. Under these conditions the decomposition showed only a rather short induction period. The apparent first-order rate constant, as measured from the slope of the plot of log $(1 - SO_2/SO_{2\infty})$ *vs.* time, is, however, much smaller than one might have expected, given the slope of the plot of the data for the decomposition in benzene at 55°. Thus the slope after the induction period in curve A of Figure 3 corresponds to a rate constant of 1.1×10^{-4} sec^{-1} for the decomposition of **1b** in benzene at 55°, which is just about the same as the rate constant of 1.5×10^{-4} sec^{-1} calculated from the slope of a first-order plot of the data for the decomposition in diphenylmethane at 80°.

Rate of Free-Radical Production in the Decomposition of 1b in Benzene.—This was investigated over the temperature range of 55–80° using the same scavenging technique employing the Koelsch radical **3** outlined in detail in the accompanying paper[4] on the decomposition of **1c**. As was also true in the decomposition of **1c**, the disappearance of **3** followed good zero-order kinetics under conditions where **1b** was present in considerable excess over **3**. A typical plot is shown in Figure 4. The results for the various runs are summarized in Table II.

From the zero-order rate constants, k_0, for the disappearance of **3** one can calculate k_i, the first-order rate constant for the decomposition of **1b** into pairs of scavengable free radicals, by assuming that $k_0 = 2k_i[\mathbf{1b}]$. At 55° in benzene, k_i is only 6% of the apparent overall rate of decomposition of **1b**, as determined from the rate

(7) C F. Koelsch, *J. Amer. Chem. Soc.*, **79**, 4439 (1957).
(8) R. C. Lamb, J. G. Pacifici, and P. W. Ayers, *ibid.*, **87**, 3928 (1965).
(9) R. C. Lamb and J. G. Pacifici, *ibid.*, **86**, 914 (1964).

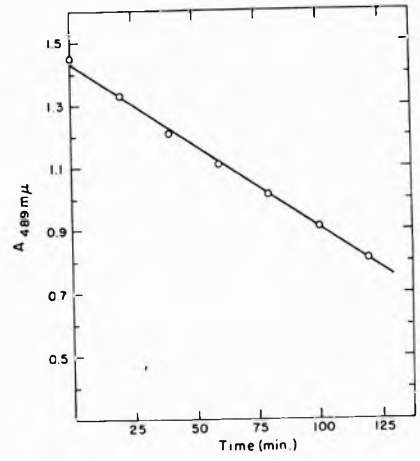

Figure 4.—Plot of the optical density at 489 mμ *vs.* time for the decomposition of **1b** (1.0×10^{-4} *M*) in the presence of **3** (5×10^{-5} *M*) in benzene at 60°.

TABLE II

DECOMPOSITION OF 1b IN THE PRESENCE OF 3 IN BENZENE

$[\mathbf{1b}] \times 10^4$, *M*	$[\mathbf{3}]_0 \times 10^4$, *M*	Temp, °C	$k_0 \times 10^9$, *M* sec^{-1} [a]	$k_i \times 10^6$, sec^{-1} [b]
1.0	0.50	54.8	1.2	0.60
		60.0	2.7	1.3
		65.0	6.2	3.1
		70.0	12	6.0
		80.0	24	12

[a] k_0 is the zero-order rate constant for disappearance of **3**. [b] k_i is the first-order rate constant for dissociation of **1b** into radicals, estimated by assuming $k_0 = 2k_i[\mathbf{1b}]$.

of evolution of SO_2 in the absence of added Koelsch radical (curve A, Figure 3), but it is almost exactly equal to the rate constant (0.7×10^{-5} sec^{-1}) estimated from curve B of Figure 3 from the rate of evolution of SO_2 from **1b** in the presence of added Koelsch radical at this same temperature. One also finds that k_i at 80° in benzene is approximately the same as the rate constant for the decomposition of **1b** in diphenylmethane at this temperature, as measured by the SO_2-evolution method.

Discussion

Several features of the results suggest that in benzene the decomposition of the benzyl diazo sulfone **1b** is a chain reaction. Thus there is the fact that the overall rate of decomposition of **1b** under such conditions is *ca.* 20 times faster than the apparent rate of dissociation of **1b** into free radicals, as measured using the Koelsch radical as a radical scavenger; *i.e.*, in benzene k_d for **1b** $= 20k_i$ for **1b**. More important is the fact (Figure 3) that the addition of Koelsch radical results in a dramatic decrease in the rate of disappearance of **1b**, as measured by SO_2 evolution, k_d in the presence of Koelsch radical being about equal to k_i, rather than 20 times larger, as it is in the absence of added **3**.

As shown by the nmr experiment in Figure 1, decomposition of **1b** in benzene leads to the formation of appreciable amounts of an unstable intermediate compound. This compound decomposes on further heating of the solution, and, in view of the large amount of it which is present, must in so doing yield chiefly benzaldehyde phenylhydrazone, which is the principal final organic product of the decomposition of **1b**. The un-

stable intermediate compound has a sharp singlet in the nmr at τ 4.92. It also appears to have a weak maximum in the visible at 405 mμ. Both of these observations, plus the fact that it presumably goes on chiefly to benzaldehyde phenylhydrazone, are consistent with its being formulated as 1′-phenyl benzeneazomethane ($PhCH_2N{=}NPh$). O'Connor[6] has shown that compounds of the structure $RN{=}NPh$ have a low-intensity absorption maximum (ϵ 128–156) in the 400–407-mμ region, and the methylene protons of ω-azotoluene ($PhCH_2N{=}NCH_2Ph$) appear as a sharp singlet at τ 5.15.[10] Also 1′-phenyl benzeneazomethane is known to isomerize readily to benzaldehyde phenylhydrazone.[11,12]

There would seem to be two possible ways that 1′-phenyl benzeneazomethane might be formed in a chain-type decomposition of **1b**. The first of these (eq 1) involves addition of a benzyl radical to the N=N double bond of **1b**, followed by cleavage of the radical **4** thus formed into 1′-phenyl benzeneazomethane, sulfur dioxide, and a benzyl radical; the benzyl radical can then

$$PhCH_2\cdot + PhCH_2\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}{-}N{=}N{-}Ph \longrightarrow PhCH_2SO_2\underset{\underset{CH_2Ph}{|}}{N}{-}\dot{N}{-}Ph \quad (1a)$$

4

$$PhCH_2SO_2\underset{\underset{CH_2Ph}{|}}{N}{-}\dot{N}{-}Ph \longrightarrow PhCH_2\cdot + SO_2 + PhCH_2N{=}NPh \quad (1b)$$

add to another molecule of **1b**. The alternate possibility (eq 2) involves a reaction sequence initiated by abstraction of one of the hydrogens of the methylene group of **1b** (eq 2a). This is followed (eq 2b) by an intramolecular addition to the N=N double bond, which gives **6**. This latter radical loses sulfur dioxide rapidly (eq 2c) to give radical **7**, which can continue the chain by abstracting a hydrogen atom from another molecule of **1b** (eq 2d). This last hydrogen atom

$$R\cdot + PhCH_2SO_2N{=}NPh \longrightarrow RH + PhCHSO_2N{=}NPh \quad (2a)$$

5

$$PhCHSO_2N{=}NPh \longrightarrow Ph{-}CH\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}{-}N{-}\dot{N}{-}Ph \quad (2b)$$

6

$$Ph{-}CH\underset{\underset{O}{\|}}{\overset{\overset{O}{\|}}{S}}{-}N{-}\dot{N}{-}Ph \longrightarrow SO_2 + PhCH{-}N{=}N{-}Ph \quad (2c)$$

6 **7**

$$7 + PhCH_2SO_2N{=}NPh \longrightarrow PhCHSO_2N{=}NPh + \begin{matrix} PhCH{=}NNHPh \\ \text{and} \\ PhCH_2N{=}NPh \end{matrix} \quad (2d)$$

transfer to **7** should lead to a mixture of 1′-phenyl benzeneazomethane and benzaldehyde phenylhydrazone.

Both eq 1 and 2 involve the addition of a free radical to an N=N double bond as a key step. Although such additions have received little study, one should note that the reaction of azobenzene with benzaldehyde in the presence of *t*-butyl peroxide to produce 1-benzoyl-1,2-diphenylhydrazine is believed[13] to involve the addition of a benzoyl radical to the N=N double bond of azobenzene, and Pryor and Guard[14] have remarked that $Ph_3CN{=}NPh$ appears to capture free radicals rather effectively and suggested that this is because addition of a free radical to the N=N double bond of a phenylazo compound gives rise to a relatively stable free radical, $>N{-}\dot{N}{-}\dot{P}h$. Therefore it is reasonable to suggest that additions such as those shown in eq 1a or 2b could be part of the chain decomposition of **1b**.

Initiation of the chain decomposition in benzene presumably involves radicals derived from the homolytic dissociation of **1b** (eq 3). If eq 2 is the correct representation of the chain-decomposition sequence, then initiation of individual chains is most reasonably formulated as proceeding by abstraction of a hydrogen atom from **1b** by a phenyl radical (eq 2a, $R\cdot = Ph\cdot$), and their termination would presumable involve coupling of radical **7** with a benzyl radical (eq 4), thereby accounting for the small amount of N-benzyl benzaldehyde phenylhydrazone also found as a reaction product.

$$PhCH_2SO_2N{=}NPh \longrightarrow [PhCH_2SO_2\cdot + PhN_2\cdot] \xrightarrow[-N_2]{-SO_2} PhCH_2\cdot + Ph\cdot \quad (3)$$

$$PhCH{=}N{-}\dot{N}{-}Ph + PhCH_2\cdot \longrightarrow PhCH{=}N{-}\underset{\underset{CH_2Ph}{|}}{N}{-}Ph \quad (4)$$

7 **2**

Alternatively, if eq 1 is the correct representation of the reaction sequence responsible for the chain decomposition, initiation would be *via* attack of a benzyl radical from eq 3 on **1b**, in the manner shown in eq 1a. In that event it seems most reasonable to assume that the phenyl radicals also produced in eq 3 would disappear chiefly by abstracting hydrogen atoms from either $PhCH_2N{=}NPh$ or **1b**, and then to assume that a sizable fraction of the radicals **7**, which would result either directly or indirectly from this process, would then terminate chains by reacting with benzyl radicals in the manner shown in eq 4.

Either chain-decomposition sequence can therefore be satisfactorily reconciled with the behavior of the decomposition of **1b** in benzene. As far as the results in the other solvents are concerned, one will recall that in diphenylmethane the ratio of the yield of N-benzyl benzaldehyde phenylhydrazone to that of benzaldehyde phenylhydrazone is *ca.* five times larger than it is in benzene, and that the overall rate of disappearance of **1b** is considerably slower in this solvent than in benzene. Both of these results are consistent with the idea that the chain length for the decomposition of **1b** is much smaller in diphenylmethane. *A priori* one might have expected diphenylmethane to have such an effect, since abstraction of one of its hydrogens by either an initiating or a chain-carrying radical would lead to a

(10) J. P. Freeman, *J. Org. Chem.*, **28**, 2508 (1963).
(11) D. Y. Curtin and J. A. Ursprung, *ibid.*, **21**, 1221 (1956).
(12) J. Thiele, *Justus Liebigs Ann. Chem.*, **376**, 239 (1910).
(13) M. S. Kharasch, M. Zimmerman, W. Zimmt, and W. Nudenberg, *J. Org. Chem.*, **18**, 1045 (1953).
(14) W. A Pryor and H. Guard, *J. Amer. Chem. Soc.*, **86**, 1150 (1964).

$Ph_2CH\cdot$ radical, which should be relatively unreactive and therefore reluctant to continue the chain. The only problem is that one would also expect as a result of this process to see various compounds containing a benzhydryl group among the products of the decomposition of **1b** in diphenylmethane. We did not isolate any such compounds, although it is possible that they might have either been missed, or, alternatively, that most of the Ph_2CH groups wound up in the intractable, tarry fraction that is always part of the products of the decomposition of **1b**.

Another point of some concern is the fact that in diphenylmethane, where chain decomposition of **1b** is presumably considerably repressed, the yield of benzene is still only 0.15 mol/mol of **1b** decomposing. One might have expected it to be considerably higher, although one should certainly also note that even in the decomposition of the methyl diazo sulfone (**1c**) in this solvent it was only 0.25 mol/mol of **1c**;[4] in that case there was presumably less chain (or induced) decomposition of the diazo sulfone than in the present system.[4] Perhaps in both cases one has a portion of the diazo sulfone decomposing by an acid-catalyzed, nonradical route. Certainly there was some evidence for this in the decomposition of **1c**.[4]

From the last two paragraphs of the preceding discussion it should be clear that, despite the fact that either eq 1 or 2 seem to offer a plausible explanation for the rapid, chain-type decomposition of **1b** in benzene, there are still a number of aspects of the decomposition of **1b**, particularly in other solvents, that are either not well understood or somewhat difficult to rationalize with either of the suggested mechanisms. For this reason, any speculation about which of the two, eq 1 or 2, is the more reasonable mechanism for the chain decomposition seems unwarranted at this time. Neither may in fact be correct, although, despite a great deal of thought, we have been unable to come up with any alternatives that come as close to explaining all the experimental facts as do either eq 1 or 2.

The important point that does seem, however, to emerge clearly from both this study and that described in the accompanying paper[4] is that the thermal decomposition of alkyl benzenediazo sulfones can be an extremely complex process that certainly is worth further investigation. It is our hope that this presentation of our experimental results will stimulate others to do the additional definitive work necessary to establish with real certainty just what is going on mechanistically in systems of this type.

Experimental Section

Synthesis of 1b.—Crude α-toluenesulfinic acid, 7.1 g, prepared by the reaction sequence outlined by Kice, Engebrecht, and Pawlowski[15] was dissolved in 150 ml of methanol. To this solution was added 5 ml of water and 38.2 g of sodium bicarbonate. The solution was stirred until evolution of carbon dioxide ceased and filtered, and the filtrate evaporated to dryness under reduced pressure at room temperature. The sodium α-toluenesulfinate so obtained, 6.76 g (38.0 mmol), was dissolved in 40 ml of cold water. This solution was extracted with one 20-ml portion of ether, the ether layer was discarded, and the aqueous layer was stirred at 0–5° while a solution of 7.25 g (38.0 mmol) of benzenediazonium fluoroborate in 250 ml of water was slowly added. Ten minutes after the addition was complete the yellow precipitate which had formed was filtered off and washed with cold water. After drying, the precipitate was dissolved in 70 ml of benzene, and the solution was filtered through some magnesium sulfate. *Ca.* 200 ml of hexane was added to the benzene filtrate. After the solution had cooled, the bright yellow precipitate which had formed was filtered off, and the crystals were again recrystallized from benzene–hexane, yielding 6.0 g (62%) of benzyl benzenediazo sulfone: mp 97–99° dec; ultraviolet spectrum (cyclohexane) λ_{max} 290 mμ (ϵ 14,200) and 438 (129); ir (chloroform) 1350 (s) and 1145 and 1162 cm^{-1} (s), all owing to the sulfone group.

Anal. Calcd for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.65; N, 10.76; S, 12.32. Found: C, 60.38; H, 4.64; N, 10.64; S, 12.54.

Purification of Solvents.—These were purified as described in an accompanying paper.[4]

Thermal Decomposition of 1b. Product Studies.—The general procedure for carrying out the decompositions was the same as that described for **1c** in the accompanying paper,[4] as was the method used for determining the amount of sulfur dioxide evolved.

Decomposition in Benzene.—After the decomposition was complete, a small aliquot of the final solution was withdrawn and subjected to glpc on a 15-ft XF-1150 (15% on firebrick) column. The chromatogram showed benzene (the solvent) to be the only volatile component. The remaining solution was evaporated under reduced pressure to remove the solvent, and the residue was chromatographed on alumina. Elution with hexane gave biphenyl, 0.02 mol/mol of **1b**. Elution with 80:20 hexane–benzene afforded a very small amount of azobenzene. Elution with 50:50 hexane–benzene gave N-benzyl benzaldehyde phenylhydrazone, mp 108–109° (lit.[16] mp 111°), identical in all respects with a known sample.[16] Elution with pure benzene gave benzaldehyde phenylhydrazone, mp 156–158°, identical in all the usual respects with a known sample.[17]

Decomposition in Cumene.—At the end of the decomposition a glpc analysis on a small aliquot showed three peaks with retention times identical with those of a prepared mixture of benzene, toluene, and cumene.

The cumene and other volatiles were removed from the remainder of the final solution by vacuum distillation. The dark residue was chromatographed on alumina. Elution with 75:25 hexane–benzene gave N-benzyl benzaldehyde phenylhydrazone and elution with 20:80 hexane–benzene afforded benzaldehyde phenylhydrazone. No bicumyl could be found in the hexane eluates.

Decomposition in Diphenylmethane.—At the end of the decomposition an aliquot of the final solution was subjected to glpc analysis using a column temperature of 160°. The chromatogram showed four peaks, three of which had retention times identical with those of benzene, toluene and diphenylmethane, respectively. The identity of the small fourth peak was not determined.

The remaining solution was carefully vacuum distilled to remove the solvent and other volatiles. The residue was then chromatographed on alumina in the same manner as for the decompositions in cumene and benzene. The only materials eluted which could be identified were N-benzyl benzaldehyde phenylhydrazone and benzaldehyde phenylhydrazone. In particular, no *sym*-tetraphenylethane could be isolated.

Identification of the Intermediate in the Decomposition of 1b in Benzene.—Part of a 0.20 *M* solution of **1b** in benzene was placed in an nmr tube and degassed, and the tube was sealed. The tube was heated at 55° and from time to time the nmr spectrum was recorded. The sharp singlet owing to the methylene group of **1b** at τ 5.75 decreased steadily in intensity and finally disappeared. During this time a sharp singlet began to appear at τ 4.92. This reached a maximum at about the time when the signal at τ 5.75 had completely disappeared and then subsequently itself disappeared (see Figure 1).

At the same time that the nmr experiment was being carried out, the remainder of the 0.20 *M* solution of **1b** in benzene, which had also been degassed, was also heated at 55°. When the nmr measurements indicated that the maximum amount of the intermediate with the singlet at τ 4.92 was present, heating of this second portion of the solution was terminated, the solution was frozen, and the benzene was removed from the frozen mixture under reduced pressure. Part of the residue which remained

(15) J. L. Kice, R. H. Engebrecht, and N. E. Pawlowski, *J. Amer. Chem. Soc.*, **87**, 4131 (1965).

(16) A. Michaelis, *Justus Liebigs Ann. Chem.*, **252**, 266 (1889).

(17) E. G. Cowley and J. R. Partington, *J. Chem Soc.*, 1252 (1933).

was dissolved in chloroform, and the infrared spectrum was recorded. A second weighed portion was dissolved in cyclohexane and the ultraviolet and visible spectra were determined. A third portion was redissolved in benzene and examined in the nmr. The singlet at τ 4.92 was still present, showing that removal of the benzene from the original solution did not cause any significant destruction of the intermediate.

In a separate experiment a 0.20 *M* solution of **1b** in benzene, containing a small but known amount of cyclohexane, was also examined in the nmr with time in the same fashion as in the earlier experiment. The integrated intensity of the singlet at τ 4.92 was compared with that of the added cyclohexane.

Kinetic Study of the Decomposition of 1b. Sulfur Dioxide Evolution Method.—The same apparatus and procedure used to follow the decomposition of 1c[4] was employed.

Nmr Method.—A *ca.* 0.20 *M* solution of **1b** in benzene, to which 1 drop of cyclohexane per 1 ml of solution had been added to serve as an internal proton standard, was transferred to an nmr tube having a constricted neck. The solution was then deaerated, and the tube was finally sealed off under *ca.* 100 mm pressure of prepurified nitrogen. The tube was then transferred to the thermostated nmr probe and the relative intensities of the singlet at τ 5.75 and the cyclohexane standard were determined as a function of time by integration.

Rate of Free-Radical Production in the Decomposition of 1b.—This was followed, using the Koelsch radical[7] as the radical counting reagent, in the same way as for the decomposition of 1c in the accompanying paper.[4]

Registry No.—1b, 23264-06-4.

The Reaction of Diborane and Bistriphenylmethyl Disulfide to Give a Carbon–Sulfur Bond Cleavage

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Diborane has been found to cleave the carbon–sulfur bond in bistriphenylmethyl disulfide to produce triphenylmethane, hydrogen, and $(HBS)_x$ polymer. Triphenylmethyl mercaptan reacted with diborane in benzene solution to yield the identical products. Hydrogen sulfide in benzene solution was found to react with diborane much more rapidly to form the $(HBS)_x$ polymer than previously reported for the vapor-phase reaction. The $(HBS)_x$ polymer prepared by these methods was a white, amorphous solid. No characteristic X-ray powder pattern could be obtained. The infrared spectrum corresponded to that reported in the literature. The elemental analysis and hydridic hydrogen determination confirm the stoichiometry. The ion fragments observed in the mass spectrum are consistent with the proposed formulation. The broad-line nmr of the solid indicated tetrahedral coordination of the boron.

Reactions of boron hydrides with elemental oxygen were studied soon after the discovery of the boron hydrides because of the spontaneous nature of the reaction.[1] This was followed by the study of the reactions with oxygen-containing compounds.[2] The study of the reactions with the analogous sulfur compounds, on the other hand, has lagged. For example, in Steinberg's comprehensive monograph,[3] boron–oxygen chemistry requires some 800 pages compared with 20 pages for boron–sulfur chemistry. Recently, however, interest in boron–sulfur chemistry has been increasing.[4–6]

In general, sulfur compounds do not react so fast as their oxygen analogs. Experience in our laboratories indicates that many organic disulfides are unreactive with diborane at −65°. Because of the relative stability of the sulfur–sulfur bond, it was felt that a preferential sulfur–carbon bond cleavage might be observed by properly selecting the carbon group. Furthermore, it was of interest to see whether the sulfur–sulfur bond might not be a sufficiently weak oxidizing agent that it could coexist in the same molecule with a boron–hydrogen bond.

Experimental Section

Reagents.—The benzene, toluene, and diethyl ether were reagent grade solvents stored in glass over calcium hydride. These were transferred by distillation into the vacuum line as needed.

Diborane.—The diborane was prepared by slowly adding 0.5 g of sodium borohydride to 20 ml of concentrated H_2SO_4. It was purified by distilling successively through a −111° trap and two −126° traps.

Triphenylmethyl Mercaptan.—The compound was used as obtained from the Aldrich Chemical Co.

Bistriphenylmethyl Disulfide.—The method of Vorlander and Mittag[7] which involves the treatment of triphenylmethyl mercaptan in alcoholic alkali solution with sulfuryl chloride was used. The sulfuryl chloride was purified by distilling the practical grade from Matheson Coleman and Bell into glass ampoules. These ampoules were sealed and not reopened until just prior to use.

The product obtained directly from the synthesis was a crystalline material, with mp 155–156°. Recrystallization of the disulfide from benzene, toluene–ethanol, and ether–benzene gave rise to some decomposition products and low recoveries. The disulfide used for all of these experiments was, therefore, unrecrystallized.

Bistriphenylmethyl Tetrasulfide.—The method described by Nakabayashi and coworkers[8] involving the reaction of triphenylmethyl mercaptan with sulfur monochloride was used. The product was recrystallized from chloroform–ethanol.

Reaction of Bistriphenylmethyl Disulfide with Diborane.—The reaction was carried out in an inverted U tube which could be sealed off under vacuum and which also contained a break-off so that it could be opened under vacuum. These tubes varied in size. The standard tubes, which were used for most of the experiments, had legs 300 mm long and 18 mm in diameter. The legs were *ca.* 80 mm apart. At the top, perpendicular to the plane of the inverted U, a 14/35 through joint with a 3-mm extension tube was attached. The volatile contents of the tube could be removed by breaking this 3-mm tube with a tube breaker. An accurately weighed amount of 0.3–0.5 g of bis-

(1) A. Stock, "Hydrides of Boron and Silicon," Cornell University Press, Ithaca, N. Y., 1957, p 55.

(2) R. M. Adams, "Boron, Metallo-Boron Compounds and Boranes," Interscience Publishers, Inc., New York, N. Y., 1964, pp 596–603.

(3) H. Steinberg, "Orgaoboron Chemistry," Vol. I, Interscience Publishers, Inc., New York, N. Y., 1964.

(4) H. Cragg, *Quart. Rept. Sulfur Chem.*, **3**, 1 (1968).

(5) R. W. Kirk and R. L. Timms, *Chem. Commun.*, 18 (1967).

(6) B. F. Spielvogel and E. F. Rothgery, *ibid.*, 765 (1966).

(7) D. Vorlander and E. Mittag, *Chem. Ber.*, **46**, 3453 (1913).

(8) T. Nakabayashi, J. Tsurugi, and T. Yabuta, *J. Org. Chem.*, **29**, 1236 (1964).

triphenylmethyl disulfide was put into one arm of the tube along with a glass-covered iron stirrer (*ca.* 10 × 3 mm. The tube was then placed on the vacuum line and evacuated thoroughly. *Ca.* 10 ml of dry benzene was then transferred into this leg by condensation of the vapor with liquid nitrogen. Diborane was measured in the vacuum line and a quantity in excess of an equimolar amount was added. The reaction tube was then opend to the vacuum while keeping the volatiles frozen with liquid nitrogen. The apparatus was then sealed off. The ratio between the volume of the reaction vessel and the amount of the reagents used was chosen so that the diborane pressure at room temperature would fall roughly in the calculated range of 500–700 mm, neglecting solubility or complexing phenomena. On some runs a small amount of solid failed to go into solution. If solution was not effected after 2 days, the residue was assumed to be an impurity and the liquid was carefully decanted to the other arm of the reaction tube. This precipitate when it occurred was a deep red-brown solid which was estimated to be no more than 1 or 2 mg. By the third or fourth day a white precipitate had started to form. After *ca.* 1 week, the reaction mixture was opened and analyzed. With liquid nitrogen cooling the appropriate arm of the reaction tube, the vessel was opened to the line and the hydrogen was tranferred with a Toepler pump and measured. The tube was then allowed to warm, and the benzene solution was decanted from the precipitate to the opposite leg by swinging the apparatus about the 14/35 joint. All the volatiles were then removed to the vacuum line. By distillation through −63.5 and −126° traps, the benzene was separated from the excess diborane. Triphenylmethane was the major benzene-soluble, nonvolatile product.

Hydrogen was identified by mass spectrometry. Diborane was characterized by its infrared spectrum. Triphenylmethane was identified by its melting point, 88–94° (lit. mp 92°), comparisons of its infrared spectrum with that of a known sample, its characteristic behavior in a column chromatogram with alumina and Skelly B, and its characteristic mass spectrum.

Purification and Characterization of $(HBS)_x$.—The insoluble precipitate formed in the reaction was washed as free of triphenylmethane as possible by transferring benzene from the vacuum line, decanting to the other arm, and reevaporating the solvent back to repeat the process. Even after three of these wash operations, the product could not be freed completely from triphenylmethane.

The infrared spectrum of this solid was determined by preparing a KBr pellet in an inert atmosphere. The bands were generally broad (4000–670 cm^{-1}): 3300–3000 (m), 2450 (s), 1350 (s), 1125 (w), and 975 cm^{-1} (s) and a strong band that starts at 750 cm^{-1} and continues off the scale of the instrument.

X-Ray powder diffraction was carried out in a capillary using a Deybe–Scherrer powder camera. Several determinations on products from different runs indicated an amorphous material.

Elemental analysis of a precipitate obtained from the bistriphenylmethyl disulfide reaction gave the following results: C, 15.24: H, 4.92; S, 54.18; B, 18.18 (Calcd: B:S, 1:1. Found: B:S, 0.99:1). The presence of carbon indicates triphenylmethane impurities.

Reaction of Triphenylmethyl Mercaptan with Diborane.—A reaction mixture containing 1.61 mmol of diborane and 1.02 mmol of triphenylmethyl mercaptan in benzene was placed in the apparatus described for the bistriphenylmethyl disulfide reaction. The original yellow color increased in intensity after 2.5 hr. After 4 hr the solution became cloudy but was still quite yellow. *Ca.* 24 hr later the usual copious white precipitate had formed and the solution was colorless. Because of the press of other work, the reaction was not worked up for 20 days. At that time 1.14 mmol of hydrogen were recovered and 0.89 mmol of diborane were collected and identified by its infrared spectrum. Benzene extraction of the solid residue yielded 0.914 mmol of triphenylmethane, which was identified by melting point and infrared spectrum. The infrared spectrum of the $(HBS)_x$ precipitate was identical with that obtained from the bis(triphenylmethyl)disulfide reaction. The $(HBS)_x$ precipitate obtained from a similar reaction gave hydrogen and hydrogen sulfide in a molar ratio of 1:1.18 on hydrolysis. Identification of the gases was by mass spectrometry. Elemental analysis gave the following results: S, 44.85; B, 17.18 (Calcd: B:S, 1:1. Found: B:S, 1.13:1).

Reaction of Hydrogen Sulfide with Diborane.—A reaction was carried out with 0.74 mmol of diborane and 1.03 mmol of hydrogen sulfide in benzene using a reaction apparatus of sufficient volume to give a calculated pressure of 488 mm at 25°, ignoring solubility effects. In 2 days the white precipitate started to form. After 9 days the reaction yielded 2.38 mmol of hydrogen and 0.18 mmol of diborane. The white residue gave the infrared bands for the $(HBS)_x$ polymer. Elemental analysis gave the following results: S, 53.60; B, 23.3 (Calcd: B:S, 1:1. Found: B:S, 1.28:1).

Reaction of Bistriphenylmethyl Tetrasulfide with Diborane.—A reaction of 0.51 mmol of bistriphenylmethyl tetrasulfide with 1.63 mmol of diborane was carried out in a benzene solution under the same conditions as described for the bistriphenylmethyl disulfide reaction. A precipitate formed in *ca.* 2 days, and the original yellow color of the solution changed to colorless in *ca.* 4 days. The volatle fraction consisted of 1.62 mmol of hydrogen and 0.4 mmol of diborane. Triphenylmethane and $(HBS)_x$ were isolated from the residue.

Analytical Methods.—The mass spectral data were obtained for all the solid samples and some of the gases with an AEI MS-12 single-focusing mass spectrometer operated with a nominal resolution of 1000 and an ionizing voltage of 70 eV. Some of the hydrogen and hydrogen sulfide qualitative identifications were determined with an AEI MS-10.

The quantitative analyses of hydrogen, hydrogen sulfide, and diborane were accomplished by standard vacuum-line techniques. Microanalyses of boron and sulfur were carried out by Spang Microanalytical Laboratories, Ann Arbor, Mich.

Nuclear Magnetic Resonance Spectra.—The ^{11}B nmr spectrum, in powdered $(HBS)_x$ was observed at room temperatues using a Varian nuclear induction crossed-coil apparatus. The measurements were carried out at transmitter frequencies of 16 and 22 MHz, corresponding to polarizing fields of *ca.* 11.8 and 16.2 kG. Excellent signal to noise ratios were possible with the high magnetic fields obtainable with a 15-in. Varian electromagnet. The transmitter frequency was crystal controlled while the external field was swept through the resonance value. Quartz sample tubes were used to eliminate the strong background signals arising from boron nuclei in the usual glass sample tubes.

Results and Discussion

The early experiments in unsealed systems indicated a slow reaction, as evidenced by a gradual increase in hydrogen pressure. Triphenylmethane was also separated from these reaction mixtures by column chromatography. This indicated a carbon–sulfur bond cleavage in the early stages of the reaction. The reactions carried out in the sealed reaction tubes indicated, as shown in Table I, a stoichiometry of 1 mol of diborane

TABLE I

Expt no.	Calcd pressure of B_2H_6 at start, mm	Molar ratio,[a] B_2H_6 used to $C_{38}H_{30}S_2$ added	Molar ratio, B_2H_6 used to H_2 collected	Molar ratio, triphenylmethane recovered to $C_{38}H_{30}S_2$ used
G-1	688	1.09:1	1.20:1	
G-4	509	0.77:1	1.50:1	
G-5	465	1.18:1	0.855:1	
G-6	436	1.20:1	0.839:1	
G-9	509	1.14:1	0.934:1	
G-10	507	1.26:1	1.00:1	
G-11	477	1.02:1	1.10:1	1.83:1
G-12	496	1.11:1	1.09:1	1.73:1
G-13	486	1.12:1	1.11:1	1.88:1

[a] The amount of diborane used was determined by subtracting the excess diborane collected from the amount originally used.

reacting with 1 mol of bistriphenylmethyl disulfide to yield 1 mol of hydrogen and 2 mol of triphenylmethane. The insoluble reaction product was characterized as having a hydridic hydrogen and a sulfur atom which could be easily hydrolyzed with water to form hydrogen sulfide. Strangely, hydrolysis with dilute HCl is very slow. The reason for this observation has not been

elucidated. Quantitative studies are summarized in Table II. These determinations pointed to the possibility that the boron–sulfur product reacts with water to produce hydrogen and hydrogen sulfide in a 1:1 molar ratio. The low hydrogen sulfide ratios for the larger samples may be due to incomplete conversion of the sulfur into hydrogen sulfide.

TABLE II

Wt, mg	H_2S, mmol	H_2, mmol	Molar ratio, $H_2:H_2S$
172.6	0.32	0.48	1.5:1
142.8	0.22	0.26	1.2:1
88.3	0.16	0.18	1.1:1

The mass spectra (Table III) were obtained by transferring the sample to the solid probe of the instrument in a nitrogen-filled glove bag. The spectra were usually run with a source temperature of 200–250°. The largest peak in the spectrum was at *m/e* 78, which is the parent peak of the solvent benzene. The *m/e* 44 peak was attributed to the ion HBS^+ and is the largest peak in the spectrum except for the *m/e* 78 peak from benzene and the *m/e* 32, 33 and 34 peaks which correspond to the ions S^+, HS^+, and H_2S^+. The *m/e* 131–132 group is essentially due to $(BSH)_3^+$ with very little contribution from ions where hydrogen has been lost. The other B_3 and B_2 groupings are overlaps of patterns from several ions which differ in number of hydrogens. The significant peaks are summarized in Table III. The normalization is based on *m/e* 44 and includes peaks which are major fragments that cannot be assigned to benzene or hydrogen sulfide. In many cases the boron–sulfur peaks could be distinguished from the carbon peaks by their mass defect, many of the peaks appearing as doublets or triplets. Assignment was also aided by the isotope distribution of the boron-containing peaks.

TABLE III

m/e	Normalized peak height	Isotope distribution patterns	Fragment assignment
133	2.0		
132	10.4	10.4	$(BSH)_3^+$
131	7.8	7.2	$B_3S_3H_2^+$
130	2.6	1.6	$B_3S_3H^+$
129	1.3		$B_3S_3^+$
102	22.1	22.1	$B_3S_2H_5^+$
101	16.9	15	$B_3S_2H_4^+$
100	26.0	3.6 26.0	$B_3S_2H_3^+$
99	24.7	18	$B_3S_2H_2^+$
98	13.0	4.2 24.7	$B_3S_2H^+$
97	6.5	17	$B_3S_2^+$
96	2.6	4	
92	3.9		
91	6.5		
90	2.6		
89	3.9		$B_2S_2H_3^+$
88	28.6	28.6	$(BSH)_2^+$
87	38.4	13.2 38.4	$B_2S_2H^+$
86	24.7	1.5 17.8 24.7	$B_2S_2^+$
85	7.8	2 10.4	
84	0	1.3	
83	3.9		
82	2.6		
77 c[a]	11.6	11.6	$H_2BS_2^+$
76 c[a]	12.7	2.7 12.7	BHS_2^+
75 c[a]	12.6	2.9	BS_2^+
58	2.6		$B_2SH_4^+$
57	23.4	23.4	$B_2SH_3^+$
56	24.7	10.9 24.7	$B_2SH_2^+$
55	23.4	1.2 11.5	B_2SH^+
54	11.7	1.3	B_2S^+
47	5.2		
46	44.9		H_3BS^+
45	87.2		H_2BS^+
44	10.0		HBS^+
43	40.4		BS^+
42	5.8		$^{10}BS^+$
24	2.6		$B_2H_2^+$, C_2^+
23	7.8		$^{11}B_2H^+$
22	14.3		$^{11}B_2^+$
13	9.1		$^{11}BH_2^+$, CH^+
12	7.8		$^{11}BH^+$, $^{10}BH_2^+$, C^+
11	14.3		$^{11}B^+$, $^{10}BH^+$
10	3.9		$^{10}B^+$

[a] Low mass.

These results, along with the elemental analysis of boron and sulfur, led to the identification of the insoluble precipitate as $(HBS)_x$ polymer. This substance had been described by Burg and Wagner[9] as a product obtained from a 137-day gas-phase reaction of hydrogen sulfide and diborane and by Kirk and Timms[5] as a high-temperature reaction product of hydrogen sulfide on boron. The infrared spectrum reported by Kirk and Timms agreed with the infrared spectrum obtained in a KBr pellet on our product except for a weak band at 1125 cm^{-1} and the final band that drops off scale at *ca.* 750 cm^{-1}, which were observed in these studies but were not reported by Kirk and Timms.

On the basis of these experimental results, the reaction was postulated to proceed by an initial Lewis acid–Lewis base adduct of borane to sulfur, the transfer of hydride from the borohydride to triphenylmethyl, and the loss of hydrogen by an internal redox reaction involving a sulfur–sulfur bond cleavage (eq 1). It is

$$Ph_3CSSCPh_3 + B_2H_6 \longrightarrow Ph_3CS(BH_3)SCPh_3(BH_3) \longrightarrow 2Ph_3CH + H_2BSSBH_2 \longrightarrow (HBS)_x + H_2 \quad (1)$$

quite evident that the sulfur–sulfur bond cannot coexist in the same molecule as a boron–hydrogen bond. Because there is still the possibility that the sulfur–sulfur bond may be undergoing cleavage before the carbon–sulfur bond, a similar experiment was carried out with diphenyl disulfide. There appears to be a slow reaction which is as yet uncharacterized, but it is evident that the sulfur–sulfur bond cleavage is not a fast initial step.

On the basis of this mechanism, it was predicted that triphenylmethyl mercaptan would also form the $(HBS)_x$ polymer (eq 2). This was found to be the case.

$$Ph_3CSH + B_2H_6 \longrightarrow Ph_3CSH(BH_3) \longrightarrow Ph_3CSBH_2 + H_2 \longrightarrow Ph_3CH + (HBS)_x \quad (2)$$

A repetition of Burg and Wagner's experiment in our reaction vessel in the presence of benzene indicated that

(9) A. B. Burg and R. I. Wagner, *J. Amer. Chem. Soc.*, **76**, 3307 (1954).

the $(HBS)_x$ polymer could be formed much faster in solution than in the gas phase. The reaction in solution was certainly complete after 9 days. Judging from the appearance of the reaction tube, it may well have been complete after 4 days.

The infrared spectrum of the $(HBS)_x$ polymer from all the reactions was identical. The boron–sulfur elemental analysis was not so satisfying. The results are summarized in Table IV. The high boron content

TABLE IV

Reactant	Expt no.	Boron, %	Sulfur, %	Ratio, boron:sulfur
Bistriphenylmethyl disulfide	G-9	18.18	54.18	0.99:1
Triphenylmethyl mercaptan	G-14	17.18	44.85	1.13:1
Hydrogen sulfide	G-20	23.37	53.60	1.29:1
Bistriphenylmethyl tetrasulfide	G-16	22.60	51.17	1.40:1

very likely reflects loss of hydrogen sulfide by hydrolysis. Boron, forming a nonvolatile boric acid or an intermediate, is not lost to the analysis. The low percentages found for the boron–sulfur analyses of the products obtained from the triphenylmethyl derivatives indicate a triphenylmethane contaminant. This was substantiated not only by the presence of carbon in the sample but also by the triphenylmethane lines in the X-ray powder pattern and the characteristic triphenylmethane peaks in the mass spectrum.

The reaction of diborane with bistriphenylmethyl tetrasulfide has been initiated. Hydrogen, triphenylmethane and $(HBS)_x$ polymer are formed. Preliminary experiments seem to indicate that all the sulfur atoms are converted into $(HBS)_x$, but this remains to be proven.

The $(HBS)_x$ polymer did not give evidence of dissolving in chloroform, benzene, toluene, ether, carbon disulfide, triglyme, or dioxane. The only X-ray powder pattern lines which could be seen were the lines from the triphenylmethane contaminant. After hydrolysis boric acid lines appeared.

Because an appropriate solvent could not be found for high-resolution nmr studies, only the broad-line spectrum of the solid was studied. The ^{11}B nmr spectrum consisted of three lines resulting from the nuclear quadrupole interaction. The nuclear spin of ^{11}B is $^3/_2$ and thus the three-line spectrum is expected from the interaction of the quadrupole moment with electric field gradients which exist in the vicinity of a boron nucleus. The field dependence of the absorption indicated that the two satellite lines were indeed a result of first-order quadrupole interaction and were not a splitting of the central line. A small amount of second-order quadrupole broadening was observed in the central line. In addition it is believed that the central line is a composite line with two components, reflecting boron atoms at two crystallographically inequivalent sites. From the splitting of the satellites the quadrupole coupling constant eqQ was determined to be *ca.* 0.07 MHz.

The ^{11}B nuclear quadrupole interaction is a sensitive internal probe of the electron environment of the boron nucleus. The main contribution to the electric field gradient is expected to arise from incomplete filling of the 2p orbitals. The atomic quadrupole coupling constant for the boron atom has been calculated[10] to be 5.39 MHz from atomic beam experiments. The reduction by a factor of *ca.* 100 of the value of eqQ given in the preceding paragraph compared with the atomic value indicated high symmetry in the structural arrangement of HBS. The small value of eqQ strongly favors tetrahedral coordination as opposed to planar trigonal sp^2 hybrid covalent bonding. The ^{11}B quadrupole coupling constants of trigonal compounds, with few exceptions, have been found to lie in the range of 2.5–2.8 MHz.[11] These results should be compared with the tetrahedral borates, in which eqQ was in the range of 0.05–0.09 MHz.

Another structural possibility that has not been ruled out is that involving a double-bond character, which would also greatly decrease the quadrupole interaction. The mechanism in this case would be that of boron atoms attracting electrons from neighboring atoms into the vacant boron orbitals to form double bonds which exhibit resonance. Further work is being done on the broad-line nmr spectra of boron compounds and will be reported by R. J. Snodgrass at a later date.

Registry No.—Diborane, 19287-45-7; bistriphenylmethyl disulfide, 15446-31-8; triphenylmethyl mercaptan, 33695-77-0; bistriphenylmethyl tetrasulfide, 23264-36-0.

Acknowledgments.—We wish to thank Dr. R. J. Snodgrass for obtaining the broad-line nmr spectra and for discussing the results. For help in obtaining the mass spectra, we wish to thank Dr. S. R. Smith and Mr. Oliver Norton. Assistance of the University of Connecticut Research Foundation is gratefully acknowledged.

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Proton Magnetic Resonance Studies of Rotational Isomerism around the 2-Propyl–Nitrogen Bond in Some Thionamides

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Received July 24, 1969

Slow rotation around the 2-propyl–nitrogen bond in five N,N-di-2-propyl thionamides was studied by proton magnetic resonance (pmr). The barrier (ΔF^*) to this rotation in N,N-di-2-propyl thionacetamide is *ca.* 14 kcal/mol. The pmr signal sets were all assigned to specific rotational isomers and to *cis* and *trans* 2-propyl groups within each isomer.

We have previously reported evidence for slow rotation around the *sec*-alkyl–nitrogen bond in some N,N-di-*sec*-alkyl amides.[1] This evidence was in some cases indirect and in others depended on proton magnetic resonance (pmr) spectra that were necessarily of poor quality because of the complex molecules and low temperatures required to demonstrate the effect. However, when sulfur replaces oxygen, rotation slows around the (thio)carbonyl–nitrogen (amide) bond[2-9] and stiffens the amide framework. The more rigid framework and the larger size of the sulfur atom should work together to increase rotational barriers and to make the effects more readily observable. This paper reports a study of rotation in five N,N-di-2-propyl thionamides, $CH_3C(S)N(2\text{-}Pr)_2$ (I), $PhCH_2C(S)N(2\text{-}Pr)_2$ (II), 2-propyl $C(S)N(2\text{-}Pr)_2$ (III), $CH_3CH_2C(S)N(2\text{-}Pr)_2$ (IV), and cyclohexyl–$C(S)N(2\text{-}Pr)_2$ (V).

Experimental Section

Spectra were obtained at 60 MHz with a Varian A-60 and a Varian HR-60 spectrometer. Decoupling was done by strongly irradiating the methine protons and observing the methyl doublet collapse. Complete decoupling was obtained in all cases. Samples for signal shape analysis were sealed under nitrogen.

The thionamides were prepared in the conventional manner[10] by treating the corresponding amides in boiling xylene with a 100% excess of P_2S_5. Initial purification was obtained by vacuum distillation. Small quantities of unconverted amides usually distilled with the thionamide but were easily removed by crystallization of the distilled product. Methylcyclohexane was the best and most convenient solvent for this purpose. Pure white crystals were obtained, which tended to yellow on standing. Purity and identity were confirmed by pmr and infrared (ir) spectra and by elemental analysis.

Signal Shape Analysis.—Signal shape analyses to provide rotational rate data is complicated for these compounds because of the necessity for treating exchanging multiplets and because two types of rotational processes are involved.[1] However, an approximate treatment was developed and applied to the simplest of the molecules studied, $CH_3C(S)N(2\text{-}Pr)_2$. This treatment is described briefly below.

Signal shape analysis to obtain rotational barriers was based on the Gutowsky–Holm equation.[11] Nakagawa's[12] formulation of this equation was used to calculate spectra for exchanging carbonyl methyl groups [$CH_3C(S)$ singlets]. For exchanging β-methyl groups (CH_3CHCH_3, doublets), the signal shapes for two sets of two exchanging singlets were superimposed. For exchanging methine protons (CH_3CHCH_3, septets), seven sets of two exchanging singlets were superimposed. Calculated spectra were then matched with observed spectra to obtain exchange times. This type of superposition procedure has already been used and reported.[13] Further details of our application of this method here will be reported elsewhere.

Signal shape analysis gave $\Delta F^* = 19$ kcal/mol at 105° for the rotational barrier around the amide bond and 14 kcal/mol at −13° for the barrier to 2-propyl rotation.

Results

Description of the Spectra (See Figure 1). $CH_3C(S)N(2\text{-}Pr)_2$ (I).—At high temperature (>130°), the β-methyl protons give one doublet, the $CH_3C(S)$ protons one singlet, and the methine protons one septet, as would be expected for rapid rotation around all relevant bonds. Below this temperature, the methine signals split into two broad sets of signals of equal intensity. The expected two doublets for β-methyl protons do not at first appear; the splitting into two doublets, very closely spaced, is observable only below 70°. The doublet at higher field is very much broader than the doublet at lower field. With deuteriotoluene as the solvent, separate doublets are observable even at 100°. The near degeneracy of β-methyl signals is removed in this solvent. However, the signals are reversed—the broadened doublet comes to lower field.

As the temperature is lowered below 100°, the high-field methine set sharpens and can be resolved into the expected septet. On the other hand, the low-field methine set broadens at first as the temperature is lowered. A sharp septet is not obtained until *ca.* −20°. At this point, the high-field methine signals obviously consist of *two* or more septets. The high-field set of signals is more intense than the low-field septet (*ca.* 1.6:1).

Below room temperature, the β-methyl doublets broaden but finally emerge as four doublets at −20° with intensity 3:1:3:1 (high field → low field) for $CDCl_3$, 1.5:1:1.5:1 for C_7D_8; 1.3:1:1.3:1 for CH_3OH; and 1.4:1:1.4:1 for deuterioacetone. At the same temperature the signal for $CH_3C(S)$ splits into two signals of the same ratios for the respective solvents.

No further changes in any signals were observed down to −80°, the lowest temperature obtainable without precipitation in a 50:50 mixture of $CDCl_3$–$CFCl_3$ (except for some preferential broadening of the doublet of triple intensity at higher field).

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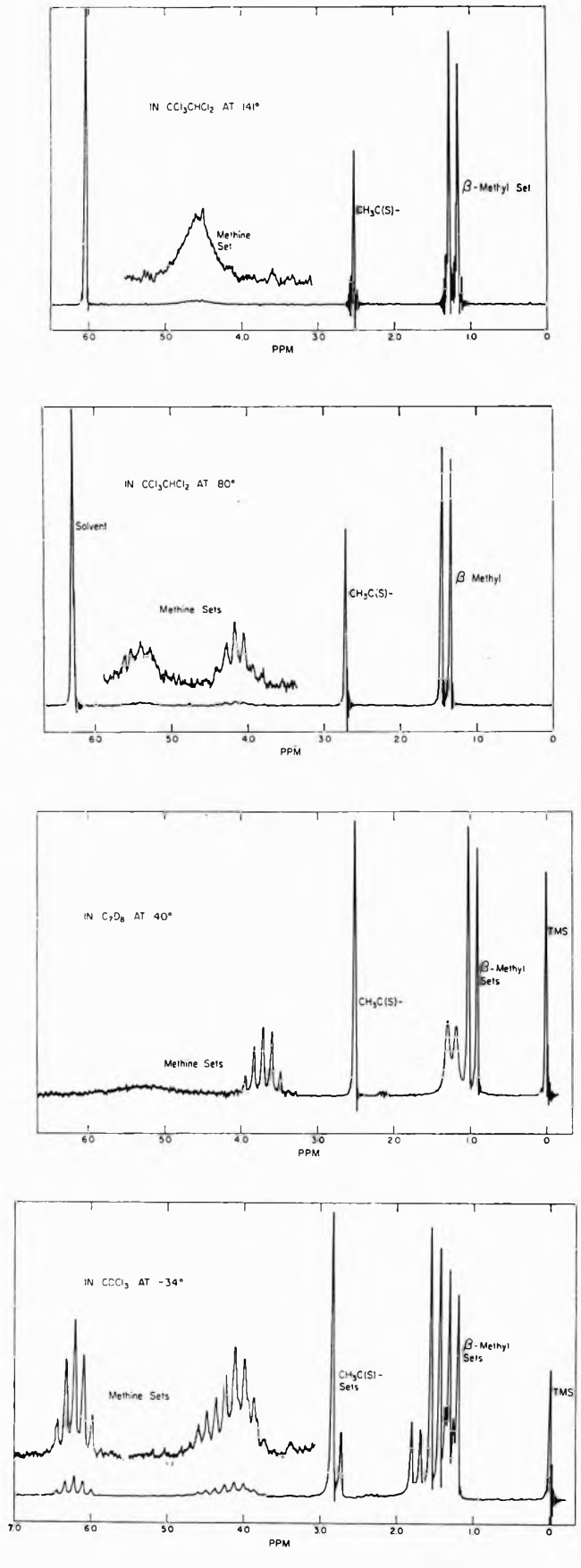

Figure 1.—The pmr spectra of $CH_3C(S)N(2\text{-}Pr)_2$.

We interpret the changes on coming down to *ca.* 80° as being due to the slowing of rotation around the thiocarbonyl–nitrogen (amide) bond (except for the selective broadening of one doublet). The barrier, 19 kcal/mol, is normal for rotation around this bond. Corresponding changes take place in N,N-di-2-propyl acetamide, but at *ca.* 70° lower temperature. An increase of 2–6 kcal in the barrier to rotation around the amide bond is to be expected in going from the amide to the thionamide.

We interpret the further sequence of changes on down to *ca.* −20° as the slowing of rotation around the 2-propyl–nitrogen bonds. Two rotational isomers exist on the pmr time scale. Each isomer is a separate and distinct molecule with a complete set of signals. These sets are assigned to the isomers in Table I. One isomer (major isomer) is about three times as abundant as the other (minor) in $CDCl_3$, 1.4:1 in $CD_3C(O)CD_3$, 1.3:1 in CH_3COH, and *ca.* 1.5:1 in toluene. Either one of these apparent isomers represents the average of two rapidly interchanging isomers, or one of the three expected isomers is missing.[1]

A few spectra of $CH_3CH_2C(S)N(2\text{-}Pr)_2$ (IV) were also obtained. These closely paralleled those for I. An isomer ratio of 3:1 was obtained at low temperature in $CDCl_3$. The degeneracy of the β-methyl doublets at higher temperature was also observed. Because of this close parallel, IV was not investigated further.

$PhCH_2C(S)N(2\text{-}Pr)_2$ (II).—The change of the pmr spectrum of this compound with temperature closely resembles that of the acetamide (I). The β-methyl doublets, however, are well separated at all temperatures. This, in part, may reflect the effect of the anisotropic field of the benzene ring. The chief difference between the compounds is that the isomer abundance apparently is reversed. The isomer with methine signals at low field is now the minor isomer with only one third the abundance of the major isomer in $CDCl_3$.

2-PrC(S)N(2-Pr)$_2$ (III).—This compound exhibits the spectra characteristic of slow, intermediate, and rapid rotation around the amide bond. No signals are obtained that could be ascribed to rotational isomerism. However, the low-field methine signal set is selectively broadened over a wide temperature range (−10 to 70°) in a manner reminiscent of the oxygen analog at lower temperature. The high-field set is sharp throughout this range and downward. This behavior suggests that one isomer (with low-field methine) predominates highly at low temperature, but that a small amount of a second isomer is present in the region of intermediate exchange at higher temperature.

Almost precisely the same behavior was obtained in preliminary work with cyclohexyl–C(S)N(2-Pr)$_2$ (V). For that reason V was not investigated in further detail.

Decoupling Experiments.—In both the major and minor isomers of I, the low-field methine proton was coupled to the high-field methyl group. The same results were obtained in $CDCl_3$ and in C_7D_8. The same coupling behavior, low methine to high methyl, was observed for II and III.

Discussion

The behavior of these thionamides can be rationalized within the framework of hypotheses utilized to explain the behavior of related amides.[1] The symbolism of the previous study[1] is repeated here to aid in the discussion.

This symbolism can be visualized with the aid of Figure 2. It is assumed that the angle θ for the methine

TABLE I

PROTON SIGNALS[a] AT −20°

Compd[b]	Solvent	β-Methyl		Methine		R-C(S)-	
		Minor	Major	Minor	Major	Minor	Major
$CH_3C(S)N(2\text{-}Pr)_2$	$CDCl_3$	1.32, 1.76[c]	1.27,[c] 1.52	~4.0,[c] 4.36	4.12, 6.21[c]	2.76	2.84
	$C_6D_5CD_3$	0.73, 1.68[c]	0.85,[c] 0.90	~3.4,[c] 3.80	3.39, 6.32[c]	2.40	2.53
	CH_3OH	1.27, 1.67	1.20, 1.43	Overlap	~4.1, 6.12	2.63	2.72
	$CD_3C(O)CD_3$	1.30, 1.70	1.18, 1.47	~4.0, 4.53	4.12, 6.19	2.65	2.73
$PhCH_2C(S)N(2\text{-}Pr)_2$	$CDCl_3$	1.32,[c] 1.46	0.95, 1.76[c]	6.2[c]	3.83,[c] 4.3	4.37 (CH_2); only one signal; 7.34 (complex) (aromatic)	
	70% C_7D_8–30% $CDCl_3$	1.07,[c] 1.11	0.59, 1.70[c]	3.53, 6.3[c]	3.37,[c] 4.06	4.24 (CH_2); only one signal; 7.2 (complex) (aromatic)	
$2\text{-}PrC(S)N(2\text{-}Pr)_2$	$CDCl_3$	*d*	1.23,[c] 1.50		4.10, 6.32[c]	3.37 (methine)	1.33 (β-methyl)
	$C_6D_5CD_3$		0.88,[c] 1.08		3.48, 6.42[c]	3.07	1.33

[a] In parts per million from tetramethylsilane. [b] 100 mg + 0.5 ml of solvent. [c] Assigned *cis* to sulfur. [d] No observable minor sets for this compound.

proton of a 2-propyl group (a tetrahedron) may assume multiples of 60° with respect to the amide frame (a trigonal plane on the pmr time scale) to produce minima of rotational energy. Since six such minima exist for each 2-propyl group, there are 36 combinations or conformations. These can be symbolized as C_iT_j, where the index 1 corresponds to $\theta = 30°$, 2 to $\theta = 90°$, etc., C represents the 2-propyl group *cis* to sulfur and T, *trans* to sulfur. However, six of these conformations (where $j = i + 3$) ought to have lower energy than the rest; these six minimize the repulsion between β-methyl groups. Figure 2 represents one of these conformations.

The six isomers exist as three *dl* pairs: C_1T_4, C_6T_3; C_2T_5, C_5T_2; and C_3T_6, C_4T_1. The spectrometer does not respond to the *dl* distinction within a pair. A maximum of three complete signal sets are to be expected. However, since these isomers are asymmetric molecules, the β-methyl groups within a 2-propyl radical are nonequivalent and could give separate signals, provided that interconversion of *d* and *l* forms (racemization) is slow on the pmr time scale. Similar nonequivalence would be expected for all other geminal pairs or other appropriate arrays.[14]

All transitions between the six isomers are accomplished *via* synchronous (or immediately sequential) rotation of 2-propyl groups. Rotation of one 2-propyl group at a time produces one of the 30 remaining high-energy conformations ($j \neq i + 3$). Of these 30 the conformation(s) that is appropriate might serve as the transition state between the favored six isomers, the C_iT_j with $j = i + 3$. Rotation into a transition state does not of itself complete an isomer (or proton site) interchange, but must be followed by rotation of the other group.

Signal Assignments for I (See Table I).—The C_1T_4, C_6T_3 *dl* pair is responsible for the low-field methine signal. The *cis* methine proton for this pair is close to the thiocarbonyl group and therefore deep into the magnetic field that surrounds the amide frame. The average value of θ_C in this pair (see Figure 2) may be smaller than 30° because the methine proton is smaller than the β-methyl groups. This places the methine protons near the amide plane. Positions both near to the amide plane and near to the (thio)carbonyl group

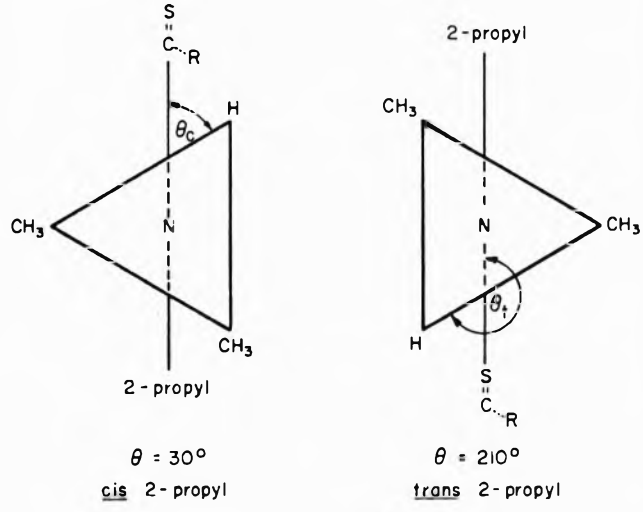

Figure 2.—Conformation C_1T_4.

are known to be very much deshielded.[15–20] The *trans* methine proton, while near the amide plane, is turned away from and is remote from the amide field, and resonates at higher field.

In the solvent toluene, the high-field methine signal of the major isomer is shifted 0.7 ppm upfield from its position in $CDCl_3$, but the low-field methine signal is shifted downfield by 0.11 ppm. This behavior is consistent with the assignment of the high-field methine signal to the *trans* methine proton.[21]

From the decoupling experiments, the high-field major doublet (in $CDCl_3$) is assigned to the β-methyl protons of the *cis* 2-propyl group of the major isomer. This doublet is shifted upfield in toluene, but not so much so as the other (*trans*) doublet. This, too, is consistent with the assignment.[21]

For the minor isomer, the low-field β-methyl doublet is assigned *cis*. This doublet shows the smallest shift

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(almost no shift) of the four doublets. This would be expected for the *cis* β-methyl groups of the C_3T_6, C_4T_1 *dl* pair. For this pair the *cis* β-methyl groups are very close to the sulfur atom and therefore not affected by solvent.

From the decoupling experiments the high-field minor methine signals are assigned *cis*. This methine proton is close to the amide plane, but remote (in the C_3T_6, C_4T_1 pair) from the amide field, while the *trans* methine proton is deeper in this field. The *trans* signal is, therefore, found downfield. This signal also has the larger solvent shift of the two minor methine signals.

There is one apparent contradiction in these assignments. They require that methine protons close to sulfur have downfield shifts relative to methine protons remote to sulfur, but that β-methyl signals be upfield for β-methyl groups near to sulfur. We believe that this contradiction is not real and that it can be explained on the basis of whether the proton(s) in question is rotated nearly into the amide plane or well out of this plane. The amide field is deshielding in and near to the amide plane but shielding out of plane.[15-20]

As pointed out, for all of the C_1T_4, C_6T_3, C_4T_1, C_3T_6 isomers and for both *cis* and *trans* positions, the methine protons probably lie close to the amide plane—closer than 30°. The minimum energy for all these isomers requires a distortion from rigid 60° intervals. Such a distortion places the methine protons, with their much smaller bulk, near the amide plane and the methyl groups as much out of this plane as possible. *A major factor in setting any amide conformation must be the need to exclude as much as possible from this crowded plane.*

Our assignments also ignore the C_2T_5, C_5T_2 *dl* pair. We have in our discussion so far proceeded as though this isomer did not exist in significant abundance. Actually, the two signal sets could be assigned in any of several ways: (A) major (1)–minor (3); (B) major (1)–minor (2); or (C) any of a family of combinations of major (1 + 2 or 3)–minor (2 or 3) (the numbers designate the *dl* pair according to the lower C index occurring in the pair, *i.e.*, C_1T_4, C_6T_3 = 1). The only straightforward and certain requirement is that 1 make the major contribution to the major signal set. We have chosen to exclude B, since the barrier between the *d* and *l* isomers within the pair 2 ought to be exceptionally large. Racemization within this pair would involve a maximum transfer of β-methyl groups across the amide plane. However, there is no direct evidence for such a slow racemization. For 1 and 2 pairs only, one methyl group at a time needs to be transferred across the plane, and racemization might be fast, as is observed. Also the effects of toluene seem to exclude B. There is no obvious argument to exclude C; C might very well have been included in our discussion, but was not, since its inclusion would not alter the substance of the discussion substantially but would certainly complicate it.

Assignment for II.—The low-field methine signal set is assigned to the *cis* methine proton C_1T_4, C_6T_3 by the same arguments as for I. Since the high-field minor doublet is coupled to this methine, it too must be assigned *cis* in this *dl* pair. The rest of the assignments are also the same as for I from the decoupling experiments and the effects of toluene. No separate minor CH_2 signal is observed.

Assignment for III.—There is only one signal set for this compound and therefore either only one rotational isomer (1 = C_1T_4, C_6T_3) or a rapidly exchanging mixture of 1 + 2 or 3 that is dominated by 1. The selective signal broadening of the low-field methine signal suggests that there is a mixture at high temperature that approaches pure 1 at low temperature.

This picture is, of course, too simple, since now there is a third 2-propyl group and therefore good reason to believe that a triple designation—$C_iT_jS_k$—is required, where S designates the 2-propyl group that is attached to the thiocarbonyl group. The resulting array of 216 possible isomers leads to all sorts of possible complications.

However, one consideration may still limit the real situation to the original six likely ground states. If the 2-propyl groups are indeed so much interacting as to be interlocked, then specification of the rotational state of one group sets the conformation of the other two; thus C_1 requires T_4 and S_1. The sulfur atom may be regarded as the spatial buffer that prevents direct interaction of C (2-propyl) with S (2-propyl).

The close correspondence of chemical shifts for III with the major isomer of I suggests that the dominant isomer of III is C_1T_4, C_6T_3 for the N-2-propyl groups. Subject to the consideration of the paragraph immediately above, the full designation must be $C_1T_4S_1$, $C_6T_3S_6$.

Future Work.—Further experimental work is required to adequately test this model of interlocking tetrahedral rotors rotating against a trigonal frame. In particular, it would be desirable to improve isomer signal assignments to establish whether mixtures of isomers or a single isomer produced observed signals.

We have also not attempted to deal with the question of relative isomer abundance. There are observable differences in these abundances, and plausible explanations, but we have not yet enough data to construct a systematics or a theory to predict such abundances.

Registry No.—I, 23264-07-5; II, 23264-08-6; III, 23264-09-7.

Acknowledgments.—We are indebted to J. E. Conner for experimental assistance and for operating and maintaining the A-60 spectrometer. The information contained in this article was developed during the course of work under Contract AT(07-2)-1 with the U. S. Atomic Energy Commission.

Eliminations from 2-Butyl Halides Induced by Halide Ions in Dimethylformamide and Dimethyl Sulfoxide

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Received August 12, 1969

Olefinic products from reactions of 2-butyl halides with lithium halides and tetraalkylammonium fluorides in dimethylformamide and dimethyl sulfoxide are reported. For the iodide, bromide, and chloride ion induced eliminations, overwhelming Saytzeff orientation, high *trans*-:*cis*-2-butene ratios, and low olefin yields are observed. Tetra-*n*-butylammonium fluoride is shown to be an effective agent for dehydrohalogenation of 2-butyl iodide and bromide under mild conditions. In fluoride ion promoted eliminations, the percentage of 1-butene is dependent upon the halogen leaving group of the 2-butyl halide, increasing in the order iodide < bromide < chloride. The effects of the nature of the halide ion base and the halogen leaving group upon orientation are discussed.

Recent investigations of positional and geometrical orientation[1] in base-catalyzed dehydrohalogenations from 2-halo alkanes have given considerable insight into the nature of the olefin-forming transition states.[2] Although a number of base–solvent systems have been employed, no information is available concerning halide ion-promoted β eliminations from 2-alkyl halides. We report a study of, orientation in and synthetic utility of, eliminations from 2-butyl halides induced by halide ions in dimethylformamide and dimethyl sulfoxide with special emphasis upon the relatively unexplored fluoride ion bases.

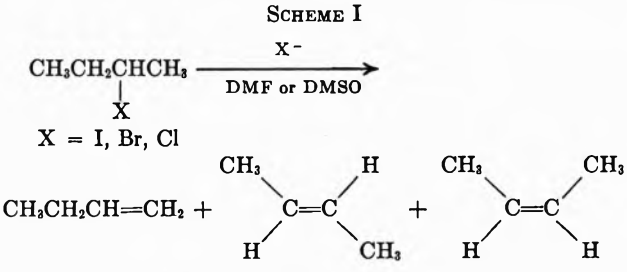
Dehydrohalogenations induced by halide ions in dipolar aprotic solvents have been reported for cyclohexyl halides,[3] tertiary alkyl halides,[3b,4] α-halocyclohexanone[5] and cyclopentanone[6] derivatives, β-phenethyl bromide,[7] and *t*-amyl bromide.[3b]

Results

Using gas–liquid partition chromatography (glpc), the relative proportions of the three isomeric olefins formed in reactions of 2-butyl iodide, bromide, and chloride with halide ions in dimethylformamide and dimethyl sulfoxide have been measured (Scheme I). In several cases, the yields of butenes were determined by a standard bromimetric method.

Reactions of 2-Butyl Halides with Lithium Halides.—The relative amounts of isomeric olefins and olefin yields found in reactions of 2-butyl halides with lithium halides in dimethylformamide and dimethyl sulfoxide at 50° are listed in Table I. The absence of entries for other 2-butyl halides and lithium halides denotes insufficient elimination. For the reported reactions a negligible contribution from E1 processes was demonstrated.

SCHEME I



Comparison of the relative olefinic proportions obtained from reactions in dimethylformamide and in dimethyl sulfoxide reveals little change in the per cent of 1-butene. However, consistently lower *trans*-:*cis*-2-butene ratios are observed in dimethyl sulfoxide. Similar variations have been reported for reactions of 2-butyl bromide with potassium *t*-butoxide in dimethylformamide and dimethyl sulfoxide.[2a]

The relative amounts of isomeric butenes obtained from reactions of lithium chloride with 2-butyl iodide in dimethylformamide were unaffected by small amounts (2%) of water in the solvent. However, a solvent mixture of 90% dimethylformamide–10% water produced noticeable change.

The per cent of 1-butene from a given 2-butyl halide is much larger with lithium fluoride than with the other lithium halides. For the chloride-, bromide-, and iodide-promoted eliminations from a given substrate, the per cent of 1-butene is constant within experimental error. The overwhelming Saytzeff orientation observed in reactions of 2-butyl iodide with lithium chloride, bromide, and iodide is the most complete favoring of internal olefin formation reported for an E2 reaction of a 2-substituted alkane.[8]

In all cases the *trans*-:*cis*-2-butene ratios are very high and are similar to those observed in eliminations from 2-butyl bromide induced by alkoxide ions in dimethylformamide and dimethyl sulfoxide.[2a,f]

The synthetic utility of these reactions is severely limited by the low olefin yields. Longer reaction times produced no yield enhancement.

Reactions of 2-Butyl Halides with Tetraalkylammonium Fluorides.—Table II lists the relative amounts

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

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(8) Reference 3b reports that the olefin mixture produced from reaction of *t*-amyl bromide with tetra-*n*-butylammonium chloride in acetone is 99.9% Saytzeff product, 3-methyl-2-butene.

TABLE I

OLEFINIC PRODUCTS FROM REACTIONS OF 2-BUTYL HALIDES[a] WITH LITHIUM HALIDES IN DMF AND DMSO AT 50.2°

X of 2-BuX	LiX	Solvent	Total butenes, yield, %	Per cent of total butenes: 1-Butene	*trans*-2-Butene	*cis*-2-Butene	*trans*-2-Butene: *cis*-2-butene
I	LiF[b,c]	DMF	2.0[d]	18.9 ± 0.3[e]	63.1 ± 0.3	18.0 ± 0.2	3.51 ± 0.03
	LiF[c]	DMSO	*f*	19.4 ± 0.2	61.5 ± 0.5	19.1 ± 0.3	3.23 ± 0.08
	LiCl[b,g]	DMF	7.9[d]	2.4 ± 0.1	78.0 ± 0.4	19.6 ± 0.4	3.95 ± 0.12
	LiCl[b,g]	DMF[h]	*f*	2.4 ± 0.1	77.9 ± 0.6	19.7 ± 0.7	3.95 ± 0.17
	LiCl[b,g]	DMF[i]	*f*	2.2 ± 0.1	75.6 ± 0.1	22.2 ± 0.1	3.40 ± 0.01
	LiCl[g]	DMSO	*f*	2.6 ± 0.1	75.8 ± 0.3	21.7 ± 0.3	3.50 ± 0.07
	LiBr[b,g]	DMF	*f*	2.1 ± 0.1	77.6 ± 0.4	20.3 ± 0.5	3.83 ± 0.11
	LiBr[g]	DMSO	*f*	3.3 ± 0.1	74.4 ± 0.4	22.3 ± 0.4	3.33 ± 0.07
	LiI[b,g]	DMF	*f*	1.5 ± 0.1	76.8 ± 0.4	21.6 ± 0.4	3.55 ± 0.09
	LiI[g]	DMSO	*f*	2.2	75.2	22.6	3.33
Br	LiF[c]	DMF	*f*	29.3 ± 0.3	55.0 ± 0.5	15.7 ± 0.4	3.50 ± 0.12
	LiF[c]	DMSO	*f*	29.5 ± 0.3	54.2 ± 0.4	16.3 ± 0.2	3.32 ± 0.06
	LiCl[g]	DMF	*f*	9.8 ± 0.1	70.1 ± 0.3	20.1 ± 0.3	3.48 ± 0.10
Cl	LiF[b,c]	DMF	*f*	39.8 ± 0.2	47.6 ± 0.3	12.6 ± 0.2	3.79 ± 0.05
	LiF[c]	DMSO	*f*	40.8 ± 0.2	45.6 ± 0.2	13.6 ± 0.1	3.36 ± 0.05

[a] [RX] = 0.3–0.4 *M*. [b] Two runs. [c] Saturated solution. [d] Reaction time, 10 min. [e] Standard deviation. [f] Yield not determined. [g] 1.0 *M*. [h] 98% DMF–2% H_2O. [i] 90% DMF–10% H_2O.

TABLE II

OLEFINIC PRODUCTS FROM REACTIONS OF 2-BUTYL HALIDES[a] WITH TETRAALKYLAMMONIUM FLUORIDES IN DMF AT 50.2°

X of 2-BuX	R of R_4NF	Total butenes, yield, %	Per cent of total butenes: 1-Butene	*trans*-2-Butene	*cis*-2-Butene	*trans*-2-Butene: *cis*-2-butene
I	Me[b]	9.5[c]	9.5 ± 0.1	71.1 ± 0.3	19.4 ± 0.2	3.66 ± 0.06
	n-Bu[d,e]	77[c]	10.6 ± 0.2	69.6 ± 0.3	19.7 ± 0.2	3.53 ± 0.06
	n-Bu[d,f]	*g*	7.6 ± 0.1	72.8 ± 0.3	19.6 ± 0.2	3.73 ± 0.06
Br	Me[b]	*g*	15.5 ± 0.1	66.5 ± 0.2	18.0 ± 0.2	3.68 ± 0.06
	n-Bu[d]	37[c]	16.7 ± 0.1	64.5 ± 0.4	18.7 ± 0.5	3.45 ± 0.11
Cl	Me[b]	*g*	22.1 ± 0.1	61.3 ± 0.4	16.6 ± 0.2	3.72 ± 0.08
	n-Bu[d]	2.0[c]	22.5 ± 0.1	61.1 ± 0.1	16.4 ± 0.1	3.76 ± 0.04

[a] [RX] = 0.3–0.4 *M*. [b] Saturated solution. [c] Reaction time, 10 min. [d] [R_4NF] = 0.7 *M*. [e] Three runs. [f] 90% DMF–10% H_2O. [g] Yield not determined.

of isomeric olefins and olefin yields observed in reactions of 2-butyl halides with tetramethylammonium and tetra-*n*-butylammonium fluorides in dimethylformamide. A control experiment demonstrated the absence of fluoride ion-catalyzed elimination of tetra-*n*-butylammonium fluoride under the reaction conditions.

Comparison of eliminations using lithium fluoride (Table I) with reactions employing the tetraalkylammonium fluorides (Table II) shows that the *trans*-:*cis*-2-butene ratios are independent of the nature of the cation and are nearly the same for the three 2-butyl halides, whereas, for a given 2-butyl halide, the per cent of 1-butene is influenced by the identity of the cation, decreasing in the order lithium > tetra-*n*-butylammonium ≈ tetramethylammonium.

Tetra-*n*-butylammonium fluoride produces reasonable yields of butenes from 2-butyl iodide and bromide under mild reaction conditions.

Discussion

Halide ions in dipolar aprotic solvents are relatively strong bases as well as powerful nucleophiles. In addition, dimethylformamide and dimethyl sulfoxide act as proton acceptors and formation of hydrogen-bonded species such as $(DMF)_2H^+$ and (DMF)HX in dimethylformamide deactivates the proton for back addition to olefinic products.[9]

Eliminations Induced by Chloride, Bromide, and Iodide Ions.—The synthetic use of lithium chloride, bromide, and iodide as dehydrohalogenating agents for 2-butyl halides is precluded by poor olefin yields, resulting from low reactivity and facile substitution reactions.

In E2 reactions of 2-substituted alkanes, the per cent of 1-alkene reflects the relative amounts of C–H and C–X bond rupture in the elimination transition states.[2f,10] The greater the per cent of 1-alkene, the greater is the ratio of C–H to C–X bond cleavage. In the chloride-, bromide-, and iodide-induced eliminations from 2-butyl iodide and bromide, the per cent of 1-butene is very low. Thus, transition states with high degrees of C–X bond scission, but nearly intact C–H bonds (*i.e.*, "paenecarbonium" type[2c]), are indicated. This postulation is consistent with the relatively weak halide ion bases and the good halogen leaving groups involved.

In base-catalyzed eliminations from 2-substituted alkanes, *trans*-:*cis*-2-alkene ratios denote the extent of double-bond formation in the internal olefin transition states.[2b,f,h] The greater the degree of double-bond character, the greater is the eclipsing of *cis*-destined alkyl groups, resulting in a higher *trans*-:*cis*-2-alkene ratio. A paenecarbonium transition state possesses only slight carbon–carbon double-bond character. Therefore, judging from the low per cent of 1-butene observed in reactions of 2-butyl iodide and bromide

(9) A. J. Parker, *Quart. Rev.* (London), **16**, 163 (1962).

(10) J. F. Bunnett, *Angew. Chem., Int. Ed. Engl.*, **1**, 225 (1962).

with lithium chloride, bromide, and iodide, low[11] *trans*-:*cis*-2-alkene ratios would be predicted. It is immediately apparent that this is not the case for the *trans*-:*cis*-2-alkene ratios are very high (3.40–3.95). These values surpass reported high ratios observed in reactions of 2-butyl bromide with potassium *t*-butoxide in dimethylformamide and dimethyl sulfoxide[2a,f] and are the highest known for base-catalyzed β elimination from a 2-substituted butane at 50°.

The *trans*-:*cis*-2-butene ratios closely approach a value of 4.0, extrapolated from the gas-phase pyrolysis of 2-butyl acetate at 450° (a known *syn* elimination process).[12] However, a *syn* elimination seems unlikely in view of the *anti* elimination stereochemistry observed in fluoride ion promoted elimination from *erythro*-3-deuterio-2-bromobutane in dimethylformamide[13] and in other halide ion induced eliminations.[3b,6]

The present results necessitate further consideration of the factors affecting *trans*-:*cis*-2-alkene ratios in eliminations from 2-substituted alkanes. A conceivable explanation of the observed *trans*-:*cis*-2-butene ratios is that eclipsing of alkyl groups may also be important in paenecarbonium transition states. Although such transition states have little double-bond character, the high degree of C–X bond rupture results in nearly trigonal α-carbon atoms. Thus, in transition states for formation of *cis*-2-butene, the *cis*-destined methyl groups are closer together than in the ground states and steric repulsions could occur. Comparable steric interactions are absent in transition states leading to *trans*-2-butene.

Eliminations Induced by Fluoride Ions.—In spite of the current interest in dehydrohalogenations promoted by halide ions, there are very few reports of the use of fluoride ion bases.[7] As shown in Table II, useful amounts of elimination are produced from reactions of 2-butyl iodide and bromide with tetra-*n*-butylammonium fluoride under mild reaction conditions. The lower reactivities of tetramethylammonium fluoride and especially lithium fluoride are probably due to limited solubility.

With all three fluoride ion bases, the per cent of 1-butene increases as the leaving group becomes poorer (*i.e.*, I < Br < Cl) in accord with the predictions of the variable E2 transition state theory.[10] Like trends and similar interpretations may be found in alkoxide ion promoted eliminations.[2b–d,h] The effect of the leaving group upon positional orientation in eliminations from 2-substituted alkanes has previously been demonstrated only with bases having oxygen as the first atom.

(11) E1 reactions of 2-butyl bromide exhibit *trans*-:*cis*-2-butene ratios near unity: W. B. Smith and W. H. Watson, Jr., *J. Amer. Chem. Soc.*, **84**, 3174 (1962).

(12) C. H. DePuy, C. A. Bishop, and C. N. Goeders, *ibid.*, **83**, 2151 (1961).

(13) P. A. Bartsch, *Tetrahedron Lett.*, 297 (1970).

The influence of the cation upon the per cent of 1-butene is not a steric effect since, in dimethylformamide, solvated alkali metal and tetraalkylammonium ions are of similar size.[9] Attempts to prepare anhydrous tetra-*n*-butylammonium fluoride have been unsuccessful; therefore both tetraalkylammonium fluorides are hydrates. A small amount of water in the reaction solvent would reduce the reactivity of the fluoride ion by specific hydrogen-bonding solvation. The water-solvated fluoride ion would be a weaker base and a lower per cent of 1-butene would be anticipated.[14] In support of this proposal is a further reduction of the per cent of 1-butene in the reaction of 2-butyl iodide with tetra-*n*-butylammonium fluoride in 90% DMF–10% H_2O.

An *anti* elimination stereochemistry has been demonstrated in reactions of *erythro*-3-deuterio-2-bromobutane with tetra-*n*-butylammonium fluoride in dimethylformamide.[13]

Experimental Section

Reagents.—Anhydrous dimethylformamide (Baker, reagent) was used directly from freshly opened bottles. Dimethyl sulfoxide was purified as before.[2d] Anhydrous lithium fluoride (Alfa Inorganics), anhydrous lithium chloride (Baker, reagent), anhydrous lithium bromide (Mallinkrodt, reagent), lithium iodide monohydrate (Alfa Inorganics), and tetramethylammonium fluoride trihydrate (Eastman) were used directly. Tetra-*n*-butylammonium fluoride hydrate was prepared according to Mohr, Wilk, and Barrow.[15] Commercially available 2-butyl halides (Eastman, Halogen Chemicals) were distilled and shown to be homogeneous by glpc.

Elimination Products from Reactions of 2-Butyl Halides with Halide Ions in Dimethylformamide and Dimethyl Sulfoxide.—Except for the modification of preparing the base–solvent solution directly in the reaction vessel, the previously described[2a] apparatus, procedure, and glpc analysis of olefinic products was employed. A 10-min reaction period was used throughout.

For measurement of olefin yields, 5.0 ml of chloroform was added to the olefins collected in the cold trap. The chloroform solution was treated with an excess of 0.1 *M* bromine in acetic acid and the amount of unreacted bromine was determined in the usual manner.

Control Experiments.—Negligible amounts of butenes (determined by glpc) were formed in reactions of 0.3 *M* 2-butyl iodide with dimethylformamide or of 0.3 *M* 2-butyl iodide with 1.0 *M* lithium perchlorate in dimethylformamide for 10 min at 50°. No butenes could be detected in the reaction of 0.7 *M* tetra-*n*-butylammonium fluoride with dimethylformamide for 15 min at 50°.

Registry No.—2-BuI, 513-48-2; 2-BuBr, 78-76-2; 2-BuCl, 78-86-4; LiF, 7789-24-4; LiCl, 7447-41-8; LiBr, 7550-35-8; LiI, 10377-51-2; Me_4NF, 373-68-2; n-Bu_4NF, 429-41-4; dimethylformamide, 68-12-2; dimethyl sulfoxide, 67-68-5.

(14) D. H. Froemsdorf and M. D. Robbins, *J. Amer. Chem. Soc.*, **89**, 1737 (1967).

(15) S. C. Mohr, W. D. Wilk, and G. M. Barrow, *ibid.*, **87**, 3048 (1965).

Reactions of 2-Acyl-1,3-indandiones with Aliphatic Diamines

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Received August 6, 1969

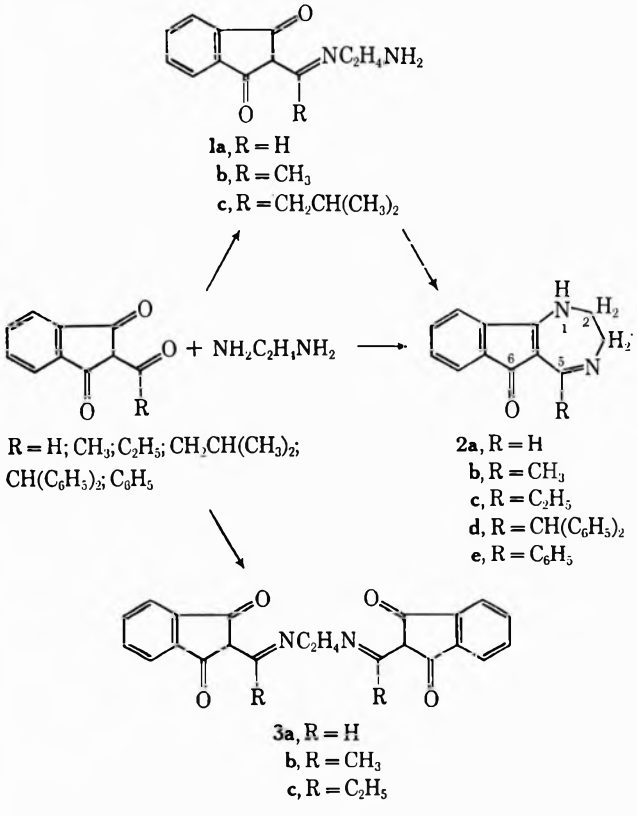
Depending upon the conditions, reaction of 2-acyl-1,3-indandiones with ethylenediamine gave 2[1-(2-aminoethylimino)alkyl]-1,3-indandiones (**1**), 2,3-dihydro-6H-indeno[1,2-*e*][1,4]diazepin-6-ones (**2**), or 2,2′-[ethylenebis(nitriloalkylidyne)]di-1,3-indandiones (**3**). The condensation with methylenediamine was unsuccessful.

Previous papers from this laboratory have reported the reactions of 2-acyl-1,3-indandiones with hydrazines to give monohydrazones[1] and indeno[1,2-*c*]pyrazol-4(1H)-ones.[2] We now report the reactions of 2-acyl-1,3-indandiones with aliphatic diamines.

The condensation of ethylenediamine with open-chain β diketones has been reported to give (a) noncyclized compounds, such as 4,4′-ethylenediiminodipentanone, with acetylacetone,[3] or (b) 2,3-dihydro-1,4-diazepines,[4] depending upon the molar ratio of the reactants.

We have found that treatment of 2-acyl-1,3-indandiones with ethylenediamine yielded three types of products depending upon the nature of the substituents in the side chain of the indandiones and the molar ratio of the reactants (Scheme I).

SCHEME I



Addition of 2-acyl-1,3-indandiones (1 mol) to a refluxing ethanolic solution of ethylenediamine (1.5 mol, except in the case of compound **1a**, where *ca.* 4 mol were used), in the presence of formic acid gave 2-[1-(2-aminoethylimino)alkyl]-1,3-indandiones (**1a–1c**) when R is hydrogen, methyl, or isobutyl, and 5-substituted 2,3-dihydro-6H-indeno[1,2-*e*][1,4]diazepin-6-ones (**2c–2e**), when R is ethyl, diphenylmethyl, or phenyl. The diazepinones **2a** (R = H) and **2b** (R = CH_3) were obtained by heating the corresponding indandiones (**1a** or **1b**), the former in the presence of formic acid and *n*-propanol, the latter in the dry state. Indandione **1c** could not be ring closed to the corresponding diazepinone.

Reverse addition of the reactants and change in molar ratio of ethylenediamine (1.2 mol) to 2-acyl-1,3-indandiones (2 mol) gave 2,2′-[ethylenebis(nitriloalkylidyne)]di-1,3-indandiones (**3a–3c**).

The structures of these compounds are based upon analyses and are consistent with the infrared spectra.

All attempts to react methylenediamine with various 2-acyl-1,3-indandiones in order to prepare 4-substituted 1,2-dihydro-5H-indeno[1,2-*d*]pyrimidin-5-ones failed. In all cases only a compound of empirical formula $(C_{10}H_7NO)_x$ was isolated. No attempts have been made to determine the structure of this compound.

Experimental Section[5]

2-Formyl-1,3-indandione.—A modification of the procedure described in the literature[6] was used. A mixture of triethyl orthoformate (35 ml, 240 mmol) and acetic anhydride (70 ml, 720 mmol) was added to 1,3-indandione (25 g, 170 mmol) with stirring at room temperature. The mixture was heated slowly for *ca.* 45 min to 80° and kept at this temperature for 1 hr. The obtained red solution was filtered hot and immediately cooled to 10° in an ice bath. Cold water (130 ml), previously boiled to remove most of the oxygen, was added at 10° with stirring and the mixture was allowed to crystallize in a refrigerator for 15 hr. The deep red crystals were collected and immediately added to refluxing absolute ethanol (400 ml) with stirring. The mixture was refluxed for 5 min and then filtered rapidly through a preheated sintered-glass funnel. The green-red filtrate, containing *ca.* 20 g of 2-formyl-1,3-indandione, was used directly in the condensation with ethylenediamine. The ethanolic solution of this indandione should not be stored for a long period of time.

All the other 2-acyl-1,3-indandiones were prepared according to known methods[7,8] from dimethylphthalate and the appropriate methyl ketones in the presence of sodium amide.[9]

2[1-(2-Aminoethylimino)alkyl]-1,3-indandiones (1a–1c). Method A.—The general procedure (method A) used to prepare these compounds is illustrated by the synthesis of 2[1-(2-aminoethylimino)ethyl]-1,3-indandione (**1b**). A solution of 2-acetyl-1,3-indandione (50 mmol) in ethanol (200 ml) was added dropwise over a 2-hr period to a refluxing mixture of formic acid (1 ml),

(1) R. A. Braun and W. A. Mosher, *J. Amer. Chem. Soc.*, **80**, 2749 (1958).
(2) R. A. Braun and W. A. Mosher, *ibid.*, **80**, 4919 (1958); *J. Org. Chem.*, **24**, 648 (1959).
(3) A. Combes and C. Combes, *Bull. Soc. Chim. Fr.*, **3**, 7, 788 (1892).
(4) G. Schwarzenbach and K. Lutz, *Helv. Chim. Acta*, **23**, 1139 (1940).
(5) Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. The infrared spectra were recorded with a Perkin-Elmer Infracord Model 137. Analyses were performed by Dr. A. Bernhardt, Mikroanalytisches Laboratorium, Max Planck Institut fur Kohlenforschung, Mülheim (Ruhr), West Germany.
(6) G. Errera, *Gazz. Chim. Ital.*, **33**, 417 (1903).
(7) L. B. Kilgore, J. H. Ford, and W. C. Wolfe, *Ind. Eng. Chem.*, **34**, 494 (1942).
(8) R. L. Horton and K. C. Murdok, *J. Org. Chem.*, **25**, 938 (1960).
(9) L. Gattermann, "Die Praxis des Organischen Chemikers," 38th ed, Walter de Gruyter and Co., Berlin, 1958, p 220.

TABLE I

2-[1-(2-AMINOETHYLIMINO)ALKYL]-1,3-INDANDIONES (1a–1c)

Compd	R	Reaction time[a]	Yield, %	Mp, °C	Empirical formula	Calcd, %	Found, %
1a	H	2 hr	59	90–100 dec	$C_{12}H_{12}N_2O_2$	C, 66.65	C, 66.85
						H, 5.59	H, 5.64
1b	CH_3[b]	2 days	80	224–225	$C_{13}H_{14}N_2O_2$	C, 67.81	C, 68.34
						H, 6.13	H, 6.01
						N, 12.17	N, 12.21
1c	$CH_2CH(CH_3)_2$	3 days	75	96–98	$C_{16}H_{20}N_2O_2$	C, 70.56	C, 69.62
						H, 7.40	H, 7.39

[a] Prepared as in method A (see Experimental Section). [b] Forms a yellow perchlorate, mp 240–242°.

TABLE II

2,3-DIHYDRO-6H-INDENO[1,2-*e*][1,4]DIAZEPIN-6-ONES (2a–2e)

Compd	R	Reaction time	Yield, %	Mp, °C	Empirical formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
2a	H[a]	...	59	104–106	$C_{12}H_{10}N_2O \cdot H_2O$	66.65	5.59	12.96	66.67	5.75	12.28
2b	CH_3[b]	...	50	220–221 dec	$C_{13}H_{12}N_2O$	73.56	5.70	13.20	73.22	6.08	13.01
2c	C_2H_5[b]	2 days[c]	70	194	$C_{14}H_{14}N_2O$	74.31	6.24	12.38	74.20	6.35	12.29
2d	$CH(C_6H_5)_2$[b]	4 days[c]	60	285–286	$C_{25}H_{20}N_2O$	82.45	5.50	7.69	82.14	5.62	8.31
2e	C_6H_5[b]	18 hr[c]	75	243	$C_{18}H_{14}N_2O \cdot {}^1/_2C_2H_5OH$	76.74	5.76	9.42	76.51	5.76	9.48

[a] Forms a formate, mp 178–180° and a perchlorate, mp >300°. [b] Forms perchlorates [c] Prepared as in method A (see Experimental Section).

TABLE III

2,2′-[ETHYLENEBIS(NITRILOALKYLIDYNE)]DI-1,3-INDANDIONES (3a–3c)

Compd	R	Reaction time	Yield, %	Mp, °C	Empirical formula	Calcd, %	Found, %
3a	H	10 min	80	300	$C_{22}H_{16}N_2O_4$	C, 70.96	C, 69.72
						H, 4.33	H, 4.58
						N, 7.52	N, 7.80
3b	CH_3	20 min	90	297	$C_{24}H_{20}N_2O_4$	C, 71.98	C, 71.77
						H, 5.04	H, 5.56
						N, 7.00	N, 7.01
3c	C_2H_5	2 hr	80	240	$C_{26}H_{24}N_2O_4$	C, 72.88	C, 73.18
						H, 5.65	H, 5.48
						N, 6.54	N, 6.70

ethanol (100 ml), and ethylenediamine (75 mmol). The mixture was refluxed for 2 days (see Table I for the refluxing time of 1c). Then most of the ethanol was removed by distillation (*ca.* 250 ml) and to the hot residue (*ca.* 50 ml) was added water (25 ml) with stirring. The mixture was kept at room temperature for *ca.* 2 days to complete the crystallization. The solid was collected by filtration and recrystallized from aqueous ethanol to give 1b as colorless needles.

For compound 1a the following quantities of reactants were used: 2-formyl-1,3-indandione (*ca.* 10 g, 57 mmol), formic acid (2 ml), ethanol (200 ml), and ethylenediamine (225 mmol). The mixture was refluxed for 2 hr. Most of the ethanol was removed by distillation and to the hot residue (*ca.* 150 ml) was added hot water (150 ml). The mixture was kept in a refrigerator for 36 hr; the colorless crystals were collected by filtration and dried.

2,3-Dihydro-6H-indeno[1,2-*e*][1,4]diazepin-6-one (2a).—A solution of 1a (*ca.* 10 g) in a mixture of *n*-propanol (250 ml) and formic acid (15 ml) was heated at reflux for 2 hr. The solution was then allowed to stand at room temperature. The formed golden leaflets of the formic acid salt of 2a, mp 178° dec, were collected by filtration, treated with an excess of aqueous ammonia in 1:1 water–ethanol, and crystallized from acetone to yield 2a as colorless needles.

2,3-Dihydro-5-methyl-6H-indeno[1,2-*e*][1,4]-diazepin-6-one (2b).—Compound 1b (10 mmol) was heated at 250° for 5 min without solvent. The resulting dark powder, after crystallization from aqueous ethanol (Darco), gave 2b as colorless needles.

5-Ethyl-, 5-phenyl-, and 5-diphenylmethyl-2,3-dihydro-6H-indeno[1,2-*e*][1,4-]diazepin-6-ones (2c–2e) were prepared following method A. The refluxing time varied from 18 hr to 4 days, as reported in Table II. Colorless or pale yellow needles were obtained after crystallization from ethanol (Darco).

The above 2,3-dihydro-6H-indeno[1,2-*e*][1,4]diazepin-6-ones show absorption peaks at *ca.* 3300 (NH), *ca.* 1655 (C=O), and *ca.* 1600 cm^{-1} (C=N). They form crystalline yellow perchlorates and formates, which show bright yellow fluorescence in alcoholic solution as well in the solid state and give phenylhydrazones with phenylhydrazine.

2,2′-[Ethylenebis(nitriloalkylidyne)]di-1,3-indandiones (3a–3c) were prepared by the following general method. A solution of formic acid (0.5 ml) and ethylenediamine (2 ml, 30 mmol) in ethanol (100 ml) was added dropwise to a refluxing solution of the appropriate 2-acyl-1,3-indandione (50 mmol) in ethanol (150 ml) with stirring, and the mixture was refluxed for an additional time, as given in Table III. After cooling to room temperature, the resulting solid was collected by filtration, washed with cold ethanol, and recrystallized from ethanol to give colorless or pale yellow needles.

Compounds 3a–3c exhibit absorption peaks at *ca.* 1705 (C=O) and *ca.* 1500 and 1600 cm^{-1} (C=N). They show practically no absorption in the 3300-cm^{-1} region.

Reaction of 2-Acyl-1,3-indandiones with Methylenediamine.—Methylenediamine dihydrochloride (2.4 g, 20 mmol) and anhydrous sodium acetate (3.3 g) were added to cold ethanol (100 ml) with stirring. After 10 min the mixture was filtered to remove the precipitated sodium chloride and to the filtrate was added a solution of the appropriate 2-acyl-1,3-indandione (2-acetyl, 2-isovaleryl, and 2-diphenylacetyl) (15 mmol) in ethanol (100 ml). The clear solution was refluxed for 5 hr. Most of the ethanol (150 ml) was removed by distillation, and the residue, after standing overnight at room temperature, gave colorless, fine needles (1.5 g), mp >300°.

Anal. Calcd for $(C_{10}H_7NO)_x$: C, 76.41; H, 4.49; N, 8.91. Found: C, 76.63; H, 4.54; N, 8.81.

The infrared spectrum showed a strong doublet at 1670 and 1720 cm^{-1} (C=O), an intense band at 1600 cm^{-1} (probably C=N), and two weak bands in the 3050–3450-cm^{-1} region (OH or NH).

Treatment of this compound with 5 *N* hydrochloric acid in ethanol yielded a red, crystalline product, mp >300°.

Anal. Calcd for empirical formula $C_{20}H_{14}NO_3$: C, 75.94; H, 4.46; N, 4.43; O, 15.18. Found: C, 75.81; H, 4.44; N, 4.35; O, 15.24.

Registry No.—**1a**, 23265-38-5; **1b**, 23265-39-6; **1b** formate, 23282-25-9; **1c**, 23265-40-9; **2a**, 23265-41-0; **2a** formate, 23282-31-7; **2a** perchlorate, 23265-43-2; **2b**, 23265-42-1; **2c**, 23282-32-8; **2d**, 23265-44-3; **2e**, 23265-45-4; **3a**, 23265-46-5; **3b**, 23265-47-6; **3c**, 23265-48-7.

Acknowledgment.—We gratefully acknowledge the valuable assistance of Dr. Mario F. Sartori in connection with this research.

Inter- and Intramolecular Cyclization of Bisdiazo Ketones. The Formation of the Novel 3,3′-Spirobi(bicyclo[3.1.0]hexane)-2,2′-dione System

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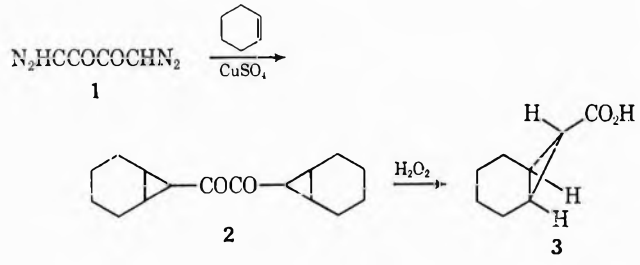
Received September 22, 1969

Two examples of double addition of bisdiazo ketones to olefinic bonds are described. Addition of 1,4-bisdiazo-2,3-butanedione (**1**) to cyclohexene afforded the *exo*-di(7-norcaryl)ethanedione (**2**). Catalytic decomposition of bisdiazo ketone **8** yielded the isomeric spiro diketones **10** and **11**. Nmr spectral properties and some reactions of this novel spiro system are discussed.

α-Ketocarbenes generated by the copper-catalyzed decomposition of diazo ketones have been found to react with olefins to produce cyclopropanes. Both intermolecular[1-3] and intramolecular[4-13] additions have been reported.

Recently we initiated the study of the corresponding reactions of bisdiazo ketones which do not appear to have been investigated. In the present paper we describe two cases in which double addition of intermediate bisketocarbenes to olefinic bonds occurred.

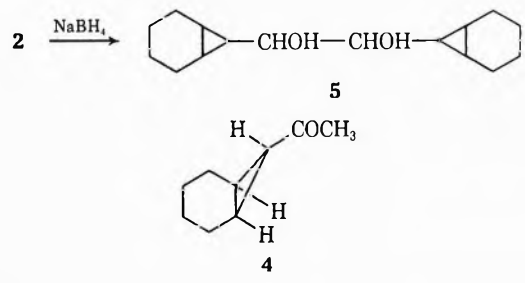
Decomposition of 1,4-bisdiazo-2,3-butanedione (**1**)[14] in boiling cyclohexene in the presence of anhydrous copper sulfate afforded the *exo*-di(7-norcaryl)ethanedione **2** in low yield.



The presence of an α-diketone system was demonstrated by formation of the corresponding quinoxaline derivative. The low carbonyl frequency (1680 cm^{-1}) observed in the infrared spectrum of **2** indicates a significant conjugative overlap between the cyclopropane rings and the adjacent carbonyl groups, presumably enhanced by a preferred geometry of the molecule with respect to the pertinent groups. Conjugative ability of the electron-rich cyclopropane ring has been observed for many years by infrared and ultraviolet spectroscopy.[15,16]

The *exo* configuration was proved by oxidation of **2** with alkaline hydrogen peroxide, affording the *exo* isomer of norcarane-7-carboxylic acid (**3**).[17,18] Thus the configuration agrees with previous experience concerning copper-catalyzed decomposition of ethyl diazoacetate in the presence of olefins. Here also addition favored the formation of the less hindered *exo* product.[17-20]

Nmr data also support the *exo* configuration. It has been shown[21] that in α-cyclopropylcarbonyl compounds the *cis* ring protons with respect to the carbonyl group are shifted to low field. This should obtain in all *exo* isomers of a norcaryl system adjacent to a carbonyl group. (In the *exo* isomer the carbonyl group is located *trans* to the cyclohexane ring.) Indeed, for **2** and **3** no proton resonance has been observed at δ values lower than 1.17 and 1.10 ppm, respectively. Similarly, in methyl norcaryl ketone **4** no proton resonance has



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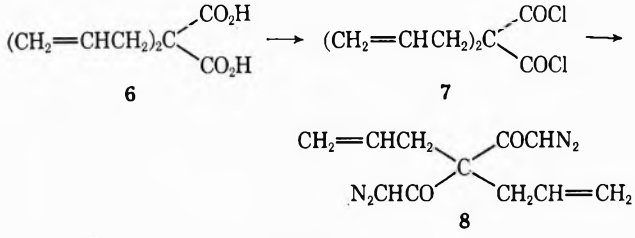
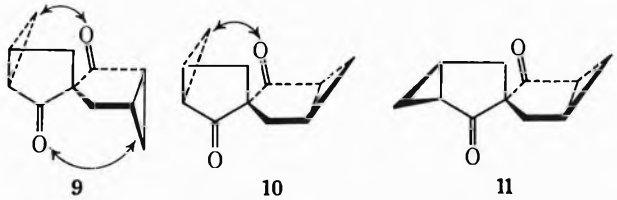
been reported at δ values less than 1 ppm.[22] Sodium borohydride reduction of **2** afforded the diol **5**, the nmr spectrum of which exhibited a broad six-proton multiplet at high field (δ 0.4–1.0 ppm) as expected for the cyclopropyl protons once the "carbonyl effect" present in **2** has been removed.

In order to study the case of intramolecular cyclization, the bisdiazo ketone **8** was prepared by the addition of diazomethane to diallyl malonyl chloride **7** obtained from the corresponding acid **6** with oxalyl chloride.



6 **7** **8**

The decomposition of the bisdiazo ketone **8** was then investigated under varying conditions of temperature, solvent, and catalyst. In each case two isomeric crystalline products, A (mp 154°) and B (mp 118°), were isolated, representing two of the three theoretically possible stereoisomers, **9**, **10**, and **11**. The distribution



9 **10** **11**

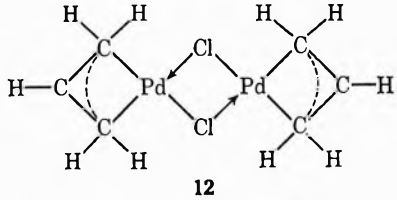
of isomers A and B in the crude reaction mixture was analyzed by glpc and is summarized in Table I.

TABLE I

DECOMPOSITION OF **8** UNDER DIFFERENT CONDITIONS

Catalyst	Temp, °C	Solvent	A + B, %	A, %	B, %
$CuSO_4$	100	Dioxane	15	67	33
Pd complex	5–15	Dioxane	35	86	14
Pd complex	5–15	THF	24	85	15
Pd complex	5–15	Ether	22	85	15
Pd complex	5–15	Benzene	23	74	26

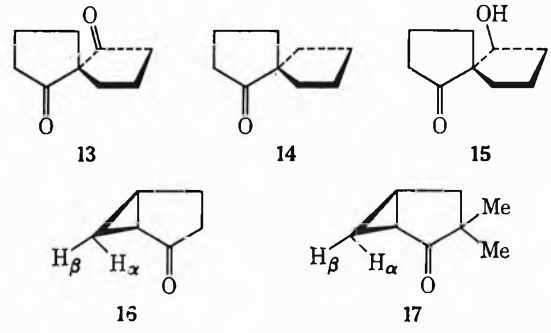
The higher yields obtained by using the π-allylic palladium chloride complex **12**[23] instead of $CuSO_4$ are presumably due to the milder conditions necessary to effect decomposition with this complex,[24] lessening concurrent polymer formation.



12

Although the infrared and ultraviolet spectra of the spiro diketones A and B are similar the striking difference observed in their nmr spectra permitted establishment of their relative configuration.

Both compounds showed two distinct carbonyl stretching bands in their infrared spectra (see Experimental Section). In the ultraviolet region both A and B had a maximum at 280 nm (ϵ 96 and 127, respectively). Similarly, a high ϵ value (121) was found for the n $\rightarrow$ π^* transition band of the spiro ketone **13**[25] in contrast to the low ϵ values of 13, 22, and 24 observed for cyclopentanone and two related monoketones, **14** and **15**. The effect was discussed by Cram for the



13 **14** **15**

16 **17**

diketone **13**,[25] where the π orbitals of two apparently nonconjugated chromophores appear to interact because they are held in rigid proximity, although orthogonal to one another. Considering the ϵ values of 57 and 46 reported for the bicyclo ketones **16**[26a] and **17**,[26b] the values of 96 for compound A and 127 for B appear to be normal (double the value for a single carbonyl chromophore). Consequently, our spiro ketones do not obey the "spiro conjugation" effect discussed recently for interactions observed between p-orbital systems (olefins and oxygen or nitrogen lone-pair electrons) in numerous spiro compounds.[27] The already existing conjugation in the α-cyclopropyl ketone system presumably overhelms this spiro effect.

It is important to recognize the difference in the symmetry properties of **9**, **10**, and **11**. Since **10** lacks any symmetry element, it is asymmetric. Both **9** and **11** have one twofold symmetry axis (C_2) and are therefore dissymmetric. This symmetry difference must be reflected also in the corresponding nmr spectra, permitting structural assignments to be made for the isomers actually isolated, A and B, provided that one of them is **10**. Indeed, the spectra of both A and B exhibited four distinct multiplets, integrated for an even-numbered distribution of protons only in the case of A but not in that of B (*vide infra*). Isomer B must therefore be the asymmetric **10**. In order to decide whether the major product A is **9** or **11**, its nmr spectrum was compared with those of the bicyclo[3.1.0]hexan-2-ones **16** and **17**, in which H_α and H_β have been reported to resonate as multiplets at δ 0.8–1.3 and 0.6–1.5 ppm, respectively.[27] In the spectrum of A there were four distinct multiplets centered at δ 0.72 (2 H), 1.22 (2 H), 1.98 (6 H), and 2.54 ppm (2 H). The two upfield multiplets, corresponding to the geminal cyclopropyl protons, appear in a range similar to that of the corresponding methylene signals in both model compounds **16** and **17**. This close accord would be expected only for structure **11**, where the geminal cyclopropyl protons

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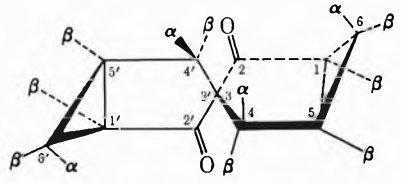
TABLE II

COUPLING CONSTANTS[a] FOR SOME 3,3′-SPIROBI(BICYCLO[3.1.0]HEXANE) DERIVATIVES

Compd	$J_{2\beta,1\beta}$	$J_{2'\beta,1'\beta}$	$J_{4\beta,5\beta}$	$J_{4\alpha,4\beta}$	$J_{6\beta,4\beta}$	$J_{6\beta,1\beta}$	$J_{6\alpha,1\beta}$	$J_{6\alpha,6\beta}$
10	...	...	5.5	13.0	1.5	...	4.5	3.5
11	...	...	5.5	13.0	1.5	...	4.5	3.5
22	4.5	5.0	5.0	13.0	...	8.0	5.0	5.0
23	5.0	...	5.5	13.0	...	...	...	...
34	...	5.0	5.5	13.0	1.5	...	...	...

[a] Reported in hertz.

would not experience any additional anisotropic effects of the distant carbonyl group. (Compare, for example, the relative locations of $H_{6\alpha}$ and the $C_{2'}$ carbonyl group in I.) On the other hand, both *endo* methylene protons

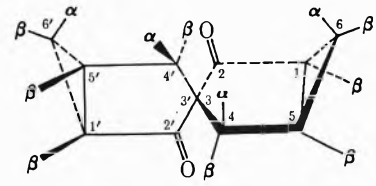


I

of the cyclopropyl rings in **9** are located in close proximity to the carbonyl groups (see **9**), and their chemical shifts would be expected to differ significantly from those observed in the model compounds **16** and **17**. These assumptions are confirmed by the nmr spectrum of the asymmetric isomer B (**10**), which indeed combines the characteristic configurations of both **9** and **11** (*vide infra*).

The assignment of the geminal cyclopropyl protons was made on the basis of the order $J_{cis} > J_{trans}$, established for vicinal coupling constants in cyclopropane derivatives.[19,28–30] Consequently, the narrower multiplet ($W_{1/2}$ = 13 Hz) at highest field (δ 0.72 ppm) represents the magnetically equivalent *endo* protons $H_{6\alpha}$ and $H_{6'\alpha}$ (see I) appearing as a six-line pattern present in an unsymmetrical triplet. The broader multiplet ($W_{1/2}$ = 24 Hz) centered at δ 1.22 ppm corresponds to the resonance of the *exo* protons $H_{6\beta}$ and $H_{6'\beta}$. An unsymmetrical doublet of quartets represents the protons $H_{4\beta}$ and $H_{4'\beta}$, with a splitting pattern corresponding to coupling of $H_{1\beta}$ with the protons $H_{4\alpha}$, $H_{5\beta}$, and $H_{6\beta}$. (Owing to the symmetry of the molecule, $H_{4'\beta}$ is similarly coupled to $H_{4'\alpha}$, $H_{5'\beta}$, and $H_{6'\beta}$.) The coupling constants obtained from the spectrum and confirmed by double-irradiation experiments are summarized in Table II.

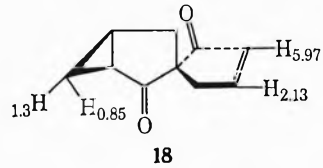
The nmr spectrum of the isomer B consisted of four multiplets centered at δ 0.89 (1 H), 1.20 (2 H), 2.00 (8 H), and 2.96 ppm (1 H). The integration, compared with the integration values of isomer A (*vide supra*), suggests that isomer B has the asymmetric configuration shown in II. Here, in contrast to the symmetric molecule (I), one cyclopropyl group is inverted. This change in the relative configuration of one cyclopropane ring eliminates the anisotropic shielding effect of this ring[31–34] on $H_{4\beta}$ which exists in the symmetric molecule.



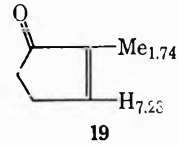
II

This proton, now affected only by the anisotropic effect of the $C_{2'}$ carbonyl group, is shifted downfield (from 2.54 to 2.96 ppm). Simultaneously, $H_{4'\beta}$, located in the shielding volume above the plane of both cyclopropyl rings, undergoes an upfield shift into the area of the complex multiplet centered at δ 2.00 ppm. The *endo* proton $H_{6'\alpha}$, affected by the C_2 carbonyl group, is shifted downfield, leaving a one-proton multiplet at highest field (δ 0.89 ppm) corresponding to $H_{6\alpha}$.

A different product, **18**, has been isolated from the reaction mixture of the copper-catalyzed decomposition of **8** in hydrocarbons (hexane, cyclohexane, or benzene) rather than dioxane. The structure of **18** was substantiated by elemental analysis and spectral data. The relative configuration of the cyclopropane ring was



18



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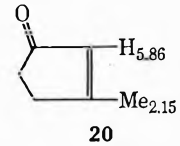
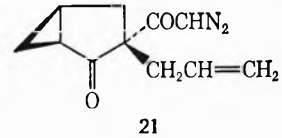


20

determined from the chemical shifts of the geminal cyclopropyl protons, which appeared in the range similar to that for the corresponding methylene signals of **11**. For the relative configuration of the methyl group and the vinylic hydrogen, support has been found in nmr data reported for compounds **18** and **19**.[35]

Compound **18** cannot result from rearrangement of A or B, since, when both were refluxed in benzene in the presence of copper sulfate, work-up of the solutions gave only recovered starting material. A monocyclized intermediate such as **21** may serve as a common precursor for all three compounds, **10**, **11**, and **18**.



21

Reduction of **11** with sodium borohydride afforded a mixture of neutral and acidic fractions. The neutral fraction consisted of two of the three stereochemically possible diols **22**, **23**, and **24** separated by chromatography or, alternatively, by preparative glpc of the corresponding trimethylsilyl ethers followed by hydrolysis.

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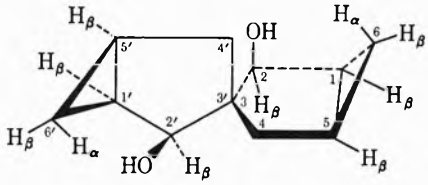
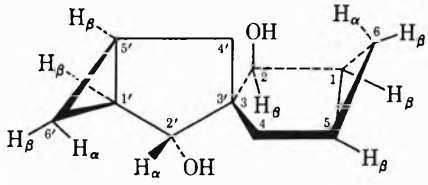
Metal hydride reduction of conjugated cyclopropyl ketones has been shown to give (in over 90% yield) the isomer in which the hydroxyl and cyclopropane groups are *cis*.[36,37]

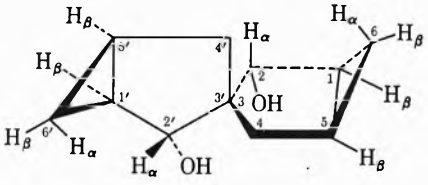
The two isomeric diols were obtained in a ratio of *ca.* 85:15, and it is reasonable to assume that in the major product (mp 171°) each set of hydroxyl group and cyclopropyl ring are in the *cis* orientation, as depicted in **22**. This assumption was confirmed by the nmr data. The presence of a clearly resolved doublet in pyridine-d_5 at δ 4.88 ppm (2 H, J = 4.5 Hz) attributed to the tertiary protons $H_{2\beta}$ and $H_{2'\beta}$ supports symmetrical disposition of the two hydroxyl groups about the C_2 axis, a feature absent in **23**. The splitting of the absorption of these hydrogens is reasonably explained as resulting from coupling with the *cis* protons $H_{1\beta}$ and $H_{1'\beta}$. Although the hydroxyls in **24** are also symmetrically disposed and are thus magnetically equivalent, $H_{2\alpha}$ and $H_{2'\alpha}$ would be expected to appear as a singlet. This expectation is based on the observation in models that the relevant dihedral angles ($H_{2\alpha}$–C–C–$H_{1\beta}$ and $H_{2'\alpha}$–C–C–$H_{1'\beta}$) approximate 90° and therefore no spin–spin coupling should be observed.[38]



22



23



24

The asymmetric structure **23** has been assigned to the minor component, a liquid diol characterized as its bis-*p*-nitrobenzoate. Its nmr spectrum in $CDCl_3$ exhibited a one-proton doublet at δ 4.82 ppm (J = 5 Hz) and a one-proton singlet at δ 3.77 ppm corresponding to $H_{2\beta}$ and $H_{2'\alpha}$, respectively. Both protons differ in chemical shifts from that of the corresponding tertiary protons in the diol **22**. Presumably, this difference may be accounted for by the $H_{2\beta}$ resonance undergoing a paramagnetic shift owing to the neighboring $C_{2'\beta}$ hydroxyl;[36,39,40] the $H_{2'\alpha}$ proton lies in the shielding area of the neighboring cyclopropyl group.[41] The lesser symmetry of **23** is further supported by the fact that, in contradiction to the magnetic equivalence of $H_{4\beta}$ and $H_{4'\beta}$ in **22**, in **23** only $H_{4'\beta}$ is affected by the C_2 hydroxyl group, which resonated separately at δ 2.40 ppm (quartet, 1 H, $J_{4'\beta,4'\alpha}$ = 13 Hz, $J_{4'\beta,5'\beta}$ = 5 Hz). The $H_{4\beta}$ resonance was shifted to higher field into a seven-proton multiplet at δ 1.1–1.8 ppm ($H_{1\beta}$, $H_{1'\beta}$, $H_{5\beta}$, $H_{5'\beta}$, $H_{4\alpha}$, $H_{4'\alpha}$, and $H_{4\beta}$).

The infrared spectra of the two diastereoisomeric diols **22** and **23** in the OH stretching region furnished further support for the above configurational assignment. The infrared spectrum of **22** exhibited a sharp band at 3595 cm^{-1} and a broad one at 3415 cm^{-1}. At low concentration the broad (intermolecular) band disappears. The diol **23** also showed two infrared bands, at 3570 and 3470 cm^{-1}, but they remain relatively unchanged even at low concentration. The geometry of **22**, with *trans* hydroxyl groups, permits no intramolecular hydrogen bonding. In the isomer **23**, however, intramolecular bonding may exist owing to the relative proximity of the hydroxyl groups.[42,43]

The acidic fraction, obtained as a by-product, consisted of a mixture of two isomeric hydroxy acids, one of them present as a minor component but detectable in the nmr spectrum of the crude acidic fraction. The major acidic component (mp 131°) was separated by chromatography on silica gel.

The formation of hydroxy acids may be explained by a two-step reaction, in which the basic sodium borohydride first cleaves the β diketone **11**. Whether the enolate anion **25** is further reduced or first converted into epimeric keto acids **26** and **27** by proton abstraction has not been investigated. This uncertainty in the mechanism requires consideration of four isomeric hydroxy acids, **28**–**31**, as potential reaction products.

Configurational assignment for the actually isolated hydroxy acid was attempted by considering the presence of a one-proton resonance at δ 4.05 ppm in the nmr spectrum owing to the proton α to the hydroxyl group. Table III summarizes the expected splitting pattern of this signal in the four hydroxy acids **28**–**31**. Dihedral angles were measured in Dreiding models and coupling constants were derived from the Karplus curve.[38] Since a boat conformation is preferred for bicyclo[3.1.0]-hexan-2-ol and -3-ol,[44,45] our analysis also uses this conformation.

Although this analysis is only approximate, the presence of an ill-resolved multiplet, centered at δ 4.05 ppm in the nmr spectrum of the hydroxy acid (mp 131°), together with the well-established fact of obtention of *cis* hydroxyl groups in metal hydride reductions of conjugated cyclopropyl ketones,[36,37] it is suggested that the hydroxy acid be either **28** or **30**. Clear-cut differentiation between these two configurations, however, was not possible, since the data provide insufficient evidence concerning the configuration of the side chain.

One keto acid (**26** or **27**) was isolated in 95% yield

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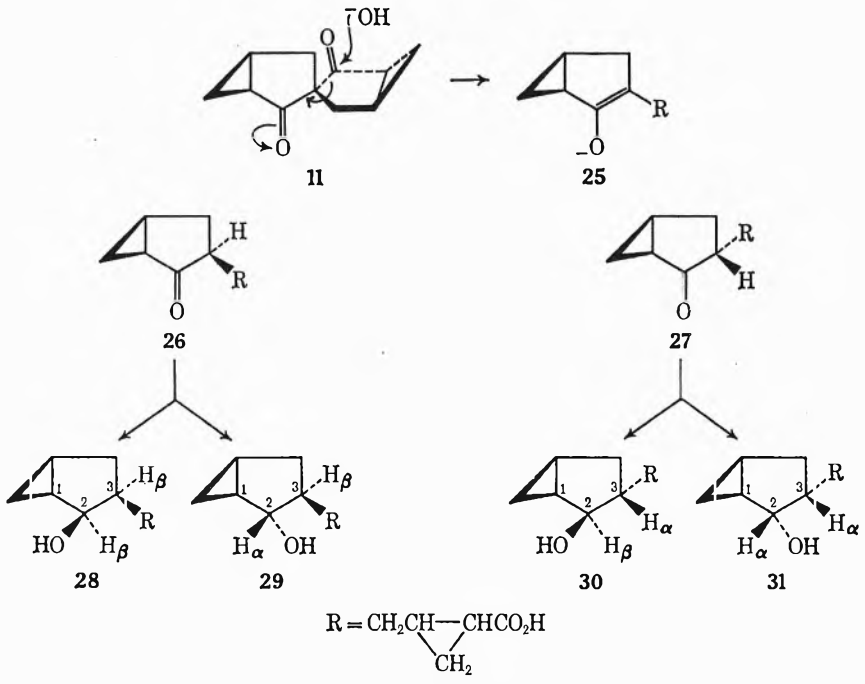


TABLE III

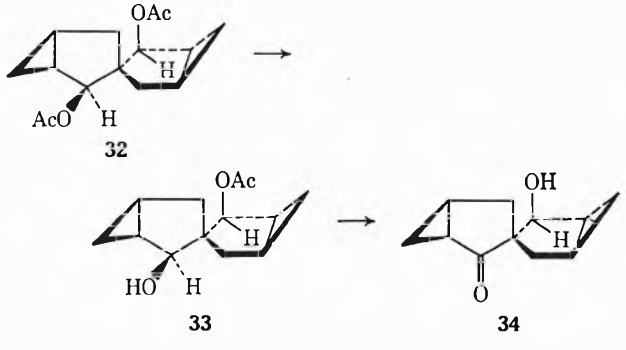
ESTIMATED COUPLING CONSTANTS[a] FROM MEASURED DIHEDRAL ANGLES IN BICYCLO[3.1.0]HEXAN-2-OL DERIVATIVES

Compd	Coupled protons	Dihedral angle, deg	J	Expected H_2 resonance
	$H_{1\beta}$, $H_{2\beta}$	45	4	
28				Quartet
	$H_{2\beta}$, $H_{3\beta}$	30	6	
	$H_{1\beta}$, $H_{2\alpha}$	75	0	
29				Singlet
	$H_{2\alpha}$, $H_{3\beta}$	90	0	
	$H_{1\beta}$, $H_{2\beta}$	45	4	
30				Quartet
	$H_{2\beta}$, $H_{3\alpha}$	150	7	
	$H_{1\beta}$, $H_{2\alpha}$	75	0	
31				Doublet
	$H_{2\alpha}$, $H_{3\alpha}$	30	6	

[a] Reported in hertz.

when the diketone **11** was refluxed with sodium hydroxide followed by acidification. Presumably under these conditions the thermodynamically more stable isomer is formed. Its methyl ester showed a single sharp peak upon glpc on two different columns. This keto acid, on reduction with sodium borohydride, yielded the same hydroxy acid as was obtained from the diketone **11** as described above.

The diacetate **32** of the diol **22** served as a starting material for preparing the ketol **34**. Partial hydrolysis of the diacetate gave, besides unchanged diacetate and diol, the monoacetate **33**, which on oxidation with chromic acid followed by hydrolysis furnished the ketol **34**. Its structure was confirmed by analysis and spectroscopic methods.



Experimental Section

All melting points were taken in capillaries and are uncorrected. The ir spectra were determined on a Perkin-Elmer Infracord and the uv spectra on a Perkin-Elmer 137 or on a Cary 14 spectrophotometer. The nmr spectra were recorded either on a Varian A-60 or on a Varian HA-100 spectrometer in $CDCl_3$ solution if not otherwise stated, using TMS as internal standard. Gas chromatographic analyses were done on a F & M Model 810 or on a Aerograph HY-FI Model 600D gas chromatograph.

exo-**Di(7-norcaryl)ethanedione (2).**—A stirred mixture of 1,4-bisdiazo-2,3-butanedione[14] (3.58 g), redistilled dry cyclohexene (*ca.* 700 ml), and anhydrous copper sulfate (20 g) was heated under reflux under N_2 until the ir bands characteristic for the diazo ketone disappeared (*ca.* 15 hr). The mixture was cooled and filtered from copper sulfate and polymeric materials, and the solvent was removed. The oily residue (4.8 g) was chromatographed on a column of Florisil (60–100 mesh, 100 g). Elution with hexane and crystallization from MeOH gave the ethanedione **2** (0.35 g): mp 130–131°; ir ($CHCl_3$) 1678 cm^{-1}; uv max (MeOH) 240 mμ (ε 9700).

Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.0; H, 9.0. Found: C, 77.8; H, 9.0.

A sample of diketone **2**, on treatment with *o*-phenylenediamine, yielded **2,3-di(7-norcaryl)quinoxaline**, mp 72° (from EtOH).

Anal. Calcd for $C_{22}H_{26}N_2$: C, 83.0; H, 8.2; N, 8.8. Found: C, 82.4; H, 8.5; N, 8.6.

exo-**Norcarane-7-carboxylic Acid (3).**—A mixture of the diketone **2** (0.13 g), MeOH (20 ml), aqueous NaOH (15%, 15 ml), and H_2O_2 (30%, 9 ml) was kept at room temperature overnight. Excess H_2O_2 was decomposed with $FeSO_4$, and the solution was acidified with cold, aqueous HCl and extracted with ether. The organic layer was dried ($MgSO_4$) and filtered, and the solvent was removed. The crude acid was recrystallized from pentane (0.10 g), mp 96–97.5° (lit.[18] mp 96.5°).

exo-**Di(7-norcaryl)ethanediol (5).**—To a solution of diketone **2** (0.25 g) in EtOH (30 ml), sodium borohydride (0.04 g) was added in small portions and the mixture was kept at room temperature overnight. Ethanol was then removed under reduced pressure, water was added, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water until neutral reaction, dried, and evaporated. The crude diol (0.23 g) was purified by recrystallization from hexane, mp 99–100°.

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.8. Found: C, 76.6; H, 10.8.

1,5-Bisdiazo-3,3-diallyl-2,4-pentanedione (8).—To a magnetically stirred and ice-cooled mixture of diallyl malonic acid (36.8 g), dry benzene (200 ml), and anhydrous pyridine (1 ml) was added dropwise a solution of freshly distilled oxalyl chloride (80 ml) in dry benzene (80 ml). The addition was regulated according to rate of gas evolution. After the addition was completed, the ice bath was removed and the mixture was slowly heated to 40° and kept at this temperature for 2 hr and then at 60° for an additional 2 hr. Excess oxalyl chloride and benzene were removed and the residue was washed three times with 150 ml of dry ether. For characterization the solvent was removed from a small sample and the ir spectrum of the residual oil was taken in dry CCl_4, ν_{max} 1800 (–COCl) and 1650 cm^{-1} (CH_2=CH–).

The combined etheral extracts were added dropwise under cooling and swirling to an etheral diazomethane solution (prepared from 160 g of nitrosomethylurea). After standing for 1 hr the solution was filtered and concentrated until the product started to crystallize. The bisdiazo ketone was isolated by suction filtration and recrystallized from benzene–cyclohexane (1:1): mp 81–82°; ir ($CHCl_3$) 2110, 1645, and 1630 cm^{-1}; nmr δ 2.6 (d, 4), 5.5 (s, 2), and 4.9–5.8 ppm (m, 6).

Anal. Calcd for $C_{11}H_{12}O_2N_4$: C, 56.9; H, 5.2; N, 24.1. Found: C, 57.3; H, 5.2; N, 23.8.

Decomposition of Bisdiazo Ketone 8 with $CuSO_4$.—A stirred mixture of diazo ketone **8** (6.0 g), redistilled dry cyclohexane (600 ml), and anhydrous $CuSO_4$ (12 g) was heated under reflux under N_2 until the ir bands characteristic for the diazo ketone disappeared (*ca.* 40 hr). The mixture was cooled and filtered from $CuSO_4$, and polymeric material and the solvent were removed. The dark, oily residue was purified by column chromatography on Florisil (60–100 mesh, 150 g). Elution with hexane–benzene (1:1) gave crude **18**, which was recrystallized from *i*-PrOH (0.28 g): mp 135°; ir ($CHCl_3$) 1730, 1696, and 1628 cm^{-1}; uv max (MeOH) 225 mμ (ϵ 10,200); nmr δ 5.97 (vinylic proton) and 2.13 ppm (methyl).

Anal. Calcd for $C_{11}H_{12}O_2$: C, 75.0; H, 6.9. Found: C, 75.0; H, 6.9.

Decomposition of Bisdiazo Ketone 8 with Complex 12.—To an ice-cold solution of 1,5-bisdiazo-3,3-diallyl-2,4-pentanedione (30 g) in absolute ether (3 l.), the Pd complex **12**[23] (0.3 g) was added. Vigorous gas evolution started immediately. After the reaction subsided, the ice bath was removed and the mixture was stirred overnight at room temperature. After filtration and concentration of the solution, crude crystalline diketone **11** was obtained (3.28 g), purified by recrystallization from *i*-PrOH: mp 154°; ir ($CHCl_3$) 1736 and 1706 cm^{-1}; uv max (MeOH) 280 mμ (ϵ 96).

Anal. Calcd for $C_{11}H_{12}O_2$: C, 75.0; H, 6.9. Found: C, 74.9; H, 7.0.

Removal of the solvents of the combined mother liquors gave a crude oil which was chromatographed on a column of Florisil (60–100 mesh). Elution with hexane–benzene (4:1) gave diketone **10** (0.68 g). The analytical sample was obtained by recrystallization from *i*-PrOH: mp 118°; ir ($CHCl_3$) 1734 and 1710 cm^{-1}; uv max (MeOH) 281 mμ (ϵ 127).

Ancl. Calcd for $C_{11}H_{12}O_2$: C, 75.0; H, 6.9. Found: C, 74.8; H, 7.0.

Elution with hexane–benzene (1:1) gave an additional amount (1.03 g) of isomer **11**, mp 154°.

Reduction of Diketone 11 with Sodium Borohydride.—To a solution of diketone **11** (2.0 g) in *i*-PrOH (150 ml) kept at 40°, sodium borohydride (2.0 g) was added. The mixture was left at room temperature overnight, the solvent was removed, and water was added. The solution was neutralized (pH 7) with diluted HCl and extracted with $CHCl_3$. After the usual work-up, an oil was obtained which on trituration with $CHCl_3$ gave the crystalline diol **22** (1.07 g). The analytical sample was obtained by recrystallization from acetonitrile: mp 171°; ir (CCl_4) 3595 and 3415 cm^{-1}; the broad band at 3415 cm^{-1} disappears at a concentration of 2×10^{-3} mol/l.; mass spectrum *m/e* 162 ($M^+ - H_2O$).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.3; H, 9.0. Found: C, 73.0; H, 8.8.

The bis-*p*-nitrobenzoate melted at 271° ($CHCl_3$).

Anal. Calcd for $C_{25}H_{22}N_2O_8$: C, 62.8; H, 4.6; N, 5.9. Found: C, 62.4; H, 5.0; N, 6.2.

Removal of the solvents ($CHCl_3$ and *i*-PrOH) of the combined mother liquors gave a thick oil which was chromatographed on a column of basic Alumina (Merck). Elution with C_6H_6–$CHCl_3$ (1:1) gave an additional amount (0.38 g) of diol **22**; C_6H_6–$CHCl_3$ (1:2) eluted the isomeric oily diol **23** (0.26 g). For purification it was rechromatographed on neutral Alumina (Merck), ir (CCl_4) 3570 and 3470 cm^{-1}. Both peaks remain relatively unchanged at a concentration of 4×10^{-4} mol/l., mass spectrum *m/e* 162 ($M^+ - H_2O$).

The bis-*p*-nitrobenzoate melted at 182–183° (CH_3CN).

Anal. Calcd for $C_{25}H_{22}N_2O_8$: C, 62.8; H, 4.6; N, 5.9. Found: C, 62.7; H, 4.7; N, 5.8.

The aqueous layer from the first $CHCl_3$ extraction was acidified with cold, diluted HCl to pH 2 and extracted again with $CHCl_3$. After the organic layer had been dried (Na_2SO_4) the solvent was removed and the nmr spectrum of the crude residue (0.26 g) was taken. The presence of a multiplet at δ 4.05 ppm, together with a doublet at δ 4.40 ppm, indicated the crude residue to be a mixture of two hydroxy acids. Trituration with benzene and recrystallization of the crude crystalline product from benzene–chlorform gave pure hydroxy acid, mp 131°. Alternatively, the crude acidic mixture was chromatographed on silica gel (28–200 mesh, Davison Chemical), and elution with $CHCl_3$ afforded an oil which crystallized on standing. Recrystallization from benzene–chlorform gave the hydroxy acid, mp 131°. The nmr spectrum exhibited a one-proton multiplet at δ 4.05 ppm, but the doublet observed in the spectrum of the crude acid at δ 4.40 ppm was absent.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.3; H, 8.2. Found: C, 66.9; H, 8.3.

In an alternative procedure a portion of the neutral fraction obtained from the sodium borohydride reduction described above was converted into a mixture of the corresponding trimethylsilyl ethers using a modification[46] of a standard method.[47] The ether mixture was analysed by glpc on a 6 ft × 0.25 in. column packed with SE-30 (3%) on 80–100 mesh Chromosorb W at a column temperature of 155°. Three peaks with relative area of 86:8:6 were observed. The major fraction was collected and hydrolyzed for 5 min with boiling MeOH. The product, mp 171°, was identical with the symmetrical diol **22** (*vide supra*). Glpc comparison of the product with relative area intensity 8 with the trimethylsilyl ether of diol **23** showed the identity of these two compounds. The product corresponding to the third peak was not investigated.

Alkaline Cleavage of Diketone 11.—A solution of diketone **11** (0.12 g) in a mixture of EtOH (4 ml) and NaOH (6 *N*, 1 ml) was heated under reflux for 30 min. After removal of the alcohol under reduced pressure and acidification with cold, diluted HCl to pH 3, a keto acid **26** or **27** precipitated (0.12 g). Recrystallization from benzene gave the analytical sample: mp 123°; ir 1712 cm^{-1}; mass spectrum *m/e* 194 (M^+).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.0; H, 7.3. Found: C, 67.8; H, 7.4.

Reduction of the Keto Acid.—A solution of the keto acid (0.28 g), mp 123°, in *i*-PrOH (28 ml) at 40° was treated with sodium borohydride (0.28 g), and the mixture was left at room temperature for 20 hr. After removal of the solvent, water was added and the acidified (pH 2) solution was extracted with $CHCl_3$. After the usual work-up, an oil (0.27 g) was obtained, which on trituration with benzene and recrystallization from benzene–chloroform gave the hydroxy acid, mp 131°, identical with that described above.

Acetylation of Diol 22.—A mixture of diol **22** (0.70 g), anhydrous pyridine (5 ml), and acetic anhydride (2.5 ml) was heated at 100° for 50 min and then cooled, and all the volatile compounds were removed under reduced pressure. Sublimation of the residue at 80° (0.05 mm) afforded diacetate **32** (0.92 g). The analytical sample was obtained by recrystallization from pentane, mp 93–94°; in the nmr spectrum the protons α to the acetoxy groups resonated at δ 5.20 ppm (d, 2 H).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.2; H, 7.6. Found: C, 68.2; H, 7.5.

Preparation of Ketol 34.—Diacetate **32** (0.80 g) in dioxane (20 ml), water (8 ml), and 40% aqueous dioxan (18.7 ml) containing KOH (9 mg/ml) was refluxed for 30 min. The addition of phenolphthalein showed that this time was required for the consumption of the KOH. The cooled solution was concentrated to dryness under high vacuum, water was added, and the

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mixture was extracted with $CHCl_3$. The crude material (*ca.* 0.70 g) obtained from the dried $CHCl_3$. solution was chromatographed on neutral alumina (50 g, Merck). Elution with benzene gave unchanged diacetate (0.21 g), identified by melting point and mixture melting point. Elution with benzene–chloroform (9:1) afforded the oily monoacetate **33** (0.36 g), characterized as its *p*-nitrobenzoate, mp 119–121° (from methylcyclohexane).

Anal. Calcd for $C_{20}H_{21}O_6N$: C, 64.7; H, 5.7. Found: C, 64.3; H, 5.7.

Elution with $CHCl_3$ gave diol **22** (0.08 g), identified by melting point and mixture melting point.

The crude oily monoacetate (0.28 g) in "Analar R" acetone (20 ml) was treated with Jones solution[48] (0.6 ml) at 0°. After the solution had been stirred for 5 min, excess oxidant was destroyed by adding methanol (2 ml). After the solution had been neutralized ($NaHCO_3$) and filtered, the solvent was removed and the residue was extracted with CH_2Cl_2. The crude keto acetate (0.28 g), obtained from the dried CH_2Cl_2 solution, in dioxane (8 ml), and 40% aqueous dioxane (7.5 ml) containing KOH (9 mg/ml) was refluxed for 30 min (negative phenolphthalein reaction). The cooled solution was concentrated to dryness under high vacuum, water was added, and the mixture was extracted with $CHCl_3$. After the usual work-up, a thick oil (0.2 g) was isolated which solidified on standing. Trituration with ether and recrystallization from methylcyclohexane afforded the ketol **34**, mp 124–125°.

Anal. Calcd for $C_{13}H_{14}O_2$: C, 74.1; H, 7.9. Found: C, 74.2; H, 7.9.

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

Registry No—**2**, 23346-32-9; **5**, 23346-30-7; **8**, 23346-31-8; **10**, 23353-38-0; **11**, 23353-39-1; **18**, 23353-40-4; **22**, 23353-41-5; **22** bis-*p*-nitrobenzoate, 23353-42-6; **23**, 23353-43-7; **23** bis-*p*-nitrobenzoate, 23353-44-8; **26**, 23359-84-4; **27**, 23353-45-9; **28**, 23353-46-0; **29**, 23359-83-3; **30**, 23353-34-6; **31**, 23353-35-7; **32**, 23353-36-8; **33** *p*-nitrobenzoate, 23353-37-9; **34**, 23353-56-2; 2,3-di(7-norcaryl)quinoxaline, 23346-33-0.

Acknowledgment—We are indebted to Dr. Y. Kashman (Tel Aviv University) for the 100-MHz nmr spectra and to Dr. O. E. Edwards (N. R. C. of Canada) for a sample of dimethylbicyclo[3.1.0]hexanone.

Organometallic Reaction Mechanisms. IV. The Mechanism of Ketone Reduction by Aluminum Alkyls

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Received August 25, 1969

A product analysis, kinetic study, and Hammett study of the reaction of triisobutylaluminum with benzophenone has been carried out in diethyl ether solvent. There is no significant participation of the second alkyl group in triisobutylaluminum reduction of benzophenone up to 94% yield of benzhydrol, which is the only product formed in the reaction. The kinetic data shows a well-behaved second-order reaction, first order in aluminum alkyl and first order in ketone. The formation of a complex between the ketone and aluminum alkyl was observed spectroscopically. Accumulation of kinetic data at several temperatures provided a linear Arrhenius plot, which allowed for calculation of activation parameters ($\Delta S^* = -10.1$ eu, $\Delta H^* = 15.8$ kcal/mol, and $\Delta G^* = 18.8$ kcal/mol). A ρ value of +0.362 was determined from a Hammett study, which indicates that the rate-determining step involves nucleophilic attack of the carbonyl group by the aluminum alkyl. All of the accumulated data is consistent with a two-step mechanism in which the first step involves a fast equilibrium to form a complex according to the equation $(i\text{-}C_4H_9)_3Al + (C_6H_5)_2C{=}O \rightleftarrows (i\text{-}C_4H_9)_3Al{\cdot}O{=}C(C_6H_5)_2$. The second step is rate determining and is consistent with a cyclic intramolecular β-hydrogen attack at the carbonyl group (eq 15).

Organoaluminum compounds react with carbonyl compounds in a similar way to Grignard reagents to give products of either addition, reduction, or enolization reactions or any combination of these reactions. Although the reaction of triethylaluminum with carbonyl compounds produces a mixture of addition and reduction products,[1] the primary reaction of organoaluminum compounds with branched alkyls is reduction.[2] For example, the reaction of triisobutylaluminum with carbonyl compounds is very characteristic in that no addition product is formed with most carbonyl compounds.[1b,c,3]

Recent successes in kinetic studies on the addition reaction of trimethylaluminum with benzophenone in benzene[4] and diethyl ether[5] and the reduction reaction of *t*-butylmagnesium compounds with di-*t*-butyl ketone in tetrahydrofuran[6] have encouraged the study of the mechanism of the reduction reaction of trialkylaluminum compounds with carbonyl compounds by kinetic methods. An ideal system for this study involves the reaction of triisobutylaluminum with benzophenone, since only the formation of reduction product in high yield has been reported.[1b,c] Since this reaction was reported too fast to follow kinetically in benzene,[1c] kinetic studies on this reaction were carried out in diethyl ether, a solvent which provided a convenient reaction rate for kinetic measurements. Furthermore, since triisobutylaluminum is monomeric in diethyl ether[7] and the reaction of the first alkyl group is reported to be much more rapid than that of the second alkyl group, this particular aluminum alkyl should provide the least complicated kinetic data.

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(7) (a) E. C. Ashby, J. Carter, and J. R. Sanders, unpublished results; (b) E. G. Hoffman, *Ann. Chem.*, **629**, 104 (1960); (c) K. Ziegler, W. R. Kroll, W. Larbig, and O. W. Steudle, *ibid.*, **629**, 53 (1960).

Experimental Section

Instrumentation and Apparatus.—The disappearance of benzophenone in the kinetic experiments and the determination of extinction coefficients of the ketones studied was accomplished by uv spectroscopy. A Kewaunee inert atmosphere box equipped with a recirculating system to remove moisture and oxygen[8] was used during the manipulation of air-sensitive reagents.

Temperatures were monitored with a calibrated thermometer reading to 0.1° with estimating to 0.02° possible. Reactions were timed to 0.1 sec. Calibrated syringes equipped with 8-in. stainless steel needles were used for transfer of reagents. All-glass 120-ml heavy-walled bulbs were used for all kinetic studies. The only opening to the bulb was through a three-way Teflon stopcock. The stopcock was designed so that a flow of nitrogen could be maintained on the system when samples were added or withdrawn.

Chemicals.—Triisobutylaluminum was obtained from Texas Alkyls Inc. This material was further purified by distillation in the dry box through a 1-ft packed column under vacuum (0.2 mm), taking the center cut for kinetic studies. The pot temperature was kept at 60–70° in order to minimize olefin elimination.[9] The infrared spectrum of triisobutylaluminum after distillation showed no absorption in the range of 1700–1800 cm^{-1} characteristic of the aluminum–hydrogen bond in diisobutylaluminum hydride.[10] Eastman reagent grade benzophenone was recrystallized from 95% ethanol twice and distilled under vacuum at 88° (0.05 mm), taking the center cut for kinetic studies. Glpc analysis indicated a purity of at least 99.95%. Eastman reagent grade benzhydrol, biphenyl, and the 4-substituted benzophenones (bromo, chloro, fluoro, methyl, and methoxy) were purified by recrystallation from hexane six times. Glpc analysis of these compounds indicated a minimum purity of 99%. 4-Methylmercaptobenzophenone was prepared by Friedel–Crafts acylation of thioanisole with benzoyl chloride in carbon disulfide using aluminum chloride as catalyst. The product was further purified by recrystallation until glpc showed no detectable impurity. Baker reagent grade anhydrous diethyl ether was distilled under nitrogen for lithium aluminum hydride prior to use.

Product Analysis.—Product analysis of triisobutylaluminum with benzophenone was done by glpc using 6-ft, Chromosorb W supported 10% Carbowax 20M columns. Biphenyl was used as the internal standard. Glpc analysis of a solution containing benzophenone (0.6 M) and biphenyl showed an area ratio of benzophenone to biphenyl of 5.41. When 1 ml of this mixture was allowed to react with 3 ml of triisobutylaluminum solution (0.452 M) in a rubber cap sealed bottle for 60 hr, glpc analysis after hydrolysis showed an area ratio of benzhydrol to biphenyl of 5.25 without any other detectable peak. This result indicated 97.3% conversion of benzophenone into benzhydrol.

The reaction of triisobutylaluminum with benzophenone was studied at three different ratios (3:1, 2:1, and 1:2). Two milliliters of the reaction solution were withdrawn under nitrogen at appropriate time intervals and quenched in 3 ml of 10% hydrochloric acid. Glpc analyses showed that the 3:1 and 2:1 ratio experiments produced only benzhydrol after 145-min reaction. In the 1:2 ratio experiment benzhydrol was produced in 55.7% yield after 100 min, 66.2% after 13 hr, and 66.6% after 34.3 hr.

Duplicate samples of triisobutylaluminum (0.904 mmol) and excess benzophenone (1.80 mmol) in diethyl ether (5 ml) were allowed to react. After 60 hr glpc analysis showed that 62.7 and 62.5% of the benzophenone had reacted.

Triisobutylaluminum (4.408×10^{-3} M) was allowed to react with excess benzophenone (9.453×10^{-3} M) for 397 hr. Ultraviolet spectral analysis indicated 66.2% reduction.

Ultraviolet Spectra of Ketones and Complex.—For examining the complex of triisobutylaluminum and benzophenone in diethyl ether, 35 μl of a standardized benzophenone solution was introduced into a rubber-capped 10-mm quartz ultraviolet cell containing 3 ml of 33.590×10^{-3} M triisobutylaluminum solution at room temperature (22°). The absorption of the mixture was recorded at appropriate time intervals from 380 to 260 mμ and compared with that of a standard benzophenone spectrum (Figure 1).

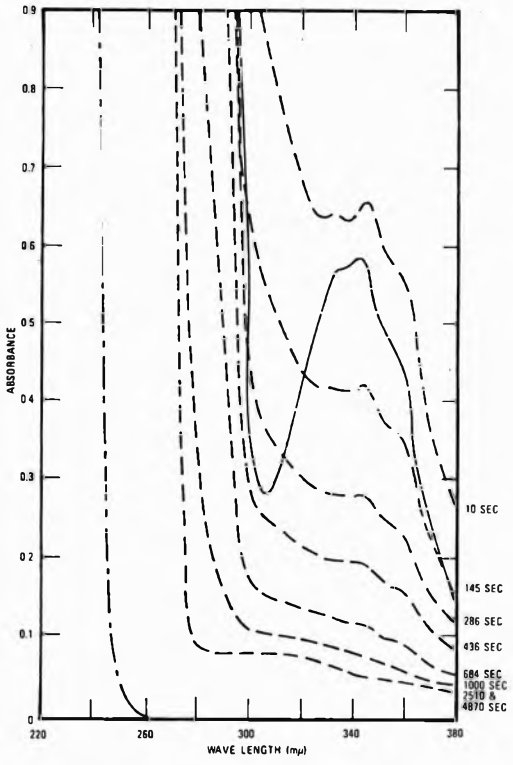


Figure 1.—Spectra of a diethyl ether solution 33.5×10^{-3} M in triisobutylaluminum and 5.19×10^{-3} M in benzophenone. Solid curve is the spectrum of a solution containing only 5.19×10^{-3} M benzophenone, and broken curve (— — — —) is the spectrum of a solution containing only 33.5×10^{-3} M triisobutylaluminum.

The extinction coefficients and uv absorption maxima of 4-substituted benzophenones in diethyl ether are recorded in Table I.

TABLE I
ULTRAVIOLET SPECTRAL DATA FOR 4-SUBSTITUTED BENZOPHENONES

Substituent	λ_{max}, mμ	ϵ
H	344.5	119[a]
Br	346	166 ± 1
Cl	345	150 ± 2
F	343	130 ± 1
Me	344	151 ± 2
MeO	330	281 ± 1
MeS	308	2120 ± 30

[a] From ref 5.

Kinetic Studies.—The kinetics of the reaction of triisobutylaluminum with benzophenone in diethyl ether were determined by following the disappearance of the benzophenone band at 344.5 mμ.

All equipment was heated over a burner flame and placed hot in the entry port of a dry box which was subsequently evacuated and refilled with nitrogen twice. All transfers of solutions were performed under a flow of prepurified nitrogen through a three-way Teflon stopcock using syringes; 100 ml of distilled diethyl ether was first added to the reaction flask followed by addition of an aliquot of triisobutylaluminum standard solution. The flask was weighed and the total volume of the solution was obtained from the density of diethyl ether at the kinetic temperature. Then the flask was wrapped with aluminum foil and placed in a constant-temperature bath (25 ± 0.05°). The flask and its contents were allowed to reach temperature equilibrium before a nitrogen line was attached to one side opening of the three-way stopcock. The stopcock was then turned to

(8) (a) T. L. Brown, D. W. Dickerhoof, D. A. Bafus, and G. L. Morgan, *Rev. Sci. Instrum.*, **33**, 491 (1962); (b) D. F. Shriver, "The Manipulation of Air Sensitive Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1969, pp 164–189.

(9) K. Ziegler, W. R. Kroll, W. Larbig, and O. W. Steudel, *Ann. Chem.*, **629**, 53 (1960).

(10) H. Reinheckel and K. Haage, *J. Prakt. Chem.*, **33**, 70 (1966).

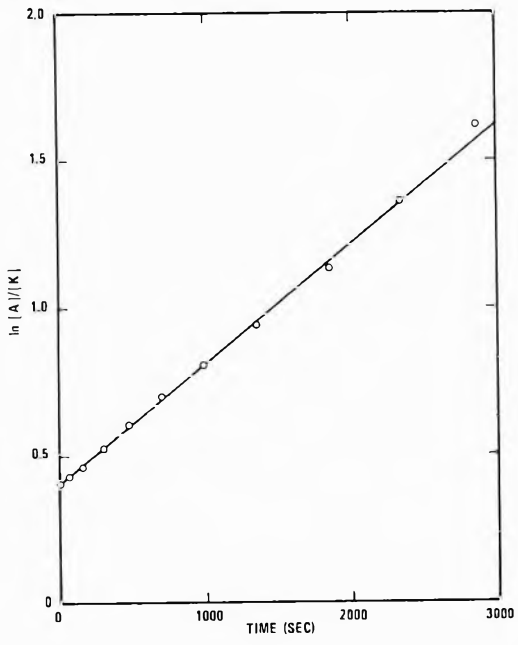


Figure 2.—Plot demonstrating second-order behavior of triisobutylaluminum and benzophenone in diethyl ether at 25° (run no. 6, Table III).

accept a syringe needle from the top with the nitrogen flow from the side, and the desired amount of benzophenone (0.25–0.65 ml) was added. A 6-ml sample was withdrawn immediately and quenched in 5 ml of ether-saturated 10% hydrochloric acid. Quenched samples were allowed to stand for 1 hr before the ether layer was transferred into a quartz cell. The amount of unreacted ketone was then determined at 344.5 mμ against a water-saturated ether sample.

The syringes (10 ml) used to withdraw the samples were flamed and purged with nitrogen by drawing gas into the barrel through the needle several times. The purging step was repeated after the syringes had cooled, after which *ca.* 5 ml of nitrogen was retained in the barrel of the syringe. This treatment was found to be necessary in order to avoid contamination of the reaction mixture during sample withdrawal. The concentration of a solution of benzophenone in diethyl ether after 14 withdrawals agreed within 0.15% of the initial concentration, and the absorbance of quenched solutions of benzophenone matched exactly the absorbance of the unquenched standard sample.

Triisobutylaluminum concentrations in diethyl ether were determined by decomposing aliquot samples with 10% hydrochloric acid, adding an excess of standard EDTA, and back titrating with standard zinc acetate solution (dithiazone indicator). The initial concentration of the triisobutylaluminum in the reaction flask was calculated from dilution. The reliability of the dilution at the kinetic concentration range was checked by diluting an aliquot of standard triisobutylaluminum solution with diethyl ether in a 200-ml volumeric flask. Some of this solution was used for kinetic runs and the remainder was weighed in order to calculate the volume from the density of diethyl ether. The solution was then hydrolyzed, decomposed, and analyzed. The analyzed concentration agreed within 0.2% of the concentration calculated by the dilution factor at the lowest concentration of triisobutylaluminum. The initial concentration of benzophenone was obtained from the extrapolation of its absorbance at 344.5 mμ *vs.* time.

Rate constants were calculated from the second-order rate equation

$$k = \frac{1}{t([A]_0 - [B]_0)} \ln \frac{[A]\,[B]_0}{[B]\,[A]_0}$$

where $[A]_0$ and $[B]_0$ are the initial concentrations of triisobutylaluminum and benzophenone and [A] and [B] represent the concentrations at time t. The average rate constant for each run was calculated from eight to twelve sets of benzophenone concentration–time values.

Results

The reaction of triisobutylaluminum and benzophenone in diethyl ether was found to produce on hydrolysis the reduction product benzhydrol in essentially quantitative yield without the side reactions of enolization or addition. In product-analysis studies, when triisobutylaluminum and benzophenone were allowed to react in the stoichiometric ratio of 1:2, the reaction proceeded to give benzhydrol in 66.6% yield after 34 hr. Previous workers have pointed out that only one of the isobutyl groups in triisobutylaluminum is available for reduction of benzophenone.[1b,c] Because of the importance of this point to the evaluation of kinetic data, the reaction of triisobutylaluminum and benzophenone in 1:2 ratio was repeated in duplicate. After 60 hr, the final product after hydrolysis contained 62.7 and 62.5% benzhydrol with unreacted ketone. The reaction at a ratio of 0.466:1 was further studied by following the disappearance of ketone absorbance. It showed 42% of the second group involved in the reaction after 397 hr (Table II).

TABLE II
REACTION OF TRIISOBUTYLALUMINUM AND BENZOPHENONE IN THE STOICHIOMETRIC RATIO OF 0.466:1 AT 25°

Time, hr	Absorbance at 344.5 mμ	Reaction of benzophenone, %
0	1.125	0
0.36	0.779	30.7
0.97	0.618	45.1
1.92	0.538	52.2
2.94	0.495	56.0
5.86	0.465	58.7
14.0	0.448	60.2
27.5	0.423	62.4
51.2	0.410	63.6
102.0	0.396	64.8
397	0.380	66.2

The absorption spectrum of 33.59×10^{-3} *M* triisobutylaluminum in a mixture with 5.19×10^{-3} *M* benzophenone in diethyl ether was recorded at appropriate intervals of time and is illustrated in Figure 1. In diethyl ether, the ultraviolet spectrum of benzophenone has maximum absorption at 344.5 mμ (ε 119) and 251 mμ (ε 1.8×10^4) with a trough at 305 mμ.[5] Triisobutylaluminum–diethyl ether solution does not show any appreciable absorbance at wavelengths longer than 270 mμ in the concentration range studied. The spectrum of the reaction mixture indicates that the absorbance is greater for the reaction mixture than for the pure ketone at the same ketone concentration and that the absorption gradually decreases as the reaction proceeds. Neither benzophenone nor triisobutylaluminum absorb at 400 mμ. The facts, that the mixtures show some absorbance at 400 mμ, the ketone trough at 305 mμ disappears completely, and stronger absorbance at 344.5 mμ is observed, indicate that complexation between triisobutylaluminum and benzophenone occurs, although only to a small extent.

The rate of disappearance of benzophenone was followed by quenching aliquot samples of the reaction mixture at appropriate intervals with 10% hydrochloric acid and determining the absorbance of unreacted benzophenone at 344.5 mμ. The reaction be-

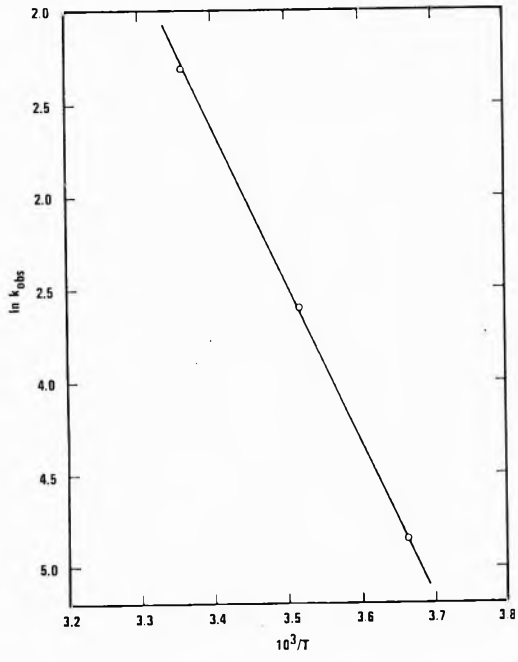


Figure 3.—Arrhenius plot of the reaction of triisobutylaluminum with benzophenone in diethyl ether over the temperature range of 0–25°.

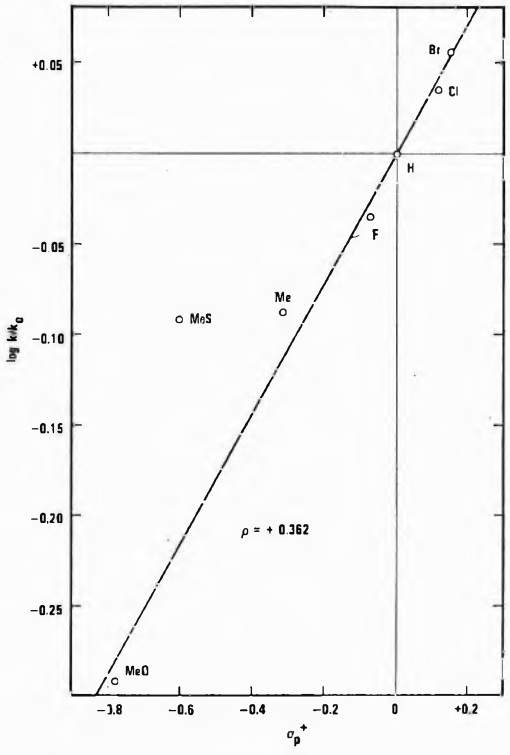


Figure 4.—Hammett plot of the reaction of triisobutylaluminum with 4-substituted benzophenones in diethyl ether at 25°.

tween triisobutylaluminum and benzophenone in diethyl ether was found to be first order in each reactant and second order overall. The average rate constant is 0.0994 ± 0.0039 l. mol^{-1} sec^{-1} at 25°. The second-order behavior was observed between 5 and 95% reaction. The rate constant was found to be independent of the reactant ratio (0.5:1 to 22:1) as well as the initial concentration of either reactant (initial benzophenone concentrations of 5.52–9.20 × 10^{-3} M and initial triisobutylaluminum concentrations of 4.408–160.6 × 10^{-3} M).

The method used for the kinetic study proved to be very satisfactory. Reaction mixtures showed no signs of hydrolysis or loss of diethyl ether owing to sample withdrawal over a period of time and the quenching procedure did not effect the actual concentration of benzophenone in solution. Data from a typical kinetic run is graphically illustrated in Figure 2 and the results of all kinetic investigations are summarized in Table III.

Measurements of reaction rates at 11.4 and 0° also showed the reaction to be second order. The Arrhenius plot is linear, as shown in Figure 3. The slope of the Arrhenius plot and the standard equations[11] were used to calculate the observed activation parameters listed in Table IV.

The second-order reaction rates of six 4-substituted benzophenones with triisobutylaluminum in diethyl ether at 25° are listed in Table V. Variation of the 4 substituents in benzophenone produced a significant but small electronic influence on the rate of reduction. The relative reactivities correlated best with Brown's substituent constant[12] σ^+ to give the Hammett equation log k/k_0 = (0.362 ± 0.070)σ^+ + 0.00 (Figure 4). The 4-thiomethyl substituent resulted in poor

(11) A. A. Frost and R. G. Pearson, "Kinetics and Mechanisms," John Wiley & Sons, Inc., New York, N. Y., 1961, pp 98–100.
(12) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

TABLE III

RATE CONSTANTS FOR THE REACTION OF TRIISOBUTYLALUMINUM WITH BENZOPHENONE IN DIETHYL ETHER

Temp, °C	Run	[(i-C$_4$H$_9$)$_3$Al]/[(C$_6$H$_5$)$_2$CO]	[(i-C$_4$H$_9$)$_3$Al] × 10^3 M	[(C$_6$H$_5$)$_2$CO] × 10^3 M	k_{obsd} × 10^2 l. mol^{-1} sec^{-1}
25	1	0.50	4.594	9.20	9.11 ± 0.42
	2	0.51	4.594	9.05	9.75 ± 0.67
	3	0.74	4.408	5.92	10.88 ± 0.50
	4	0.85	7.360	8.67	10.19 ± 0.26
	5	0.98	8.260	8.47	9.35 ± 0.12
	6	1.50	8.260	5.52	9.65 ± 0.34
	7	1.50	12.58	8.39	9.70 ± 0.22
	8	2.03	17.75	8.76	9.80 ± 0.25
	9	3.05	22.12	7.25	10.39 ± 0.21
	10	4.02	26.17	6.51	9.42 ± 0.19
	11	5.41	39.23	7.25	10.27 ± 0.11
	12	21.9	160.62	7.33	10.76 ± 0.17[a]
				Avg	9.94 ± 0.39
11.4	13	2.11	18.17	8.61	2.68 ± 0.08
	14	2.20	18.17	8.24	2.78 ± 0.07
				Avg	2.73 ± 0.05
0	15	3.26	27.15	8.32	0.785 ± 0.030
	16	3.14	27.15	8.65	0.775 ± 0.028
	17	3.38	27.15	8.04	0.791 ± 0.035
				Avg	0.784 ± 0.006

[a] Rate constant calculated from the pseudo-first-order equation $k = 1/[A]_0(1/t)\ln[B]_0/[B]$.

TABLE IV

ACTIVATION PARAMETERS FOR THE REACTION OF TRIISOBUTYLALUMINUM WITH BENZOPHENONE IN DIETHYL ETHER AT 25°

Activation energy E_a = 16.4 kcal/mol
Frequency factor A = 10^{11} l. mol^{-1} sec^{-1}
Free energy of activation ΔG^* = 18.8 kcal/mol
Enthalpy of activation ΔH^* = 15.8 kcal/mol
Entropy of activation ΔS^* = −10.1 eu

TABLE V

RATE CONSTANTS FOR THE REACTION OF TRIISOBUTYLALUMINUM WITH 4-SUBSTITUTED BENZOPHENONES IN DIETHYL ETHER AT 25°

4 substituents	Run	$[(i\text{-}C_4H_9)_3Al]/[(C_6H_5)_2CO]$	$[(i\text{-}C_4H_9)_3Al] \times 10^3$ M	$[(C_6H_5)_2CO] \times 10^3$ M	$k_{obsd} \times 10^2$ l. mol^{-1} sec^{-1}
Bromo	18	5.04	19.42	3.85	11.45 ± 0.42
	19	2.52	19.22	7.62	11.14 ± 0.23
				Avg	11.29 ± 0.15
Chloro	20	4.23	21.34	5.04	10.77 ± 0.12
	21	3.30	19.20	5.81	10.78 ± 0.05
				Avg	10.78 ± 0.01
Fluoro	22	2.30	19.33	8.42	9.21 ± 0.22
	23	2.31	19.33	8.38	9.10 ± 0.28
				Avg	9.16 ± 0.06
Methyl	24	9.76	31.73	3.25	8.11 ± 0.30
	25	3.81	31.29	8.27	8.12 ± 0.08
				Avg	8.12 ± 0.01
Methoxy	26	6.86	19.48	2.84	5.07 ± 0.30
	27	4.66	19.42	4.18	5.09 ± 0.15
				Avg	5.08 ± 0.01
Thiomethyl	28	8.68	4.749	0.547	8.15 ± 0.44
	29	8.41	3.391	0.403	7.95 ± 0.20
				Avg	8.05 ± 0.10

correlation and was excluded from the calculation of the reaction constant (ρ).

Discussion

Previous workers have reported that the reactions of trimethylaluminum[1c,4,5] and triphenylaluminum[13] with ketones proceed without any occurrence of reduction products. On the other hand, triisobutylaluminum produces entirely reduction product when allowed to react with typical ketones.[1b,c,3] It has been suggested by Wittig that the mechanism of reduction involves the migration of a β hydrogen from the alkyl group of the aluminum alkyl to the carbonyl carbon. Such a mechanism already has been reasonably well demonstrated for the reduction of ketones by magnesium alkyls (Grignard reagents).[14]

The availability of the second isobutyl group in triisobutylaluminum for reduction was indicated by reaction of triisobutylaluminum with benzophenone in 1:2 ratio. A greater than 50% yield of benzhydrol indicates reaction of the second alkyl group at some reduced rate. Fortunately, however, the reactivity of the second alkyl group turned out to be kinetically unimportant. Even when the triisobutylaluminum–benzophenone ratio was 1:2, 94% of the reaction proceeded by utilization of the first alkyl group.

Spectroscopic studies indicated complex formation between the reacting species (eq 1). Similar spectral

$$(C_6H_5)_2C{=}O + (i\text{-}C_4H_9)_3Al \rightleftharpoons (C_6H_5)_2C{=}O\cdots Al(i\text{-}C_4H_9)_3 \quad (1)$$

changes have been attributed to complex formation in the addition reaction of methylmagnesium bromide[15] and trimethylaluminum[4,5] with ketones. Unfortunately, the exact extent of complexation cannot be estimated from the spectral data alone. However, the second-order kinetic results indicate that the formation of the complex occurs either quantitatively or to a very small extent. Complexation of benzophenone and trimethylaluminum in diethyl ether was found to be very small,[5] although in benzene it was quantitative.[4] These results are easily explainable on the basis that diethyl ether will compete with benzophenone as a Lewis base for the Lewis acid, trimethylaluminum, suggesting that the equilibrium constant (K) for complex formation (eq 2) is small in diethyl ether. The spectrum of benzophenone and triisobutylaluminum in diethyl ether is similar to that of benzophenone and trimethylaluminum in diethyl ether, and therefore complex formation should be even smaller with the more sterically hindered aluminum alkyl. Since the extent of complexation is relatively small, a steady-state treatment of the kinetic data is in order. In addition, the immediate change of the spectral profile in the complex study (Figure 1) suggests that the complex-formation step is fast on the time scale of conversion of reactants into products.

The second-order kinetic data obtained for the reaction of triisobutylaluminum and benzophenone in diethyl ether are similar to those of the reduction of di-*t*-butyl ketone with di-*t*-butylmagnesium in tetrahydrofuran,[6] except that the second alkyl group reacts at a competitive rate in the case of magnesium. The kinetic data are also similar to those from reaction of benzophenone and trimethylaluminum in diethyl ether,[5] where the second alkyl group is not involved at all.

The second-order kinetic data and spectroscopic observation of a complex suggests a multiple-step mechanism involving the complex as an intermediate (eq 2 and 3). If $k_2 \gg k_{-1}$ eq 5 obtains. If $k_2 \ll k_{-1}$ eq 6 obtains.

(13) (a) G. Wittig, F. J. Meyer, and G. Gange, *Ann. Chem.*, **571**, 167 (1951); (b) T. Mole, *Aust. J. Chem.*, **16**, 807 (1963).

(14) G. E. Dunn and J. Warkentin, *Can. J. Chem.*, **34**, 75 (1956); H. S. Mosher and E. M. LaCombe, *J. Amer. Chem. Soc.*, **72**, 3994 (1950); H. S. Mosher, J. E. Stevenot, and D. O. Kimble, *ibid.*, **78**, 4374 (1956).

(15) (a) S. G. Smith, *Tetrahedron Lett.*, **7**, 409 (1963); (b) S. G. Smith and G. Su, *J. Amer. Chem. Soc.*, **86**, 2750 (1964); (c) S. G. Smith and G. Su, *ibid.*, **88**, 3995 (1966); (d) S. G. Smith and J. Billet, *ibid.*, **89**, 6948 (1967); (e) J. Billet and S. G. Smith, *ibid.*, **90**, 4108 (1968); (f) N. M. Bikales and E. I. Becker, *Can. J. Chem.*, **41**, 1329 (1962).

$$A + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C \quad (2)$$

$$C \xrightarrow{k_2} P \quad (3)$$

$$\frac{d[P]}{dt} = k_2[C] = \frac{k_2k_1}{k_{-1} + k_2}[A][B] \quad (4)$$

$$\frac{d[P]}{dt} = k_1[A][B] \quad (5)$$

$$\frac{d[P]}{dt} = k_2K[A][B] \quad (6)$$

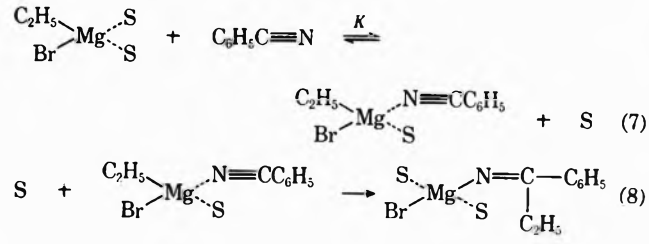
In the equations, A = triisobutylaluminum [$(i\text{-}C_4H_9)_3Al$]; B = benzophenone [$(C_6H_5)_2C{=}O$]; C = complex between reacting species; and P = product, benzhydryloxydiisobutylaluminum [$(i\text{-}C_4H_9)_2AlOCH(C_6H_5)_2$]. Equation 4 assumes a steady-state approximation. If complex formation is the rate-determining step, *i.e.*, $k_2 \gg k_{-1}$, the rate expression is given in eq 5, where $k_{obsd} = k_1$. Alternatively, if product formation is the rate-determining step, *i.e.*, $k_2 \ll k_{-1}$, the rate expression reduces to eq 6, where $k_{obsd} = k_2K$.

From the Hammett plot (Figure 4), the rate constants of the reduction reaction of triisobutylaluminum with 4-substituted benzophenones in diethyl ether at 25° were determined and a ρ value of +0.362 was calculated. The linear Hammett relationship indicates that the substituents do not shift the rate-determining step of the reaction nor produce a new reaction path to form the product. The reaction step requiring complex formation is favored by electron-releasing groups in the ketone. The transfer of the β hydrogen of the alkyl group in triisobutylaluminum to the carbon of the carbonyl group in the product formation step is aided by electron-withdrawing groups attached to the ketone. Since the overall rate of the reduction depends on both the equilibrium constant K for the complex formation (eq 2) and the rate constant k_2 for transfer of the β hydrogen atom (eq 3), the two substituent effects nearly cancel each other and thus the observed rates displayed very little variation with changing substituents. A small ρ value is also consistent with a concerted process, since substituent effects would tend to be nullified and little charge separation would be expected in the transition state.

For some multiple-step mechanisms, the sign of the overall reaction constant (ρ) is not always consistent with that of the rate-determining step.[16] However, the positive ρ value, as well as spectroscopic observation of immediate complex formation, indicates that the electrophilic complex formation step is not the rate-determining step of the reaction. Therefore, the nucleophilic product formation step is considered to be the rate-determining step. The considerable negative entropy of activation ($\Delta S^{\ddagger} = -10.1$ eu) indicates that the transition state of the rate-determining step is cyclic.

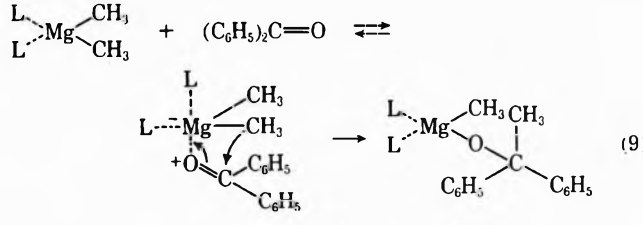
A further consequence of the small ρ value is that the complex is not formed by the attack of a hydride ion at the carbon atom of the carbonyl groups, as postulated in the reaction of sodium borohydride with ketones.[17] This mechanism is analogous to that for ester hydrolysis,[18] both reactions of which possess considerably large ρ values (+2.61–3.06).[19]

It is important to note that the reduction rate of triisobutylaluminum[1c] and the addition rate of trimethylaluminum[4,5] with benzophenone decreases drastically when proceeding from hydrocarbon to ether solvent. Also previous studies concerning the effect of solvent in the nucleophilic addition of ethylmagnesium bromide with benzonitrile indicated that the reaction rate also decreases as the basicity of the solvent increases.[20] The explanation offered for this effect was that the formation of the product proceeds through complex formation. Since the complex is formed by displacement of one of the solvent molecules coordinated to the Grignard compound (eq 7 and 8), the more basic solvent would result in more difficult displacement of the solvent and hence a smaller concentration of complex (smaller K). Similar (but less clear



cut) results have also been reported in a study of solvent effects in the reaction of ethylmagnesium bromide with benzophenone.[21]

An interesting recent report on the reaction of dimethylmagnesium with benzophenone is also concerned with the effect of solvent on the mechanism of the alkylation reaction.[22] In this study the effect of donor ligands on the rate of alkylation in diethyl ether was studied. The addition of monodentate ligands had little effect on the reaction rate; however, bidendate ligands were found to either retard or accelerate the reaction. From these observations the authors postulated that the reaction involves a pentacoordinate intermediate or transition state without the displacement of a donor ligand or solvent molecule (eq 9).



Actually, one cannot distinguish with certainty between the two possible paths involving complex formation (a tetracoordinate intermediate with solvent displacement or a pentacoordinate intermediate without

(16) W. P. Jenks, *Progr. Phys. Org. Chem.*, **2**, 63 (1964).

(17) H. C. Brown, O. H. Wheeler, and K. Ichikawa, *Tetrahedron*, **1**, 214 (1957).

(18) M. L. Bender, *Chem. Rev.*, **60**, 60 (1969).

(19) (a) G. G. Smith and R. P. Bayer, *Tetrahedron*, **18**, 323 (1962); (b) P. T. Lansbury and R. G. MacLeay, *J. Amer. Chem. Soc.*, **87**, 851 (1965); (c) J. A. Parry and K. D. Warren, *J. Chem. Soc.*, 4049 (1965); (d) K. Bowden and M. Hardy, *Tetrahedron*, **22**, 1169 (1966).

(20) A. A. Scala and E. I. Becker, *J. Org. Chem.*, **30**, 3491 (1965).

(21) R. N. Lewis and J. R. Wright, *J. Amer. Chem. Soc.*, **74**, 1253 (1952).

(22) H. C. House and J. E. Oliver, *J. Org. Chem.*, **33**, 929 (1968).

the displacement of solvent) on the basis of the data at hand. As the solvent is changed from benzene to ether, the equilibrium (eq 10) will shift to the right.

$$R_3Al + L \rightleftharpoons R_3Al \cdot L \quad (10)$$

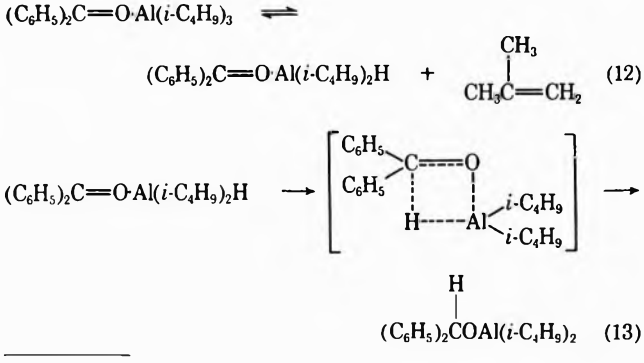
Therefore, the complexation of trialkylaluminum with ketone in ether should decrease, since solvent must be displaced, or, if solvent is not displaced, steric hindrance and decreased Lewis acidity of the metal will cause a decrease in the complexation. It would appear that the first case is more probable.

It might be suggested that, since direct spectroscopic evidence has been obtained for the occurrence of complex between the reacting species, a concerted one-step mechanism does not appear as likely. However, the question is raised whether the complex is actually an intermediate in product formation or whether it is merely involved in a nonproduct-forming equilibrium (eq 11).[15c,22] This alternative mechanism

$$P \longleftarrow A + B \rightleftharpoons C \quad (11)$$

is consistent with all observations. If the complex is not involved in product formation (eq 11), then the product must be formed by a concerted attack on the carbonyl group (aluminum on oxygen and β hydrogen on carbon). However, the drastic decrease in the reaction rate from benzene to ether solvent is best explained by the fact that the concentration of complex is much greater in benzene than in ether. Therefore, it is more reasonable to believe that the product is formed *via* complex formation with the attack of β hydrogen on the carbon atom of the carbonyl group *via* a six-center transition state.

An alternative transfer of the β hydrogen of triisobutylaluminum to the carbonyl carbon, also proposed as a possibility in Grignard reduction reactions,[23] can be explained by olefin elimination as a consequence of ketone attack, followed by reduction of the ketone by diisobutylaluminum hydride (eq 12 and 13). Since



(12)

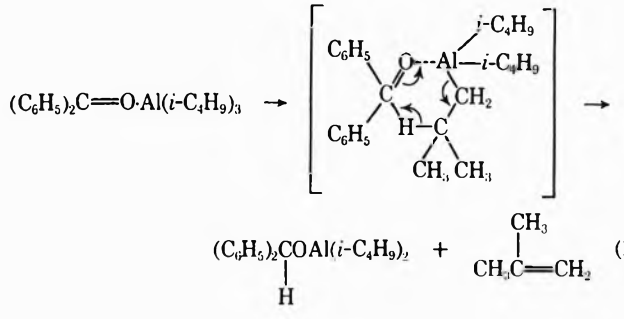
(13)

(23) K. Hess and H. Rheinboldt, *Chem. Ber.*, **54B**, 2043 (1921).

diethyl ether has already been shown to be a stronger base toward aluminum alkyls than benzophenone, if the above mechanism is correct, isobutylene ahould be displaced from triisobutylaluminum in diethyl ether solvent. However, it is known that triisobutylaluminum etherate can be distilled at 80–90° without olefin displacement. Therefore, the above mechanism does not seem probable. This alternative path could be easily tested by asymmetric reduction studies, as was carried out in Grignard reduction studies.[24]

Consistent with all observations, the detailed reduction mechanism proposed for the reaction of triisobutylaluminum with benzophenone in diethyl ether is given in eq 14 and 15.

$$(C_6H_5)_2C{=}O + Al(i\text{-}C_4H_9)_3 \rightleftharpoons (C_6H_5)_2C{=}O \cdot Al(i\text{-}C_4H_9)_3 \quad (14)$$



(15)

In eq 15, a rapid equilibrium step, benzophenone forms a complex with triisobutylaluminum in small concentration. In eq 16, an intramolecular rearrangement of the complex occurs in a rate-determining step to form the product *via* a cyclic six-center transition state as proposed in the Grignard reduction reaction.[25] Further work is in progress to determine with a higher degree of confidence whether the rate-determining step of this reaction proceeds through complex formation or is concerted.

Registry No.—Triisobutylaluminum, 100-99-2; benzophenone, 119-61-9; 4-bromobenzophenone, 90-90-4; 4-chlorobenzophenone, 134-85-0; 4-fluorobenzophenone 345-83-5; 4-methylbenzophenone, 134-84-9; 4-methoxybenzophenone, 611-94-9; 4-thiomethylbenzophenone, 23405-48-3.

Acknowledgment.—We are indebted to the National Science Foundation for partial support of this work.

(24) H. D. Morrison, *Survey Progr. Chem.*, **3**, 147 (1966).

(25) F. C. Whitmore 105th National Meeting of the American Chemical Society, Atlantic City, N. J., April 1963, as quoted by H. S. Mosher and E. Lacombe, *J. Amer. Chem. Soc.*, **77**, 3994 (1950).

Sodium Borohydride Reduction of Conjugated Aldehydes and Ketones

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Received August 21, 1969

The reduction of conjugated aldehydes and ketones by sodium borohydride leads, in general, to substantial amounts of fully saturated alcohol products. In alcohol solvents the formation of saturated β-alkoxy alcohols (involving solvent addition to the double bond) is observed. This product is enhanced by added solvent conjugate base and depressed by addition of trialkyl borate. The structural features which control the extent of simple carbonyl reduction, 1,4 reduction, and solvent addition have been examined, as well as the effects of different solvents on the course of the reaction.

Sodium borohydride reduction of carbon–carbon double bonds has been observed in conjugated esters,[3] nitroalkenes,[4] and enol acetates.[5] These examples are apparently widely regarded as exceptions to the general rule that double bonds are inert to sodium borohydride. Based on the early literature report[6] that crotonaldehyde, cinnamaldehyde, and mesityl oxide yield only allylic alcohols with this reagent, most recent textbooks[7] either state or imply that carbonyl-conjugated double bonds are unaffected by sodium borohydride. Conversely, lithium aluminum hydride is often viewed as a less selective reagent based on the well-documented complete reduction of cinnamyl derivatives.[8]

In connection with another study requiring allylic alcohols, the sodium borohydride procedure was applied to 2-cyclohexenone. A very substantial percentage of the product was the fully reduced cyclohexanol. Examination of the literature revealed several similar reports[9–13] of conjugated ketone double-bond reduction, all of which involved substituted cyclohexenones. Although the number of specific examples of enone complete reduction exceeds those where only the carbonyl group is affected, the former are still viewed as abnormal.[13]

To clarify this question, we have examined the reduction of a number of unsaturated aldehydes and ketones under a variety of conditions.

(1) NDEA Title IV Predoctoral Fellow.

(2) Alfred P. Sloan Fellow, 1967–1969.

(3) M. S. Brown and H. Rapoport, *J. Org. Chem.*, **28**, 3261 (1963); S. B. Kadin, *ibid.*, **31**, 620 (1966); J. A. Meschino and C. H. Bond, *ibid.*, **28**, 3129 (1963); H. LeMoal, R. Carrie, and M. Bargain, *Compt. Rend.*, **251**, 2541 (1960).

(4) H. Shechter, D. E. Ley, and E. B. Robinson, Jr., *J. Amer. Chem. Soc.*, **78**, 4984 (1956).

(5) W. G. Dauben and J. F. Eastham, *ibid.*, **73**, 4463 (1951); W. G. Dauben, R. A. Micheli, and J. F. Eastham, *ibid.*, **74**, 3852 (1952).

(6) S. W. Chaikin and W. G. Brown, *ibid.*, **71**, 122 (1949).

(7) For example, see H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 40; R. T. Morrison and R. N. Boyd, "Organic Chemistry," 2nd ed, Allyn and Bacon, Inc., Boston, Mass., 1966, p 639; C. D. Gutsche, "The Chemistry of Carbonyl Compounds," Prentice-Hall, Englewood Cliffs, N. J., 1965, p 65; J. March, "Advanced Organic Chemistry," McGraw-Hill Book Co., San Francisco, Calif., 1968, p 679; A. Liberles, "Introduction to Theoretical Organic Chemistry," The Macmillan Co., New York, N. Y., 1968, p 510; L. O. Smith, Jr., and S. J. Cristol, "Organic Chemistry," Reinhold Publishing Co., New York, N. Y., 1966, p 442.

(8) R. F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.*, **70**, 3738 (1948); F. A. Hochstein and W. G. Brown, *ibid.*, **70**, 3483 (1948); M. J. Jorgenson, *Tetrahedron Lett.*, 599 (1962).

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(10) T. L. Jacobs and R. B. Brownfield, *J. Amer. Chem. Soc.*, **82**, 4033 (1960).

(11) N. W. Atwater, *ibid.*, **83**, 3071 (1961).

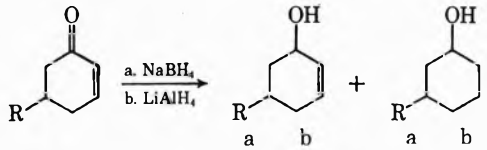
(12) W. R. Jackson and A. Zurqiyah, *J. Chem. Soc.*, 5280 (1965); K. Igbal and W. R. Jackson, *ibid.*, *C*, 616 (1968).

(13) (a) J. W. Wheeler and R. H. Chung, *J. Org. Chem.*, **34**, 1149 (1969). (b) Cyclopentenone appears to be particularly susceptible to conjugate reduction. *Cf.* P. L. Southwick, N. Latif, B. M. Fitzgerald, and N. M. Zaczek, *ibid.*, **31**, 1 (1966); H. C. Brown and H. M. Hess, *ibid.*, **34**, 2206 (1969).

Results and Discussion

As the following data clearly demonstrate, reduction of a conjugated double bond is a substantial competing process in the sodium borohydride reduction of both cyclic and acyclic ketones. Acrolein (**6**) and crotonaldehyde (**7**) (in contrast to the early report of Chaikin and Brown[6]) also exhibit some conjugate reduction. Table I compares results obtained with borohydride in 50% aqueous ethanol with those from $LiAlH_4$ reduction; the much greater carbonyl selectivity of the latter is evident. The cyclic ketones with sodium borohydride are more prone to conjugate reduction than the acyclic analogs, while both types show the anticipated effects of β-alkyl substitution. In keeping with simple steric arguments, the aldehydes exhibit a greater preference for direct carbonyl reduction; one β-methyl group (**7**) lowers the amount of 1,4 reduction, but interestingly, the effect is not so great as that of a single α-methyl substituent (as in methacrolein, **8**), where only carbonyl reduction is observed.

Two substituted 2-cyclohexenones, 5-methyl- and 5-*t*-butyl-, were also subjected to the reduction conditions used to obtain the data in Table I. Both gave results similar to those from the unsubstituted **4** (eq 1).



(1)

	a	b	a	b
R = CH_3	49%	90%	51%	9%
R = *t*-butyl	42%	92%	58%	7%

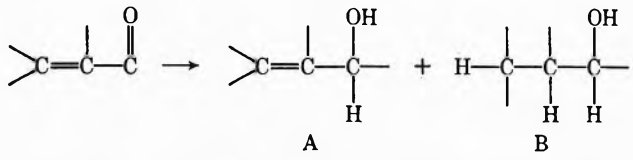
Again, as in the case of **1** and **4**, $LiAlH_4$ reduction led to a small amount of saturated ketone after hydrolysis. This product almost certainly arises by conjugate hydride addition; the saturated alcohol may be derived from hydroalumination of the allylic alcoholate[8] or reduction of the saturated ketone formed during hydrolysis.[14]

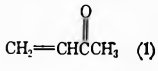
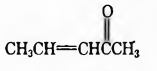
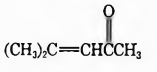
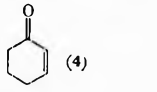
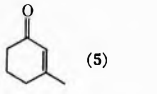
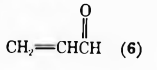
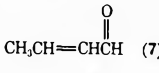
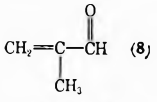
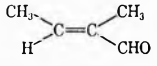
In the original work of Chaikin and Brown[6] the reductions of **3** and **7** were carried out in aqueous solution. Repetition of these reactions in water gave exactly the same results as shown for aqueous alcohol in Table I. We can only conclude that these authors were unable, because of analytical limitations, to observe the relatively small amount (8% for each) of conjugate reduction product formed from these systems.

Isopropyl alcohol (*i*-PrOH) is widely used as a solvent for sodium borohydride reductions, and the

(14) J. A. Marshall, N. H. Andersen, and A. R. Hochstetler, *ibid.*, **32**, 113 (1967).

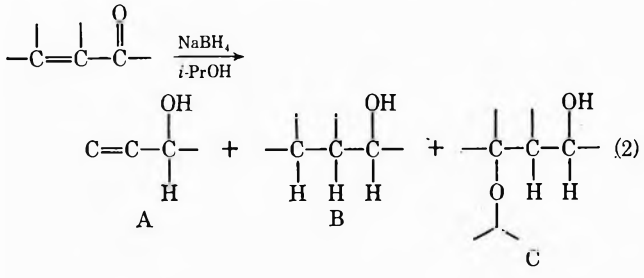
TABLE I



Substrate	$NaBH_4$, 50% aqueous EtOH			$LiAlH_4$, ether		
	Yield, %[a]	% A	% B	Yield, %[b]	% A	% B
 (1)	86	57	43	79	83	7[d]
 (2)	90	65	35	85	98	1
 (3)	89	92	8	82	100	0
 (4)	90	59	41	97	94	2[c]
 (5)	90	70	30[d]	88	100	0
 (6)	70	85	15	70	96	2
 (7)	91[b]	92	8	94	100	0
 (8)	100	≥99	≤1	98	100	0
 (9)	95	≥99	≤1	82	100	0

[a] Determined by vpc. [b] Distilled yield. [c] The $LiAlH_4$ reductions of **1** and **4** also gave 10 and 4%, respectively, saturated ketone products; small amounts of analogous materials were obtained from **2** and **6**. [d] 84% *cis* and 16% *trans*-3-methylcyclohexanol.

behavior of conjugated carbonyl compounds in this medium was therefore of interest. An unprecedented observation was the formation of saturated 3-isopropoxy alcohol product (eq 2). The data for reduction of compounds **1**–**9** are shown in Table II.



The ethereal products for several of these systems could be identified by alternate synthesis *via* isopropoxymercuration–reduction. The oxymercuration is known[15] to be primarily controlled by inductive effects and allylic alcohols tend on this basis to give largely the 3-solvoxy product.[16] However, alkyl substituents directly attached to the double bond completely override the effect of the more remote hydroxyl group, as shown by the data in Table III. The reaction is in general regiospecific,[17] with only crotyl alcohol (**16**) showing

TABLE II

REDUCTION BY SODIUM BOROHYDRIDE IN ISOPROPYL ALCOHOL

Substrate	Yield,[a] %	Product distribution[b,c]		
		% A	% B	% C
1	90	10	30	60
2	85[c]	34	33	33
3	85	65	34	1
4	85	25	48	27[d]
5	85	63	37[e]	0
6	89	53	26	21
7	85	59	15	26
8	65	≥95	≤4	≤1
9	84	98	2	0

[a] Overall distilled yield. [b] The products A, B, and C are designated in eq 2. [c] Determined by vpc. [d] 85% *cis*- (lower retention time) and 15% *trans*-3-isopropoxycyclohexanol. [e] 88% *cis*- and 12% *trans*-3-methylcyclohexanol.

evidence of any alternate positional isomer. The 2-alkoxy alcohols in all cases examined have markedly lower vpc retention times than the 3-alkoxy analogs. Compound **11** showed no evidence of positional isomer formation, but, like the cyclic compounds **13** and **14**, gave a diastereomeric mixture of 3-alkoxy derivatives. In order of increasing vpc retention times, the ratio was *ca.* 30% to 70%; the sodium borohydride in *i*-PrOH reduction of the corresponding enone **2** gave the same two ethereal products, but in a ratio of *ca.* 60% to 40%. Similar reversal in product distribution is observed for the two reactions using enone **4** and allylic alcohol **13**.

(15) J. Halpern and H. B. Tinker, *J. Amer. Chem. Soc.*, **89**, 6427 (1967).
(16) M. R. Johnson and B. Rickborn, *Chem. Commun.*, 1073 (1968); *J. Org. Chem.*, **34**, 2781 (1969).
(17) A. Hassner, *ibid.*, **33**, 2684 (1968).

SCHEME I

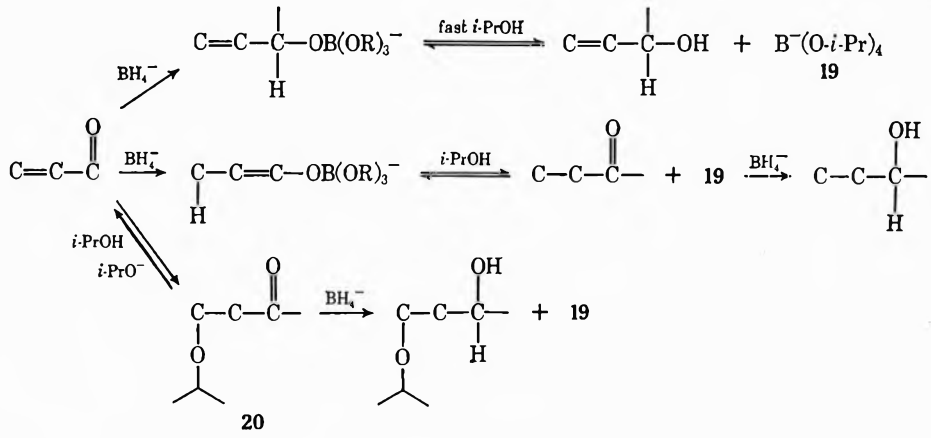
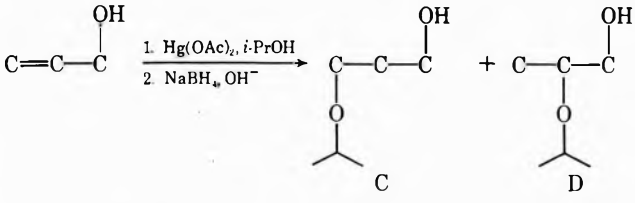
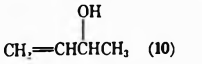
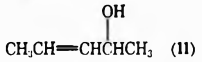
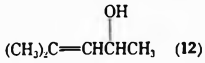
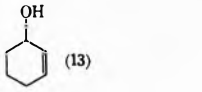
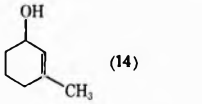
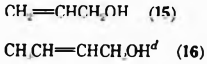
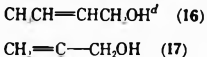
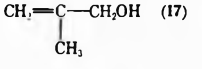
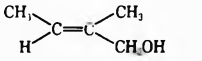


TABLE III

ISOPROPOXYMERCURATION–REDUCTION OF ALLYLIC ALCOHOLS



Substrate	Yield, %[a]	% C	% D
 (10)	46	0	100
 (11)	32	100	0
 (12)	26	100	0
 (13)	38	100[b]	0
 (14)	52	100[c]	0
 (15)	85	0	100
 (16)	38	96	4
 (17)	35	0	100
	30	0	100

[a] Distilled yield; the remainder was recovered starting material. [b] 75% *trans*- and 25% *cis*-3-isopropoxycyclohexanol. [c] 60% *trans*-3-isopropoxy-*cis*- and 40% *cis*-3-isopropoxy-*trans*-3-methylcyclohexanol. [d] The solvoxymercuration carried out in methanol and ethanol gave higher yields but very similar product distribution.

The formation of isopropoxy-substituted products in the sodium borohydride reductions in *i*-PrOH solution is of mechanistic interest. We propose that the overall reaction occurs as shown in Scheme I. In no instance was any detectable amount of product alcohol (allylic or saturated) adduct to the β position observed; the simplest explanation for this observation is that rapid exchange of alkoxide moiety on boron occurs, and the product alcohol is then present in insufficient amount to compete with the *i*-PrOH. Further, the species which adds to the enone is the isopropoxide anion *per se*, rather than, *e.g.*, the tetraisopropoxyboronate ion **19**. Although sodium salts of species such as **19** are known to be relatively stable as solids, available evidence suggests that appreciable dissociation (eq 3) may occur in

$$B(OR)_4^- \rightleftharpoons B(OR)_3 + OR^- \qquad (3)$$

solution.[18] The generation of strong base during reduction is also supported by the observation that attempted reduction of crotonaldehyde by inverse addition of reagents (*i.e.*, addition of $NaBH_4$ in small portions to a solution of the aldehyde in any hydroxylic solvent) leads to extensive polymerization.

Comparison of the data in Tables I and II indicates a solvent effect on the ratio of 1,2 to 1,4 reduction, with the latter enhanced in *i*-PrOH relative to aqueous ethanol. Jackson and Zurqiyah,[12] on the basis of their observation that only conjugate reduction of 3-methylcyclohexenone, carvenone, and cholestenone occurs in pyridine solution, have suggested that the initial hydride transfer from BH_4^- occurs exclusively at the β position, with subsequently formed (in other solvents) alkoxyborohydride species giving a mixture of carbonyl and conjugate reduction. This proposal required that at least 25% fully saturated product be formed; while this was observed with the cyclic enone systems,[12] it does not hold in the present work for compounds **3** and **6–9** (*cf.* Table I). It therefore appears that the initial hydride transfer from BH_4^- can occur at either position.

If the isopropoxide-catalyzed equilibrium between enone and 3-alkoxy ketone **20** (Scheme I) were rapidly established, the amount of ethereal alcohol product should be independent of the isopropoxide ion concentration. This is not the case, as shown by the data in Table IV. All of the systems examined except **3**, **5**, and **9** showed a significant increase in 3-isopropoxy alcohol with added NaO-*i*-Pr. The exceptions have a common feature, the double bond being trisubstituted. The lack of appreciable ether product formation may be associated with either a very low rate of attack by isopropoxide ion or a very small equilibrium constant for formation of **20**. This equilibrium probably strongly favors the unsaturated carbonyl compound in

(18) H. Steinberg, "Organoboron Chemistry," Vol. 1, Interscience Publishers, Inc., New York, N. Y., 1964, p 613.

TABLE IV

SODIUM BOROHYDRIDE REDUCTION WITH ADDED SODIUM ISOPROPOXIDE[a]

Substrate	% C[b]
1	96
2	43
3	2
4	72
5	0
6	70
7	81
8	30
9	0

[a] One mole of isopropoxide per mole of carbonyl compound. [b] The overall yields were again quite high; the remainder is a mixture of A and B (*cf.* Table II). The ratio of A to B remains unchanged within experimental error.

all of the systems investigated.[19] Formation of substantial amounts of ethereal alcohol products merely requires that the alkoxy ketone be reduced much faster than the starting material. This behavior is anticipated from the known importance of inductive effects on reduction by sodium borohydride.[21]

The data in Table IV show that, for many systems, reduction in the presence of added alkoxide can be a synthetically useful procedure for the preparation of 3-alkoxy alcohols. This is particularly evident where the solvoxymercuration procedure gives the 1,2 derivative (*cf.* Table III). Solvent addition is not restricted to *i*-PrOH; crotonaldehyde was reduced by sodium borohydride in a number of common alcohols as solvent, giving the results shown in Table V. The relatively

TABLE V

SODIUM BOROHYDRIDE REDUCTION OF CROTONALDEHYDE IN VARIOUS ALCOHOL SOLVENTS

Solvent ROH, R	*n*-BuOH	Crotyl alcohol	3-Alkoxy alcohol
Me	7	56	37
Et	9	84	7
n-Pr	11	63	26
i-Pr	15	59	26
n-Bu		(79)	(21)
i-Bu	4	68	28
sec-Bu	2	86	12[a]
t-Bu	7	93	0
Allyl	4	85	11

[a] Mixture of diastereomers.

large amount of solvent incorporation in methanol is presumably due to the methoxide generated by the fairly rapid reaction of borohydride with this medium. Only *t*-butyl alcohol failed to give any measurable solvent addition (or other possible ethereal product, *e.g.*, crotyl or *n*-butyl alcohol adducts); an attempt to force this reaction course by carrying out the reduction in the presence of potassium *t*-butoxide gave extensive polymerization, with negligible volatile products being formed. It is also worth noting in this connection that reductions in water or aqueous alcohol give high yields of carbonyl and conjugate reduction products, and consequently solvent addition cannot be an important pathway under these conditions. This may be a result of the strongly enhanced rate of reduction in aqueous solvent.

Two systems, methyl vinyl ketone (**1**) and crotonaldehyde (**7**), were examined further to see if solvent incorporation could be eliminated by trapping isopropoxide with the Lewis acid triisopropylborate. The results are presented in Table VI. Added borate ester

TABLE VI

EFFECT OF B(O-*i*-Pr)$_3$ ON ISOPROPYL ALCOHOL INCORPORATION

Substrate	Reagent[a]	% C[b]
1		60
1	B(O-*i*-Pr)$_3$, 1.35	25
7		26
7	B(O-*i*-Pr)$_3$, 1.35	16
7	NaO-*i*-Pr, 1.0	81
7	B(O-*i*-Pr)$_3$, 1.35; NaO-*i*-Pr, 1.0	65

[a] Moles per mole of substrate. [b] See eq 2.

does diminish the amount of isopropyl ether formed, but, fails to completely exclude this process. Furthermore, when triisopropyl borate (excess) and sodium isopropoxide were added to the borohydride solution prior to addition of **7**, the amount of isopropoxy alcohol was significantly increased relative to the result with neither reagent added. These observations are consistent with the view that the tetraisopropoxyborate anion is appreciably dissociated (eq 3) in *i*-PrOH solution.

Finally, mesityl oxide (**3**) provides an example of yet another possible side reaction which may occur in sodium borohydride reductions. This compound has long been known[22] to exist in equilibrium (catalyzed by either acid or base) with isomesityl oxide (**21**) (eq 4).

$$3 \underset{}{\overset{H^+ \text{ or } OR^-}{\rightleftharpoons}} \underset{\displaystyle CH_3}{\overset{\displaystyle O}{CH_2{=}C{-}CH_2\overset{\displaystyle \|}{C}CH_3}} \qquad (4)$$

21

The equilibrium (no solvent, 25°) has been shown to favor **3** (*ca.* 90% **3**, 10% **21**) by Stross and coworkers.[23] Reduction of different known mixtures of **3** and **21** (eq 5) gave the results shown in Table VII. With

$$3 + 21 \longrightarrow \underset{\displaystyle \mathbf{12}}{\overset{\displaystyle OH}{(CH_3)_2C{=}CHCHCH_3}} + \underset{\displaystyle \mathbf{22}}{\overset{\displaystyle OH}{(CH_3)_2CHCH_2CHCH_3}} + \underset{\displaystyle \mathbf{23}}{\overset{\displaystyle CH_3 \quad OH}{CH_2{=}C{-}CH_2CHCH_3}} \qquad (5)$$

TABLE VII

Starting material, % 3	Starting material, % 21	Reduction conditions	Product distribution, % 12	% 22	% 23
97	3	$LiAlH_4$, ether	97	0	3
60	40	$LiAlH_4$, ether	60	0	40
97	3	$NaBH_4$, 50% aq ethanol	80	16	4
97	3	$NaBH_4$, 50% aq methanol	87	10	3
60	40	$NaBH_4$, *i*-PrOH	56	17	25
97	3	$NaBH_4$, *i*-PrOH	54	28	17

(19) Although there is no direct evidence bearing on the magnitude of this equilibrium constant, Fedor[20] has shown that base converts 4-methoxy-4-methyl-2-pentanone quantitatively (in aqueous solution) into mesityl oxide.

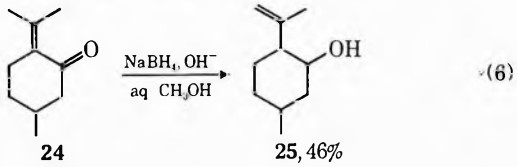
(20) L. R. Fedor, *J. Amer. Chem. Soc.*, **91**, 908 (1969).

(21) H. Kwart and T. Takeshita, *ibid.*, **84**, 2833 (1962).

(22) C. Harries, *Ber.*, **32**, 1326 (1899).

(23) F. H. Stross, J. M. Monger, and H. de V. Finch, *J. Amer. Chem. Soc.*, **69**, 1627 (1947).

both $LiAlH_4$ and sodium borohydride in aqueous solvents, the products furnish no evidence for equilibration between **3** and **21**. In *i*-PrOH, however, the data suggest that equilibrium is approached (presumably catalyzed by sodium isopropoxide) shortly after initiation of reduction. The two entries (Table VII) using *i*-PrOH suggest that an "equilibrium" value of *ca.* 20% **22** is approached from either side; it should be noted that this amount need not correlate directly with the equilibrium percentage of **21**. The nonconjugated ketone is expected to undergo reduction faster than **3**, and hence the amount of **23** formed should be larger than the percentage of **21** present (under rapid equilibration conditions). It is clear that, given the proper circumstances, the homoallylic alcohol could become the major product of borohydride reduction of an enone. In fact, an example is provided by the recent work of Wheeler and Chung,[13] who found the reduction of piperitone (**24**) by sodium borohydride in aqueous base[24] to give mostly **25** (eq 6).[13]



(6)

24 **25**, 46%

Experimental Section

Starting Materials.—With the exceptions noted below, the unsaturated aldehydes and ketones were commercial materials, spinning band distilled prior to use. Compound **5** was prepared by the method of Cronyn and Riesser.[25] $LiAlH_4$ reduction of acetylacetone gave 3-penten-2-ol (**11**), 65%, bp 65–69° (108 mm), which when subjected to Jones oxidation gave **2**, bp 122°, in 50% yield.[26] All of the starting materials were ≥99% pure by vpc, with the exception of mesityl oxide (**3**) which contained known (very small, except where otherwise noted) amounts of isomesityl oxide (**21**).

Products.—All product ratios were determined by vpc peak area integration; all analyses were carried out on a 4 m × 0.32 cm Carbowax 6M (15%) column at temperatures of from 70 to 103°.[27] The products were in many cases available materials; if not, identification was effected through alternate synthesis, *e.g.*, $LiAlH_4$ reduction for allylic alcohols and solvoxymercuration–reduction for many of the ethereal products. Where the latter procedure gave the alternate isomer, the reduction product was isolated and identified by complete spectral analysis.

The ethereal products obtained from sodium borohydride reduction of crotonaldehyde in various alcohol solvents were characterized by nmr and ir spectra, boiling points, and vpc retention times.[27]

Solvoxymercurations were carried out as described previously,[16] except that reaction times of 24–48 hr (prior to reduction) were used.

Reductions.—All reductions were carried out using 0.5 mol of reagent ($LiAlH_4$ or $NaBH_4$)/mol of unsaturated carbonyl compound. The sodium borohydride used was either commercial material or previously prepared highly purified reagent; this purification had no effect on the results presented here. Commercial reagent grade solvents were used for most reductions. *i*-PrOH dried by distillation from calcium hydride gave identical results with material containing small amounts of water. Two specific procedures will illustrate the general method used.

Crotonaldehyde in 50% Aqueous Ethanol.—Crotonaldehyde 14.0 g, (0.2 mol) was added through a dropping funnel to 3.7 g (0.1 mol) of sodium borohydride in 25 ml of H_2O and 25 ml of ethanol at 0°. After stirring at room temperature for 2 hr, the mixture was saturated with salt, extracted with ether, dried (potassium carbonate), vpc analyzed, and distilled to give 12.8 g (91%) of a mixture of *n*-butyl and crotyl alcohol, bp 118–120°.

3-Buten-2-one in *i*-PrOH.—Methyl vinyl ketone (7.0 g, 0.1 mol) was added dropwise at 0° to 1.8 g (0.05 mol) of sodium borohydride in 100 ml of *i*-PrOH. After stirring at room temperature for 8 hr, the mixture was poured into 100 ml of ice water. Potassium carbonate was added to saturate the mixture, after which it was treated as above. After distillation of the solvent, 2-butanol and 3-buten-2-ol were collected at atmospheric pressure; the residue was distilled under vacuum, bp 85° (30 mm), to give 4-isopropoxy-2-butanol. The total yield of distilled material was 90%.

Registry No.—**1**, 78-94-4; **2**, 625-33-2; **3**, 141-79-7; **4**, 930-68-7; **5**, 1193-18-6; **6**, 107-02-8; **7**, 4170-30-3; **8**, 78-85-3; **9**, 1115-11-3; sodium borohydride, 16940-66-2.

Acknowledgment.—This work was supported in part by a grant from the National Science Foundation (GP-9383).

(24) The apparent contradiction to the present work, where we found no rearrangement in aqueous solution, is due to the reduction procedure used by Wheeler and Chung.[13] A basic aqueous borohydride solution was added dropwise to the ketone **24** in methanol. These conditions will clearly favor base-catalyzed processes (rearrangement, aldol condensation, etc.) relative to direct reduction.

(25) M. W. Cronyn and G. H. Riesser, *J. Amer. Chem. Soc.*, **75**, 1666 (1953).

(26) L. P. Kyriakides, *ibid.*, **36**, 530 (1914).

(27) Details, including relative retention times, will be furnished on request.

The Reaction between 2,5-Dimethyl-2,4-hexadiene and Chlorine. *trans*-2,5-Dichloro-2,5-dimethyl-3-hexene and 4,5-Dichloro-2,5-dimethyl-2-hexene

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Received October 21, 1968

The liquid phase reaction between 2,5-dimethyl-2,4-hexadiene and chlorine yields the following compounds: 4,5-dichloro-2,5-dimethyl-2-hexene (by 1,2 addition), *trans*-2,5-dichloro-2,5-dimethyl-3-hexene (by 1,4 addition), 3,4,5-trichloro-2,5-dimethyl-1-hexene (*threo* and *erythro*), and 1,4,5-trichloro-2,5-dimethyl-2-hexene. These compounds are not the same as those previously reported. A kinetic study was made of the allylic rearrangement of *trans*-2,5-dichloro-2,5-dimethyl-3-hexene to 4,5-dichloro-2,5-dimethyl-2-hexene,

The addition of chlorine to 2,5-dimethyl-2,4-hexadiene (**1**) in chloroform has been reported by Tishchenko, Abramova, and Yarzhemskaya[2] to give 3,4-dichloro-2,5-dimethyl-1,5-hexadiene (**2**) as the primary product and 3,6-dichloro-2,5-dimethyl-1,4-hexadiene (**3**) and 1,6-dichloro-2,5-dimethyl-2,4-hexadiene (**4**) as secondary products. Sharefkin and Pohl[3] have reported the preparation of 2,5-dichloro-2,5-dimethyl-3-hexene from **1**.

The dichloro compounds produced by the reaction between chlorine and **1** in carbon tetrachloride have now been identified as *trans*-2,5-dichloro-2,5-dimethyl-3-hexene (**5**) and 4,5-dichloro-2,5-dimethyl-2-hexene (**6**) in a 2:3 ratio. Identification was made by their infrared spectra and by their nuclear magnetic resonance spectra. The same compounds and in essentially the same ratio were obtained when chloroform, trichloroethylene, or *n*-hexane was used as the solvent. Pure **5** was obtained from the mixture by low-temperature crystallization. The spectrum of **6** was obtained from a mixture of **5** and **6** that was synthesized by the reaction between *trans*-2,5-dimethyl-3-hexene-2,5-diol and thionyl chloride.[4]

The formation of compounds **5** and **6** can be accounted for by the 1,2 addition and 1,4 addition of chlorine to **1**. The product distribution from the addition of chlorine to this diene appears to be kinetically controlled, since no appreciable isomerization of the allylic chlorides would be expected at the temperature used for the addition. The fact that the 1,2-addition product is kinetically favored over the 1,4-addition product indicates that the transition state leading to the 1,2-addition product is more sterically favored.

Three trichloro compounds were isolated. One was identified as 1,4,5-trichloro-2,5-dimethyl-2-hexene (**7**) and the other two, tentatively, as the 3,4,5-trichloro-2,5-dimethyl-1-hexenes (*threo* and *erythro*) (**8**).

The reaction between lithium aluminum hydride and compounds **2**, **3**, and **4** would be expected to give one product—*trans*-2,5-dimethyl-2,4-hexadiene.[5] This reaction with **5** gave 2,5-dimethyl-2-hexene (70%) by SN2 and SN2′ reactions and *trans*-2,5-dimethyl-3-hexene (30%) by SN2 reactions. A mixture of **5** and **6** gave the same products in a ratio that indicated that pure **6** would have given 94% 2,5-dimethyl-2-hexene by SN2′ reactions and 6% 2,5-dimethyl-3-hexene. The formation of 2,5-dimethyl-3-hexene from **6** can be accounted for by assuming some allylic rearrangement of **6** and **5** during the reaction. These data provide further evidence that the dichloro compounds obtained in this investigation are not the same as those reported by Tishchenko and coworkers[2] for the chlorination reaction under similar reaction conditions.

The allylic rearrangement of **5** to **6** was studied kinetically at 56.2, 80.1, and 99.2° to obtain fundamental data for this reaction. Thermodynamic data and rate data for the unimolecular isomerization are given in Table I. Specific rate constants, defined as

TABLE I

THERMODYNAMIC FUNCTIONS AND RATE CONSTANTS FOR THE ISOMERIZATION OF *trans*-2,5-DICHLORO-2,5-DIMETHYL-3-HEXENE (5) TO 4,5-DICHLORO-2,5-DIMETHYL-2-HEXENE (6)

Temp, °K	329.4	353.3	372.4
A. Thermodynamic Functions			
6,%	40.6	47.8	53.0
K_{eq}	0.673	0.895	1.13
ΔF, kcal, mol	0.259	0.078	0.089
ΔS, eu	7.31	8.21	8.91
ΔH, kcal/mol	2.66	2.98	3.23
B. Rate Constants			
k_1, hr^{-1}	0.014 ± 0.001	0.12 ± 0.01	0.73 ± 0.06
k_{-1}, hr^{-1}	0.020 ± 0.002	0.13 ± 0.01	0.65 ± 0.05

$k = X_e/at \ln [X_e/(X_e - X)]$, were determined from a plot of $\ln X_e/(X_e - X)$ *vs.* time, where X is the molar concentration of **5** at time t, a is the initial molar concentration of **5**, and X_e is the molar concentration of **5** at equilibrium. Equilibrium constants, defined as $K_{eq} = [6]/[5]$ and equal to k_1/k_{-1} at a given temperature, were also required for these calculations.[6]

Rate data permitted calculation of the following approximate data: activation energy $E_a = 21$ kcal/mol; entropy of activation $\Delta S^{\ddagger} = -21$ eu; ΔH, for all three temperatures, 21 kcal/mol.

Experimental Section

Melting points and boiling points are uncorrected. Infrared spectra measurements were made by use of a Beckman IR-5

(1) To whom correspondence should be addressed: University of Texas at El Paso, El Paso, Tex. 79999.

(2) D. Tishchenko, A. Abramova, and E. Yarzhemskaya, *Zh. Obshch. Khim.*, **27**, 227 (1957); *J. Gen. Chem. USSR*, **27**, 253 (1957).

(3) J. G. Sharefkin and S. H. Pohl, *J. Org. Chem.*, **29**, 2050 (1964).

(4) J. D. Roberts, W. G. Young, and S. Winstein, *J. Amer. Chem. Soc.*, **64**, 2157 (1942).

(5) L. F. Hatch and G. Bachmann, *Chem. Ber.*, **97**, 132 (1964); L. F. Hatch and R. E. Gilbert, *J. Org. Chem.*, **24**, 1811 (1959); L. F. Hatch, P. D. Gardner, and R. E. Gilbert, *J. Amer. Chem. Soc.*, **81**, 5943 (1959); C. W. Jefford, S. N. Mahajan, and J. Gunsher, *Tetrahedron*, **24**, 2921 (1968).

(6) K. J. Laidler, "Chemical Kinetics," McGraw-Hill Book Co., Inc., New York, N. Y., 1950, pp 19–20.

spectrophotometer. The nmr spectra were obtained on a Varian Associates A-60 spectrometer using tetramethylsilane as the internal reference. Mass spectral analyses were made by using a Consolidated 21110 C high-resolution mass spectrometer. Gas chromatographic analyses were made using a Research Specialties Model 60-30 instrument with temperature programming (Model 611-60). A 6 ft × 0.25 in. o.d. column packed with 10% by weight Carbowax 6000 on 60–80 mesh Chromosorb W was used. Element analyses were made by Clark Microanalytical Laboratory, Urbana, Ill.; The Clayton Biochemical Institute, Microanalytical Laboratory, Austin, Tex.; and Galbraith Laboratories Inc., Knoxville, Tenn. These chloro compounds are relatively unstable toward hydrogen chloride elimination, which accounts for discrepancies in element analyses.

Chlorination of 1.—A solution of chlorine (142 g, 2.00 mol) in carbon tetrachloride (1500 ml) was added slowly to redistilled **1** (220 g, 2.00 mol, furnished by Eastman Chemical Products, Inc.) in carbon tetrachloride (500 ml). The reaction temperature was maintained at 0–4°. On completion of chlorine addition, the reaction was dried over sodium sulfate. Because rearrangement of the two dichlorides (**5** and **6**) occurs at high vpc column temperatures, temperature programming was used at 55–140° during vpc analyses. Compounds **5** and **6** were detected at 65 and 70° after 4 and 6 min, respectively. A typical vpc analysis follows: 47% **6**, 31% **5**, 13% **7**, 6% **8a**, and 3% **8b**. Two peaks (**8a** and **8b**) were obtained for **8**, but the trichlorides were not characterized as to *thero* and *erythro* isomers.

***trans*-2,5-Dichloro-2,5-dimethyl-3-hexene (5).**—This compound was separated from its allylic isomer **6** by crystallization at −25°. Recrystallization of **5** from Skellysolve B at −5° produced white crystals, mp 35°. The ir spectrum of this compound had a peak at 969 cm^{-1}, which indicated a *trans* structure. Absence of a carbon–carbon double bond stretching peak (*ca.* 1660 cm^{-1}) indicated a symmetrical structure around the double bond. The nmr spectrum (CCl_4) follows: τ 4.14 (s, HC=CH), and 8.31 [s, $CCl(CH_3)_2$]. These signals have a relative intensity of 1:6.

Anal. Calcd for $C_8H_{14}Cl_2$: C, 53.05; H, 7.79; mol wt, 180.0472. Found: C, 53.2; H, 7.9; mol wt, 180.0478 (mass spectrum).

4,5-Dichloro-2,5-dimethyl-2-hexene (6).—This compound was obtained by trapping on a preparative vpc column from the chlorination reaction mixture. The best separation gave a mixture containing 87% the desired compound **6** and 13% its isomer **5**. The ir spectrum of this mixture has a characteristic absorption at 1672 cm^{-1} which indicates an unsymmetrical carbon–carbon double bond. The nmr spectrum follows: τ 4.59 (d, C=CH), 5.37 (d, CHCl, allylic), 8.19–8.26 [m, C=C-$(CH_3)_2$], and 8.39 [s, $CCl(CH_3)_2$].

Anal. Calcd for $C_8H_{14}Cl_2$: C, 53.05; H, 7.79; Cl, 39.16; mol wt, 180.0472. Found: C, 53.21; H, 7.69; Cl, 39.15; mol wt, 180.0476.

The Trichloro-2,5-dimethylhexenes (7 and 8).—Three trichloro compounds were isolated from the reaction mixture by use of a vpc preparative column, and one was identified as **7**. The ir spectrum of each of the diasteroisomers (**8a** and **8b**) has a strong absorption at 917 cm^{-1} (CR_1R_2=CH_2 out-of-plane deformation). The ir spectrum of **7** does not show a strong band in this area, which indicates the absence of a terminal methylene group. The elemental analyses of **8b** indicated appreciable loss of chlorine between isolation and analysis. The ir spectra and indices of refraction were obtained on samples immediately after vpc separation.

1,4,5-Trichloro-2,5-dimethyl-2-hexene (7) gave the following data: $n^{25}D$ 1.5045; nmr (CCl_4) τ 4.27 (d, C=CH), 5.40 (d, CHCl, allylic), 6.00 (s, CH_2Cl), 8.10 (d, C=CCH_3), and 8.30 [s, $CCl(CH_3)_2$].

Anal. Calcd for $C_8H_{13}Cl_3$: C, 44.85; H, 6.07. Found: C, 44.83; H, 5.89.

Compound **8a** gave the following data: $n^{25}D$ 1.4938; nmr (CCl_4) τ 4.75 (s, C=CH_2), 5.00 (d, CHCl, allylic), 5.80 (d, CHCl), 8.11 (s, C=CCH_3), and 8.27 [s, $CCl(CH_3)_2$].

Anal. Calcd for $C_8H_{13}Cl_3$: C, 44.54; H, 6.08; Cl, 49.06. Found: C, 44.58; H, 6.07; Cl, 49.34.

Compound **8b** gave the following data: $n^{25}D$ 1.4947; nmr (CCl_4) τ 4.8 (s, C=CH_2), 4.95 (d, CHCl, allylic), 5.75 (d, CHCl), 8.00 (s, C=CCH_3), and 8.2–8.3 [m, $CCl(CH_3)_2$].

Anal. Calcd for $C_8H_{13}Cl_3$: mol wt, 214.0083. Found: mol wt, 214.0087 (mass spectrum).

***trans*-2,5-Dimethyl-3-hexene-2,5-diol.**—This diol was prepared by the sodium in liquid ammonia reduction of 2,5-dimethyl-3-hexyne-2,5-diol (Farchan Research Laboratories). The olefin diol was recrystallized from hot toluene, mp 98° (lit.[7] mp 101.5°). The ir spectrum of this compound had the same characteristic absorption peaks as reported for *trans*-2,5-dimethyl-3-hexene-2,5-diol.[8]

Mixture of 5 and 6.—*trans*-2,5-Dimethyl-3-hexene-2,5-diol (4.32 g, 0.030 mol) was dissolved in 130 ml of dry ether. Thionyl chloride (7.85 g, 0.066 mol), dissolved in 60 ml of dry ether, was added dropwise to the alcohol at room temperature. The mixture was refluxed for 2 hr and then analyzed by vpc. Only two peaks were obtained and they had identical retention times with those of the two dichloride peaks from the addition of chlorine to **1**. The ir spectrum of the mixture had the same characteristics as the spectrum of the dichlorides from the addition of chlorine to **1**.

Reduction of Dichlorides by Lithium Aluminum Hydride.—Both **5** and a mixture of **5** and **6** were treated with lithium aluminum hydride in a previously described manner.[5] The products of these reactions are given in the Discussion. The vpc analyses were made using the column described by Smith and Ohlson.[9]

Isomerization Study.—The isomerization of **5** to **6** was carried out at 56.2, 80.1, and 99.2° by thermostating solutions of known concentrations of **5** in *n*-decane. *n*-Decane was used as the solvent because its high boiling point minimized loss due to evaporation and because there is no absorption of this solvent at the ir region used for analysis.

The course of the isomerization was followed by ir spectra analyses of the equilibrating solution at suitable time intervals. Compound **5** has characteristic absorptions at 969 and 1250 cm^{-1} that are suitable for quantitative analysis, and the compounds obeyed Beer's law over the entire concentration range used. Isomer **6** has characteristic absorption at 1672 cm^{-1}, but this band is not intense enough to be used for analysis. Solutions of known concentrations of both isomers were prepared using carbon tetrachloride and *n*-decane as solvents. The absorbance of each isomer was the same regardless of the solvent. The data are given in Table I.

Registry No.—**1**, 764-13-6; **5**, 22966-70-7; **6**, 22929-07-3; **7**, 22929-08-4; **8a**, 22966-71-8; **8b**, 22966-72-9.

Acknowledgment.—This work was supported by a grant from The Robert A. Welch Foundation, Houston, Texas.

(7) J. R. Johnson and O. H. Johnson, *J. Amer. Chem. Soc.*, **68**, 2615 (1940).

(8) K. Griesbaum, A. A. Oswald, and W. Naegele, *J. Org. Chem.*, **29**, 1887 (1964).

(9) B. Smith and R. Ohlson, *Acta Chem. Scand.*, **13**, 1253 (1959).

1,3-Bridged Aromatic Systems. V. Strained Aromatic Systems[1]

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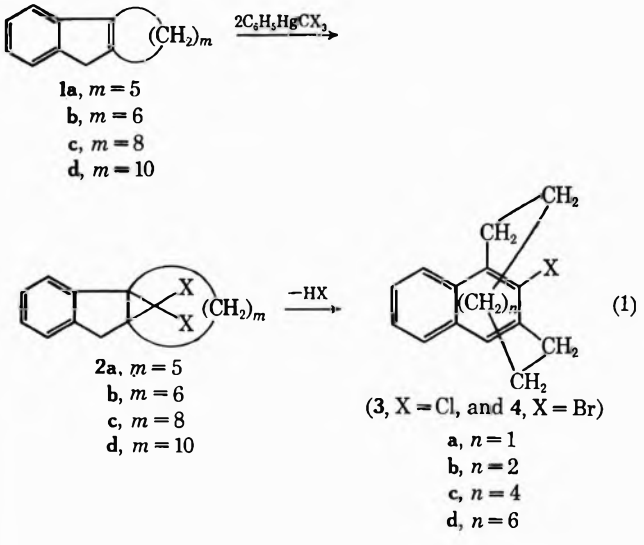
Received August 12, 1969

1,3-Bridged naphthalenes of type **3** and **4**, in which the minimum value of n is 2, have been prepared in high yield. Steric constraint in such metacyclophanes causes distortion or change in aromatic character of the aromatic ring to which the methylene bridge is attached, and this effect is noted by a variety of physical and chemical processes. Evidence is presented suggesting that **3** (with $n = 1$) can be prepared as a highly reactive, unstable intermediate; however, the principal product from the reaction of **1a** with dichlorocarbene is not a metacyclophane, but an isomer resulting from phenyl migration. The photochemistry of **3b** in ethanol is also discussed.

We have recently described[3] the preparation of 1,3-bridged naphthalenes **3c** and **3d** by the procedure summarized in eq 1. This synthesis is of particular



1a, $m = 5$
b, $m = 6$
c, $m = 8$
d, $m = 10$

2a, $m = 5$
b, $m = 6$
c, $m = 8$
d, $m = 10$

(3, X = Cl, and 4, X = Br)
a, $n = 1$
b, $n = 2$
c, $n = 4$
d, $n = 6$

(1)

interest since it involves an energetically favorable creation of an aromatic ring as the last step, in contrast to less favorable ring closures used traditionally for the preparation of related metacyclophanes.[4] This investigation was directed toward a study of the scope of this synthesis, with particular attention given to the lowest value of n in **3** and **4**, and the properties of the strained aromatic systems that resulted.[5]

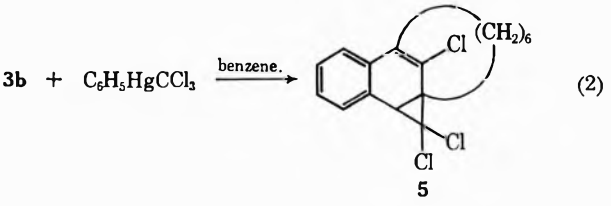
A. 3b ($n = 2$, **X = Cl**).—Inspection of models revealed that the metacyclophanes **3b** or **4b** would probably result in distortion of the benzene ring to which the methylene chain is attached. This conclusion was supported by both the physical and chemical properties of **3b** and **4b**.

The metacyclophane **3b** was obtained as a white solid in high yield (74%) by reaction of **1b** with phenyl(trichloromethyl)mercury in hot benzene. The nmr spectrum showed characteristic broad and complex methylene absorption at τ 6.34–11.12. The methylene bridge cannot pass over the chlorine atom, thereby hindering mobility of the bridge and resulting in considerable nonequivalence of the ring methylene protons. The very high field absorption of **3b** near τ 11 was expected by analogy to **3c** and **3d**, since the central bridging atoms are held closely over the face of the benzene ring and, as a consequence, are held closely in the shielding cone of the aromatic ring.

The ultraviolet spectrum of **3b** was similar to those of **3c** and **3d** but showed complete loss of fine structures together with a slight bathochromic shift.

The distortion of the benzene ring in **3b** was also evidenced by a study of its oxidation with 40% nitric acid with subsequent methylation of the derived acids by action of diazomethane. The only products isolated, under conditions identical with those described for **3d**,[3] were dimethyl phthalate and dimethyl nitrophthalate. There was no evidence for the formation of tetramethyl 4-chloro-1,2,3,5-benzene tetracarboxylate, which was a major product from **3d**.

An impurity isolated (3–5% yield) from the synthesis of **3b** was assigned structure **5** on the basis of its composition and spectra and by its synthesis (eq 2) by



(2)

5

addition of CCl_2 to **3b** (42% yield). Unactivated aromatic systems are generally resistant to reaction with dichlorocarbene; the facile addition of dichlorocarbene to **3b** is further evidence of the strain and distortion of the benzene ring to which the methylene bridge is attached.

8,9-Benzo-12-chloro[6]metacyclophane (**3b**) decolorizes neutral potassium permanganate at room temperature and reacts readily with bromine in carbon tetrachloride at room temperature with evolution of hydrogen bromide. The product of the latter reaction was shown to be **6** by its composition, by its spectra, and by

(1) Supported by the National Science Foundation Grant GP-6169X. For the preceding article in this series, see W. E. Parham, R. W. Davenport, and J. B. Biasotti, *Tetrahedron Lett.*, **7**, 557 (1969).

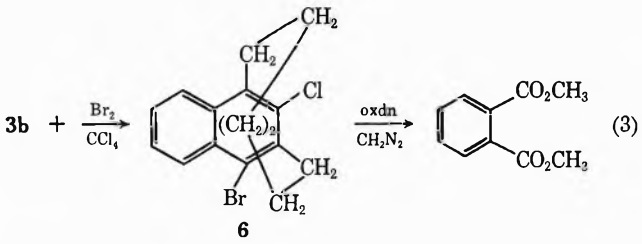
(2) Taken in large part from the Ph.D. Thesis of D. R. Johnson, University of Minnesota, 1969; National Aeronautics and Space Administration Fellow, 1966–1969.

(3) W. E. Parham and J. K. Rinehart, *J. Amer. Chem. Soc.*, **89**, 5668 (1967).

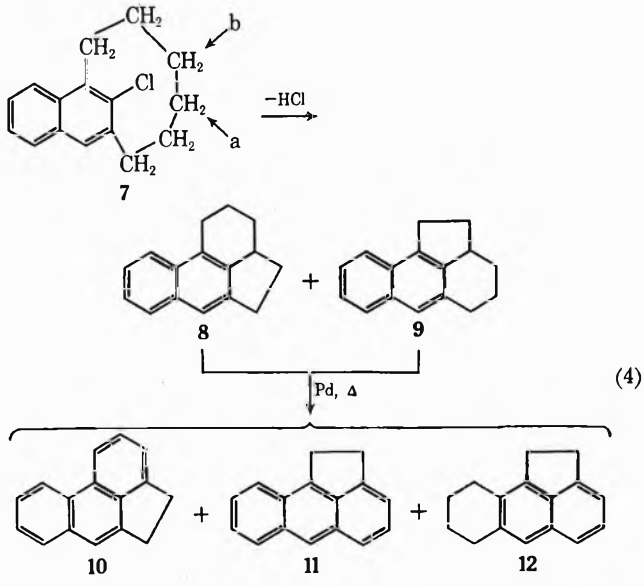
(4) For a review of methods used for cyclophane syntheses, see B. H. Smith, "Bridged Aromatic Compounds," Academic Press Inc., New York, N. Y., 1964, pp 24–185.

(5) For reviews of the chemical behavior of cyclophanes, see (a) R. W. Griffin, Jr., *Chem. Rev.*, **63**, 45 (1963); (b) R. B. Smith, "Bridged Aromatic Compounds," Academic Press Inc., New York, N. Y., 1964.

its conversion into dimethyl phthalate by oxidation and subsequent esterification of the derived acids (eq 3).



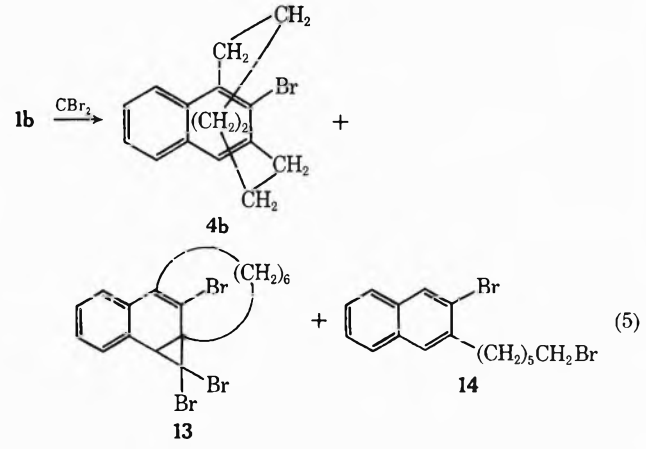
8,9-Benzo-12-chloro[6]metacyclophane (**3b**) was observed to undergo a rapid photochemical reaction in ethanol. The principal product (68–80% yield) was a mixture of two isomeric products ($C_{16}H_{16}$) shown to be 1,2,3,3′,4,5-hexahydroacephenanthrylene (**8**) and 1,2,-2′,3,4,5-hexahydroaceanthrylene (**9**) (eq 4).



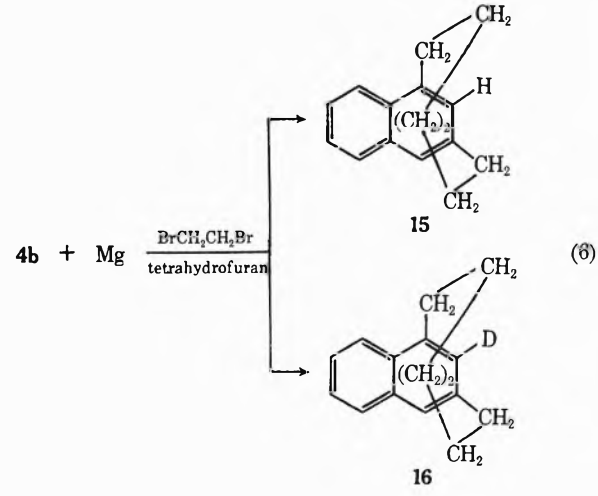
The composition, spectra, and analysis by glpc of the photoproduct was consistent for a mixture of **8** and **9** in the ratio of 70:30, respectively. These products are those expected by a photochemically catalyzed elimination of a chlorine atom followed by a series of events involving (a) naphthyl radical abstracting a proximate transannular hydrogen atom, and (b) subsequent reaction of the derived radical with the strained aromatic ring. Because of the unusual stereochemistry of the system one cannot rule out the alternate possibility that the departing chlorine atoms remove a proximate transannular hydrogen atom at a or b as shown in **7**, followed by coupling of the resulting caged diradical. The photoproduct was partially dehydrogenated by reaction with palladium on carbon to give a mixture of acephenanthrene (**10**) and aceanthrene (**11**). Both of these dehydrogenated products were known, and comparison of the ultraviolet spectrum of the mixture indicated the composition to be 65% **10** and 35% **11**, a value in close agreement to the ratio estimated for the hydrocarbon precursors by glpc. The mixture of **10** and **11** was not completely resolved by chromatography; however, a small amount of the principal product **10** was isolated pure and was shown to be identical with an authentic sample of **10**.

A third component isolated (20%) from the dehydrogenation of **8** and **9** was identified as **12** by its subsequent dehydrogenation to **11**. The product **12** was obviously formed by isomerization of **9** under conditions employed for dehydrogenation.

B. 4b ($n = 2$; **X = Br**).—The reaction of **1b** with phenyl(tribromomethyl)mercury in benzene was highly temperature dependent. Optimum yields (40%) of **4b** were obtained when the reaction was conducted in benzene at 50°. The cyclopropane **13** (mp 119–120°; spectral properties essentially identical with those described for **5**; not further analyzed) was a by-product (7.4%) in this reaction, together with unreacted starting material. At higher temperatures (60°, or reflux), 2-(6-bromohexyl)3-bromonaphthalene (**14**) was a significant by-product (14%). The dibromide **14** was identified by its composition, by its spectra, and by its synthesis from **4b**; the mechanism of its formation is discussed subsequently.



8,9-Benzo-12-bromo[6]metacyclophane (**4b**) formed a Grignard reagent readily, which gave **15** (>80% yield) or **16** (93% yield, 97% deuterium incorporation), respectively, when hydrolyzed by action of water or deuterium oxide (eq 6).



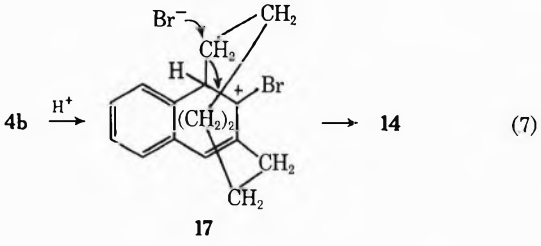
The nmr spectrum of **15** was complex and showed methylene absorption at τ 6.33–10.40. These data establish the fact that there is a barrier to ring inversion (rotation to the opposite face of the aromatic ring) in **15** whether a hydrogen or a halogen atom occupies the 2 position of the naphthalene ring. These results are in contrast to similar studies involving **4d**[6a] in which ring

(6) (a) Private communication, R. W. Davenport, The University of Minnesota. The chemistry of **4d** will be presented in a subsequent communication. (b) Reference 5b, p 343.

inversion occurs when the 2 substituent is hydrogen, but not when it is halogen. The barrier to ring inversion in **15** is thus either a result of steric interference by hydrogen at the 2 position or, more likely, simply to the required stretching needed for the strained system to go through a planar transition state. Asymmetry in related cyclophanes has been noted.[6b]

That slow inversion is occurring at room temperature, which would constitute racemization if **15** could be resolved into its optical isomers, was evident from variable temperature nmr studies. At 92° the methylene absorption changed markedly and resembled that described for the dehalogenated derivative of **4d**[4] (rapid equilibration of the methylene bridge to the two faces of the naphthalene ring); at 1° the methylene absorption remained complex and broad, but showed marked sharpening of absorption, consistent with the conclusion that ring inversion is not occurring rapidly at this temperature.

It was observed that **4b** reacts readily with anhydrous hydrogen bromide in benzene at 60° or higher, but only slowly (not detected) at 50°. The product of the reaction (59.1% yield) was 2-(6-bromohexyl)-3-bromonaphthalene (**14**). Structure **14** was assigned to this product on the basis of its composition and spectra and by analogy to **19**, described in the next section. The dibromide **14** is assumed to be formed as shown in **17** (eq 7).

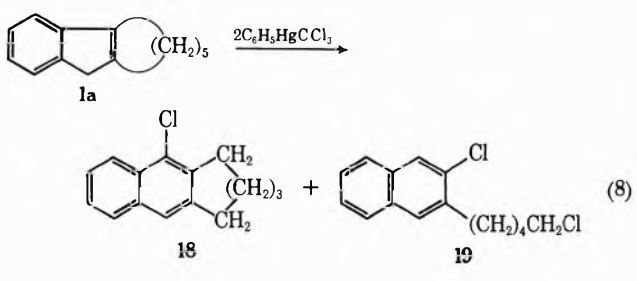


(7)

Reverse alkylations of aromatics are common when strong Lewis acids are employed (*i.e.*, isomerization of alkylbenzene with $AlCl_3$); however, cleavage of the type shown in eq 7 is exceptional.[7] In retrospect, such cleavage is not surprising in view of the demonstrated reactivity of the aromatic ring involved, and the relief of strain from such reaction.

Since the dihalocyclopropyl intermediates **2** are known[3] to decompose, with liberation of hydrogen halide, under conditions used for their formation, it is apparent that **14** could be formed as a by-product from the synthesis of **4b** by competitive reaction of the hydrogen bromide liberated with **4b** or with excess phenyl(tribromomethyl)mercury, used to remove hydrogen bromide.

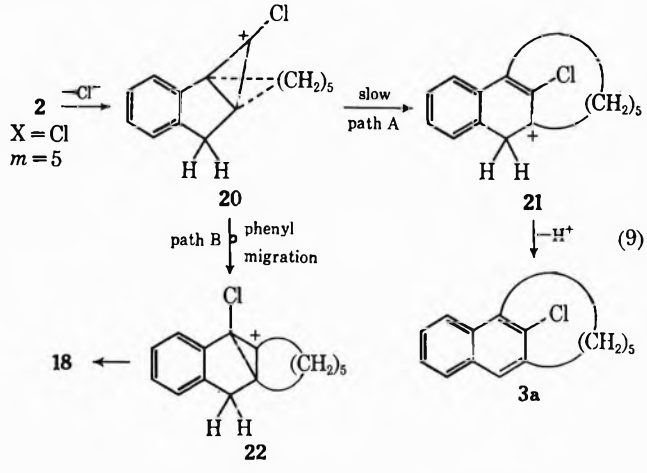
C. Reaction of 1a with Phenyl(trichloromethyl)-mercury.—Two products (eq 8) were obtained from the reaction of pentahydrocyclohept[*b*]indene (**1a**) with 2 equiv of phenyl(trichloromethyl)mercury in boiling benzene.



(8)

The major product **18** (66% yield) was identified by its composition and spectra and its structure was established by oxidation, with subsequent esterification of the derived acids with diazomethane, to tetramethyl-3-chloro-1,2,4,5-benzene tetracarboxylate. This ester was unknown and was prepared independently from monochlorodurene by a similar procedure; thus it was established that a molecular rearrangement had occurred in the carbene reaction.

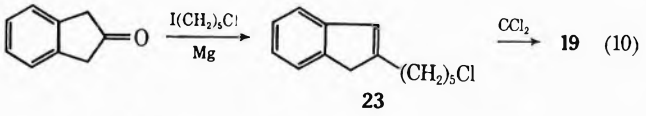
Since it is known that the rate-determining step[8] in ring expansion of the type **2** → **3** involves ionization of halogen–carbon bond, a logical mechanism for the formation of **18**, shown as a stepwise process for clarity only, involves phenyl rearrangement of the neopentyl type, shown in eq 9 (path B). It is logical to assume



(9)

that the collapse of the ion **20** by a concerted disrotatory process[9] to give **21** (path A), and subsequently **3a**, would be slow because of the high steric demands of **21** and/or **3a**. Consequently, path B, involving phenyl migration, dominates. With more than five methylene groups in the bridge, steric requirements for path A are less severe and metacyclophane formation dominates. It is interesting to note that no products analogous to **18** have been detected in reactions of indenes involving more than five methylene atoms in the bridge.

The second product shown in eq 8, isolated in 8.4% yield, was shown to be 2-(5-chloropentyl)-3-chloronaphthalene (**19**) by (a) its composition, (b) its spectra, and (c) by its independent synthesis as summarized in eq 10.



(10)

The formation of **19** probably occurs in a manner analogous to that described for **14** in section B, by cleavage of the derived metacyclophane **3a** by hydrogen

(7) Dealkylation of aromatics substituted by *t*-alkyl groups by protonic acids is common: R. W. Frank and E. G. Laser, *J. Amer. Chem. Soc.*, **91**, 1577 (1969).

(8) W. E. Parham, H. E. Reiff, and P. Swartzentruber, *ibid.*, **78**, 1437 (1956).

(9) (a) R. B. Woodward and R. Hoffman, *ibid.*, **87**, 395 (1965); (b) C. H. DePuy, L. G. Swnack, J. W. Hausser, and W. W. Wiedman, *ibid.*, **87**, 4006 (1967).

chloride liberated during the decomposition of **2a**. Formation of this product suggests that it may be possible by careful choice of conditions to isolate metacyclophanes of type **3a**; however, this objective has not been realized.

Experimental Section

Hexahydrocyclooct[*b*]indene (1b).—The indene **1b** was prepared from cyclooctanone by a procedure similar to that described for **1c–1d**,[3,10]

1. ***o*-(1-Cyclooctenyl)benzonitrile.**—*o*-(1-Cyclooctenyl)chlorobenzene, obtained from *o*-bromochlorobenzene (100 g, 0.522 mol) and cyclooctanone (65.8 g, 0.522 mol), was not obtained pure [30.2% yield as determined by glpc; bp 82.5–87° (0.12 mm), n^{25}D 1.5597]. Impure material, obtained after removing the impurities boiling below 72° (0.1–0.2 mm), was heated with cuprous cyanide in N-methylpyrolidone and the product was purified by chromatography (alumina; eluent, petroleum ether, bp 60–70°) and distillation [bp 90–90.5° (0.015 mm)] to give pure nitrile: n^{25}D 1.5647; ir (neat) 2220 cm^{-1}; uv max (95% ethanol) 288 mμ (log ε 3.43), 250 (3.72), 221 (4.29); nmr ($CDCl_3$) τ 2.35–2.84 (m, 4.4, aromatic **H**), 4.13 (t, 0.9, J = 8 Hz, olefinic **CH**), 7.29–7.88 (m, 4.3, aliphatic CH_2), 8.39 (broad s, 7.5, aliphatic CH_2).

Anal. Calcd for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63. Found: C, 85.28; H, 8.22; N, 6.93.

2. ***o*-(1-Cyclooctenyl)benzylamine Hydrochloride.**—A 70–91% yield was obtained: mp 192.5–196° dec from ethanol, 193–197° dec by sublimation; ir (Nujol-halocarbon) 3150–2720, 2690, and 2590 cm^{-1} (NH_3^+); nmr (D_2O) τ 2.41–3.18 (m, 3.9, aromatic **H**), 4.56 (t, 1.0, J = 7 Hz, olefinic **H**), 5.92 (s, 2.0, benzylic CH_2), 7.43–8.02 (broad s, *ca.* 4, aliphatic CH_2), 8.20–8.80 (broad s, 8.1, aliphatic CH_2).

Anal. Calcd for $C_{15}H_{22}ClN$: C, 71.55; H, 8.81; N, 5.56. Found: C, 71.73; H, 8.86; N, 5.50.

3. **Hexahydrocyclooct[*b*]indene (1b).**—A 53–85% yield was obtained after chromatography (alumina; petroleum ether, bp 60–70°): bp 83.0–83.3° (0.04 mm); n^{25}D 1.5784; ir (neat) 1628 cm^{-1} (C=C); uv max (95% ethanol) 282 mμ (sh) (log ε 3.21), 265 (sh), (4.04), 257 (4.14), 222 (sh) (3.90); nmr (CCl_4) τ 2.60–3.15 (m, 4.0, aromatic **H**), 6.83 (broad s, 2.0, benzylic CH_2), 7.23–7.60 (m, 4.0 allylic CH_2), 8.07–8.75 (m, 8.1, aliphatic CH_2).

Anal. Calcd for $C_{15}H_{18}$: C, 90.85; H, 9.19. Found: C, 91.05; H, 9.31.

Reaction of Hexahydrocyclooct[*b*]indene (1b) with Phenyl(trichloromethyl)mercury and with Phenyl(tribromomethyl)mercury.—The procedure used was essentially identical with that described for **1c–1d**[3] unless otherwise noted.

1. **8,9-Benzo-12-chloro[6]metacyclophane (3b).**—The crude product was obtained in 80–100% yield as a white mushy solid subsequent to column chromatography (alumina; petroleum ether, bp 60–70°): mp 43.5–45.3 (74% yield), 45.5–46.2° after chromatography on silica–petroleum ether followed by recrystallization from ethanol; white needles; uv max (95% ethanol) 321 mμ (sh) (log ε 2.49), 300 (sh) (3.59), 290 (3.70), 282 (sh) (3.67), 245 (4.74); nmr (CCl_4) τ 2.21–2.96 (m, 5.0, aromatic **H**), 6.34–6.82 (m, 3.0, benzylic CH_2), 7.36–9.58 (m, 8.2, aliphatic CH_2), 10.52–11.12 (broad s, 0.9, aliphatic CH_2).

Anal. Calcd for $C_{16}H_{17}Cl$: C, 78.51; H, 7.00. Found: C, 78.78; H, 7.01.

2. **Isolation of 5.**—Further elution of the column used to purify **3b**, above, with petroleum ether (bp 60–70°) gave **5** in 3–5% yield: white needles; mp 106.5–107.5° from petroleum ether and from ethanol; ir (KBr) 985 cm^{-1} (cyclopropyl); uv max (95% ethanol) 302 mμ (log ε 3.54), 244 (4.19), 237 (4.22); nmr ($CDCl_3$) τ 2.52–2.86 (m, 3.9, aromatic **H**), 6.63–7.36 (m, 4.2, allylic CH_2, benzylic **CH**), 7.88–9.15 (m, 9.0, aliphatic CH_2); mass spectrum (70 eV) *m/e* 326 molcular ion.

Anal. Calcd for $C_{17}H_{17}Cl_3$: C, 62.31; H, 5.23; Cl, 32.46; mol wt, 326. Found: C, 62.43; H, 5.26; Cl, 32.25; mol wt (mass spectroscopy), 326.

3. **8,9-Benzo-12-bromo[6]metacyclophane (4b).**—A mixture of **1b** (6.7 mmol) and phenyl(tribromomethyl)mercury (13.6 mmol) was heated in dry benzene, under nitrogen for 24 hr at 50°. The crude product (1.25 g), obtained subsequent to removal (by filtration and trituration) of phenylmercuric bromide, was chromatographed on alumina (eluent, petroleum ether, bp 60–70°) to give slightly impure (tlc) **4b** (yellow oil). The material was purified by recrystallization from pentane at Dry Ice–acetone temperature to give **4b** as a white powder (0.71 g, mp 51–52°, 40% yield). Pure **4b** was obtained by chromatography on silica gel with subsequent recrystallization of product from petroleum ether (bp 40–60°): mp 52–53°; uv max (95% ethanol) 238 mμ (log ε 4.71), 281 (sh) (3.72), 290 (3.74), 300 (sh) (3.64); nmr (CCl_4) τ 2.10–2.95 (m, 5.2, aromatic **H**), 6.30–6.76 (m, 3.0, benzylic CH_2), 7.26–9.53 (m, 8.2, aliphatic CH_2), 10.40–11.37 (broad s, *ca.* 0.6, aliphatic CH_2).

Anal. Calcd for $C_{16}H_{17}Br$: C, 66.44; H, 5.94; Br, 27.63. Found: C, 66.58; H, 6.01; Br, 27.38.

4. **Isolation of Compound Believed to Be 13.**—In a subsequent reaction conducted as described above (but for 40 hr at 50°), elution (petroleum ether, bp 60–70°) was continued after **4b** (65.4% yield) was removed. There was obtained 0.60 g of **13** (7.4% yield yellow needles: mp 119–120° from ethanol–water); ir (Nujol–halocarbon oil) 985 cm^{-1} (cyclopropyl); uv max (95% ethanol) 248 mμ (log ε 4.30), 321 (3.57); nmr (CCl_4) τ 2.68–2.94 (m, 3.9, aromatic **H**), 6.52–7.78 (m, 3.8, allylic CH_2, benzylic **CH**), 7.78–9.52 (m, 9.3, aliphatic CH_2). This compound was not analyzed owing to thermal instability, but assigned structure **13** by spectral analysis and by analogy to the isolation of **5** from the synthesis of **3b**.

5. **Isolation of 2-(6-Bromohexyl)-3-bromonaphthalene (14).**—When the reaction of **1b** with 2 equiv of phenyl(tribromomethyl)-mercury was carried out at 60° for 20 hr (and at reflux for 3 hr) and the crude product was chromatographed as described in 3 above, there was obtained, subsequent to removal of **4b** (*ca.* 27% yield) and unchanged indene (small amount), 0.68 g (13.9% yield) of **14** (mp 59.5–64°). Pure **14**, obtained by preparative tlc (silica gel PF_{254}; eluent, 20% ether in petroleum ether) with subsequent recrystallization of the product from ethanol, was obtained as white needles: mp 66–67°; uv max (95% ethanol) 230 mμ (log ε 4.76), 253 (sh) (3.31), 262 (3.43), 271 (3.56), 281 (3.57), 292 (3.33), 307 (2.40), 321 (2.26); nmr (CCl_4) τ 2.01 (s, 1.1, aromatic **H**), 2.18–2.86 (m, 5.0, aromatic **H**), 6.70 (t, 1.8, J = 6.5 Hz, $-CH_2Br$), 6.86–7.35 (m, 2.0, benzylic CH_2), 7.83–8.79 (m, 8.1, aliphatic CH_2).

Anal. Calcd for $C_{16}H_{18}Br_2$: C, 51.91; H, 4.91; Br, 43.17. Found: C, 51.88; H, 4.91; Br, 42.88.

Reactions of 8,9-Benzo-12-chloro[6]metacyclophane (3b). 1. **Oxidation with 40% Nitric Acid.**—The procedure used was identical with that described[3,11] for oxidation of **3d**. The crude acid (soft yellow solid, 0.12 g, from 0.15 g of **3b**, mp 135–144° after digestion with benzene and showing no methylene absorption in the nmr) was esterified with excess diazomethane. Analysis of the product by glpc (identical conditions with those described[3]) showed it to be a 60:40 mixture of dimethyl phthalate and dimethyl nitrophthalate, respectively. There was no detectible amount of tetramethyl 4-chloro-1,2,3,5-benzene tetracarboxylate present.

2. **With Phenyl(trichloromethyl)mercury.**—A mixture of **3b** (1 equiv) and phenyl(trichloromethyl)mercury (1 equiv) was heated in dry benzene under nitrogen for 66 hr at the reflux temperature. Analysis of the crude product by glpc[12] showed it to contain unreacted **3b** (46.1%), unidentified material (12.1%), and dichlorocarbene adduct **5** (41.8%). The crude product was purified by preparative tlc (silica gel PF_{254}; eluent, petroleum ether, bp 60–70°); **5** was obtained as white needles (from petroleum ether), mp 108.5–109°, and caused no depression in melting point when admixed with **5** (mp 106.5–107.5°) obtained directly from **1b** as previously described.

3. **With Bromine.**—A mixture of **3b** (1 equiv) and bromine (1 equiv) was stirred at room temperature under nitrogen in carbon tetrachloride for 6 hr, during which time evolution of hydrogen bromide was evident. Isolated from the reaction was 0.30 g of slightly impure product (by tlc) which was purified by chromatography (alumina; eluent, petroleum ether, bp 60–70°) to give 0.18 g (90.6% yield, calculated as $C_{16}H_{16}BrCl$) of product, mp 72–82°, which was recrystallized from ethanol to give pure **6** as white needles: mp 83–84°; uv max (95% ethanol) 237 mμ

(10) W. E. Parham, C. D. Wright, and D. A. Bolon, *J. Amer. Chem. Soc.*, **83**, 1751 (1961).

(11) H. Bamford and J. L. Simonsen, *J. Chem. Soc.*, **97**, 1904 (1910).

(12) Gas–liquid partition chromatography (glpc) was carried out on a Beckman GC-4 using dual flame detector with helium as a carrier (60 ml/min). The column used was 1/8 in. × 6 ft 5% DC-710 on Chromosorb W (80–100 mesh) at 200°.

(log ε 4.58), 254 (sh) (4.28), 290 (sh) (3.67), 299 (3.75), 308 (sh) (3.67), 350 (2.67); nmr (CCl_4) τ 1.78–3.16 (m, 3.6, aromatic **H**), 6.33–7.30 (m, 4.0, benzylic CH_2), 7.63–11.82 (m, 8.3, aliphatic CH_2).

Anal. Calcd for $C_{16}H_{16}BrCl$: C, 59.38; H, 4.98; Br, 24.69; Cl, 10.95. Found: C, 59.34; H, 4.94; Br, 24.42; Cl, 10.45.

The structure of **6** was established by oxidation with 40% nitric acid and subsequent esterification of the derived acids with diazomethane as described for **3d**.[3,11] Dimethyl phthalate, isolated by preparative glpc and characterized by ir, and dimethyl nitrophthalate were major products of the reaction, together with a material having a much higher retention time assumed to be tetramethyl 4-bromo-6-chloro-1,2,3,5-benzene tetracarboxylate.

4. With Light. a. A solution of **3b** (2.00 g, 8.18 mmol) in 95% ethanol was placed in a quartz tube and irradiated (Rayonet Srinivasan-Griffin photochemical reactor) under nitrogen atmosphere for 8.5 hr. The reaction progress was followed by glpc[12] which showed the disappearance of starting material to be complete after 8.5 hr. The orange oil obtained from the ethanol was chromatographed (150 g of silica gel eluent, petroleum ether, bp 60–70°) to give 1.17 g (68.7% yield, calcd as $C_{16}H_{16}$) of clear oil (containing an incompletely resolved mixture of two major components, a trace amount of starting material, and a very minor amount of another component, as determined by glpc[12]). Recrystallization of the oil from ethanol gave 0.58 g (34.1% yield) of white crystals, mp 36.0–37.0°. Analysis of the solid by glpc[12] (except at 150°) showed the photochemical product to be a mixture of 1,2,3,3′,4,5-hexahydroacephenanthrylene (**8**, *ca.* 70%) and isomeric ($C_{16}H_{16}$) 1,2,2′,3,4,5-hexahydroaceanthrylene (**9**, *ca.* 30%): uv max (95% ethanol) 320 mμ (sh) (log ε 2.93), 310 (sh) (3.18), 295 (sh) (3.72), 289 (sh) (3.76), 282 (3.80), 274 (sh) (3.73), 264 (sh) (3.59), 234 (5.04), 230 (sh) (4.96); nmr ($CDCl_3$) τ 2.13–2.86 (m, 5, aromatic **H**), 6.75–9.32 (m, 11, benzylic and aliphatic CH_2); mass spectrum (70 eV) *m/e* 208 molecular ion).

Anal. Calcd for $C_{16}H_{16}$: C, 92.26; H, 7.74. Found: C, 92.21; H, 7.76.

b.—The reaction was repeated as described above and the crude product was chromatographed on silica gel (130 g; eluent, petroleum ether, bp 60–70°) to give 1.02 g (79.8% yield) of a mixture of **8** and **9** as a clear oil (no other products visible by tlc).

Identification and Proof of Structure of 8 and 9.—A mixture (oil from b above, 0.20 g, 0.962 mmol) of the photoproducts **8** and **9** and 5% palladium on charcoal (50 mg) was heated under nitrogen at 180–210° for 50 min. Analysis of an aliquot by glpc[12] showed 53% unchanged starting material. Fresh catalyst (50 mg) was added and the heating continued for 1.5 hr. Analysis as described above showed a small amount of starting material and two principal components in a ratio of 60:40. The crude product was chromatographed (silica gel; 40 g; eluent, petroleum ether, bp 60–70°) to give (a) unreacted starting material (40 mg, 20% recovery, pure by glpc); (b) 1,2,7,8,9,10-hexahydroaceanthrylene (**12**) as a white solid, mp 74–78° (contaminated with a trace of starting material as detected by tlc); and (c) a mixture of acephenanthrene (**10**) and aceanthrene (**11**) as yellow crystals, mp 80–90° (indistinct).

The uv spectrum of the mixture, mp 80–90°, follows: uv max (95% ethanol) 212 mμ, 224, 236 (sh), 251 (sh), 257.5, 268 (sh), 279, 291, 302.5. 321, 336, 353 (instrument cut-off 360 mμ).

Pure acephenanthrene (**10**), mp 106–107° (lit.[13] mp 106°), identical with a sample of **10** (mp 105–107°, mixture melting point undepressed, mmp 106–107°) recovered from a sample of authentic picrate,[13] had the following uv spectrum: uv max (95% ethanol) 208 mμ (log ε 4.86), 224 (sh) (4.62), 238 (sh) (4.51), 250 (sh) (4.72), 257 (4.79), 267 (sh) (4.29), 278 (3.92), 290 (3.92), 302 (4.09), 319 (2.53), 334 (3.01), 350 (3.27).

The uv spectrum of aceanthrene (**11**), mp 113°, prepared by Bergman and Ikan,[14] is reported to be uv max (95% ethanol) 225 mμ (log ε 4.05), 256 (4.14), 258 (5.06), 355 (3.50), 375 (3.80), 395 (3.56).

Comparison of uv spectra of **10** and **11** revealed that acephenanthrene shows an absorption peak at 302 mμ, in which region the aceanthrene is essentially transparent. This information was used to calculate the composition of the mixture, mp 80–90°, to be 65% acephenanthrene and 35% aceanthrene. This value compares favorably with the ratio of 70:30 of **8** to **9**, respectively, observed for the mixture of the hexahydro precursors.

Chromatography of the mixture (mp 80–90°) on neutral Woelm aluminum, activity grade I, gave a small amount of the principal product, acephenanthrene (**10**, mp and mmp 106–107°), and an unresolved mixture of **10** and **11**: mp 95–102°; nmr (CCl_4) τ 2.18–3.78 (m, 8.0, aromatic **H**), 6.72 (s, 4.0, benzylic CH_2).

The white solid (mp 74–78°), isolated from the initial chromatography of the dehydrogenated photoproducts, was recrystallized from ethanol to give pure **12**: mp 80.5–81.0°; uv max (95% ethanol) 235 mμ (log ε 4.91), 260 (sh) (3.25), 276 (sh) (3.60), 286 (sh) (3.75), 297 (3.78), 305 (sh) (3.57), 309 (sh) (3.51), 320 (sh) (2.97), 324 (2.87); nmr τ 2.80–3.08 (m, 4.1, aromatic **H**), 6.50–7.53 (m, *ca.* 7.7, benzylic CH_2), 7.90–8.50 (m, *ca.* 4.1, aliphatic CH_2).

Anal. Calcd for $C_{16}H_{16}$: C, 92.26; H, 7.74. Found: C, 92.57; H, 7.98.

The structure of **13** was confirmed by its dehydrogenation, as described above, to **11**: mp 114.5–115.5° (yellow needles from ethanol) (lit.[14] mp 114–115°); uv max (95% ethanol) 224 mμ (log ε 4.15), 235 (4.31), 254 (sh) (5.00), 258 (5.20) (lit.[14] uv described above).

Reaction of 8,9-Benzo-12-bromo[6]metacyclophane (4b). 1. With HBr.—Gaseous hydrogen bromide was passed slowly through a solution of **4b** (0.20 g, 0.692 mmol) in dry benzene under nitrogen atmosphere. The reaction was followed by tlc (silica gel HF_{254}; eluent, 20% ether in petroleum ether, bp 60–70°). The reaction was very slow at 50° and after 2.5 hr the oil bath was raised to 80–90° and maintained at that temperature for 2.5 hr. Chromatography (silica gel; petroleum ether) of the mushy solid, obtained from the benzene solution, gave 0.15 g (59.1% yield) of **14** (mp 62–63.5°). A mixture melting point of the purified dibromo compound (mp 64.5–65.5° from ethanol) with **14** obtained from **1b** was undepressed.

2. Conversion into 8,9-Benzo[6]metacyclophane (15).—The reaction of **4b** (0.98 g, 3.50 mmol) with magnesium (0.24 g, 10.0 g-atoms) was carried out under nitrogen in tetrahydrofuran (20 ml, from lithium aluminum hydride) using 1,2-dibromoethane (0.66 g, 3.50 mmol) as a carrier.[15] The mixture, subsequent to formation of the Grignard reagent (>4-hr reflux), was decomposed with 5% hydrochloric acid (20 ml). The crude product was purified on alumina (150 g; eluent, petroleum ether, bp 60–70°) to give slightly impure **15** (82.7% yield) which was further purified by preparative glpc (5% SE-30 on Chromosorb W, 80–100 mesh, 4 ft × ¼ in. column; 160°; helium flow, 60 ml/min): clear oil; uv max (95% ethanol) 236 mμ (log ε 3.88), 286 (2.79); nmr (CCl_4) τ 1.88–3.04 (m, 5.9, aromatic **H**), 6.31–10.43 (m, 13.3, aliphatic and benzylic CH_2); mass spectrum (70 eV) *m/e* 210 (molecular ion).

Anal. Calcd for $C_{16}H_{18}$: C, 91.37; H, 8.63. Found: C, 91.26; H, 8.73.

3. Conversion into 8,9-Benzo[6]metacyclophane-12-^{2}H (16).—The reaction was carried out essentially as described above except that special precautions to ensure dry equipment and reagents were taken. A small amount of methylmagnesium iodide in tetrahydrofuran was added to the reaction. The reaction mixture was heated at reflux for 5 hr, during which time a small amount of 1,2-dibromoethane in tetrahydrofuran was added. The Grignard reagent was decomposed with deuterium oxide (5 ml). The product was obtained in 92.5% yield (97% deuterium incorporation by nmr): uv max (95% ethanol) 236 mμ (log ε 3.86), 286 (2.78); nmr (CCl_4) τ CCl_4) τ 1.96–3.10 (m, 5.4, aromatic **H**), 6.33–10.40 (m, 12.7, benzylic and aliphatic CH_2); mass spectrum (70 eV) *m/e* 211 (molecular ion).

Anal. Calcd for $C_{16}H_{17}D$: C, 90.94; H, 9.06. Found: C, 91.21; H, 8.97.

Reaction of Pentahydrocyclohept[*b*]indene (1a) with Phenyl(trichloromethyl)mercury.—The reaction of **1a** (12.8 g, 0.0695 mol) was carried out essentially as described for **1b** (reflux temperature 41 hr). Chromatography of the product on alumina (600 g; eluent, petroleum ether, bp 60–70°) gave 10.69 g (66.5% yield, mp 89–93°) of **18** which was recrystallized with little loss of product to give pure **18**: mp 99–99.5°; white crystals; uv max (95% ethanol) 228 (sh) (log ε 4.90), 231 (5.07), 257 (sh) (3.42), 267 (sh) (3.62), 275 (3.77), 285 (3.80), 294 (3.64), 307 (sh) (2.75), 324 (2.49); nmr (CCl_4) τ 1.67–1.95 (m, 1.01, aromatic **H**), 2.27–2.83 (m, 4.0, aromatic **H**), 6.62–6.95 (m, 4.0, benzylic

(13) L. F. Fieser and M. A. Peters, *J. Amer. Chem. Soc.*, **54**, 4373 (1932). A sample of the picrate of **10** was kindly supplied by Professor Louis L. Fieser.

(14) E. D. Bergman and R. Ikan, *J. Org. Chem.*, **23**, 907 (1958).

(15) H. Bamford and J. L. Simonsen, *J. Chem. Soc.*, **97**, 1904 (1910).

CH_2), 6.98–7.31 (m, 2.0, aliphatic CH_2), 8.02–8.63 (m, 6.0, aliphatic CH_2).

Anal. Calcd for $C_{15}H_{15}Cl$: C, 78.09; H, 6.55. Found: C, 78.33; H, 6.66.

Later fractions of the chromatograph, eluted with 75% petroleum ether (bp 60–70°) in benzene, gave 1.55 g (8.4% yield) of **19**, mp 46.5–48.5°. Pure **19** (mp 52–53° from ethanol) was obtained as white crystals: uv max (95% ethanol) 228 mμ (log ε 5.00), 252 (sh) (3.41), 262 (3.58), 270.5 (3.70), 281 (3.71), 290.5 (3.51), 302 (sh) (2.63), 317 (sh) (2.50), 323 (sh) (2.56); nmr (CCl_4) τ 2.12–2.80 (m, 6.0, aromatic **H**), 6.40–6.70 (t, 2.0, benzylic CH_2), 7.12–7.32 (t, 2.0, CH_2 Cl), 8.00–8.57 (m, 6.0, aliphatic CH_2).

Ancl. Calcd for $C_{15}H_{16}Cl_2$: C, 67.42; H, 6.04. Found: C, 67.12; H, 5.91.

Tetramethyl 3-Chloro-1,2,4,5-benzene Tetracarboxylate. 1. From Chlorodurene.—Chlorodurene (0.20 g, 0.119 mol) was oxidzed as previously described for **3d**[3,11] The crude acid (white powder, mp 155–175°) was digested in benzene to give 0.50 g (72.8% yield) of acid melting at 248° dec. This acid (0.20 g) was esterified with excess diazomethane in ether to give, subsequent to recrystallization of the product from petroleum ether (bp 60–70°), 0.22 g (91.2% yield from the acid), mp 118–122°. The pure ester was obtained by preparative tlc (silica gel PF_{254}; eluent, 70% ether in petroleum ether) and recrystallization from petroleum ether (bp 60–70°): mp 122.6–123.1°; ir (Nujol–halocarbon oil) 1730, 1740, 1760 cm^{-1} (C=O); uv max (95% ethanol) 213 mμ (log ε 4.59), 243 (sh) (3.91), 291 (3.43), 300 (3.47); nmr ($CDCl_3$) τ 1.53 (s, 1, aromatic **H**), 6.05 (s, 6, OCH_3), 6.10 (s, 6, OCH_3).

Ancl. Calcd for $C_{14}H_{13}ClO_8$: C, 48.78; H, 3.80; Cl, 10.29. Found: C, 48.74; H, 3.60; Cl, 10.39.

2. **From 18.**—The oxidation of **18** (0.25 g, 1.08 mmol) and esterification of the derived acid(s) were carried out essentially as described in 1 above. The crude ester (80 mg) was chromatographed on silica gel (30 g; eluent, petroleum ether, bp 60–70°), and the product was recrystallized from petroleum ether (bp 60–70°). The product (mp 122.6–123.4°) was identical (mixture melting point) with that described in 1 above.

Independent Synthesis of 2-(5-Chloropentyl)-3-chloronaphthalene (19). 1. 2-(5-Chloropentyl)indene (23).—The crude product, obtained by allowing 2-indanone (11.6 g, 0.80 mol) to react with the Grignard reagent [prepared from pentamethylene-chloroiodide (25.0 g, 0.108 mol) and magnesium (2.7 g, 0.108 g-atom)] was chromatographed on alumina (100 g; eluent, petroleum ether, bp 60–70°), and the oil was distilled to give 1.2 g (4.6% yield) of **23** (67% pure by glpc). Pure **23** was obtained by preparative glpc (20% SE-30 on Chromosorb W, 80–100 mesh; 225°; helium flow, 60 ml/min): nmr (CCl_4) τ 2.63 (m, 5, aromatic **H**), 3.32 (broad s, 1, olefinic **H**), 6.42 (broad t, 2, CH_2Cl), 6.70 (broad s, 2, benzylic CH_2), 7.51 (broad t, 2, allylic CH_2), 8.41 (m, 6, aliphatic CH_2).

Anal. Calcd for $C_{14}H_{17}Cl$: C, 76.16; H, 7.78. Found: C, 76.32; H, 7.79.

2. **2-(5-Chloropentyl)-3-chloronaphthalene (19).**—The crude product obtained from **23** (0.34 mg, 0.155 mmol) and phenyl(trichloromethyl)mercury (2 equiv; see preparation of **3a**) was chromatographed on alumina (10 g; eluent, 20% benzene in petroleum ether, bp 60–70°). The product was recrystallized from petroleum ether (bp 60–70°) to give pure **19** (20 mg, 49%, mp 51–52.5°) which was identical (mixture melting point) with that obtained from **1a**.

Registry No.—*o*-(1-Cyclooctenyl)-benzonitrile, 23069-13-8; *o*-(1-cyclooctenyl)-benzylamine hydrochloride, 23115-92-6; **1b**, 23069-14-9; **3b**, 23069-15-0; **4b**, 23069-16-1; **5**, 23069-17-2; **6**, 23069-18-3; **8**, 23069-19-4; **9**, 23069-20-7; **12**, 23069-21-8; **14**, 23069-22-9; **15**, 23069-23-0; **16**, 23069-24-1; **18**, 23069-25-2; **19**, 23069-26-3; **23**, 23069-27-4; tetramethyl-3-chloro-1,2,4,5-benzene tetracarboxylate, 23069-28-5.

A Study on the Condensation of Mesityl Oxide with Acetoacetic Ester

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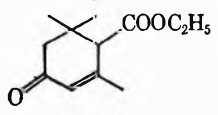
Received July 7, 1969

The zinc chloride catalyzed condensation of mesityl oxide with ethyl acetoacetate resulted in the formation of two structural isomers: 3,5,5-trimethyl-2-cyclohexen-1-one-4-carboxylic acid ethyl ester (**4**) and 3,5,5-trimethyl-2-cyclohexen-1-one-6-carboxylic acid ethyl ester (**5**). Isomer **5** was readily converted into isophorone by selective hydrolysis. The syntheses of two substituted β-ionones, 3-ethylenedioxy-β-ionone (**17**) and 3-ethoxy-3,4-dehydro-β-ionone (**20**), and a number of novel by-products are reported.

Merling and Welde[1] and Knoevenagel[2] reported the preparation of the cyclohexenone **4** from the condensation of acetoacetic ester with 2-isopropylidene acetoacetate. Rubinstein[3] obtained **4** in *ca.* 40% yield by condensing mesityl oxide and acetoacetic ester in the presence of boron trifluoride etherate. Since sub-



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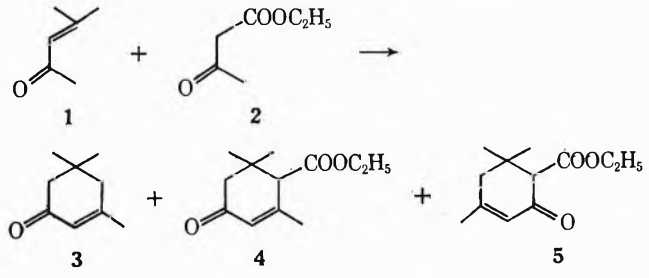
stituted intermediates which would find application for the preparation of the higher polyenes are not readily available, additional study of this interesting condensation was desirable.

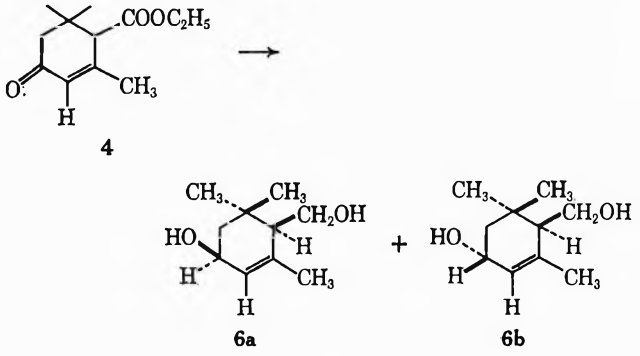
The zinc chloride catalyzed condensation of mesityl oxide (**1**) with ethyl acetoacetate (**2**) afforded 19% isophorone (**3**) and 40% a fraction distilling at 75–78° (0.2 mm). This was found to consist of two isomers, **4** and **5**, in a ratio of 4:1.



The isomeric ratio was measured by vpc, while analytical samples of **4** and **5** were prepared by column chromatography. The relative ease with which isophorone was formed by hydrolysis and decarboxylation of **5** made it convenient to prepare **4** by selectively hydrolyzing the mixture before fractionation.

(1) G. Merling and R. Welde, *Ann.*, **366**, 141 (1909).
(2) E. Knoevenagel, *ibid.*, **297**, 185 (1897).
(3) H. Rubinstein, *J. Org. Chem.*, **27**, 3886 (1962).

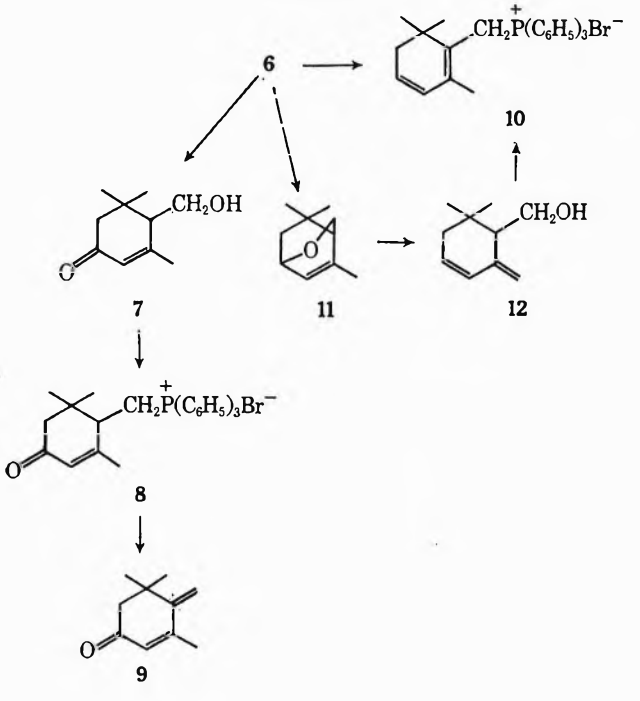
Reduction of **4** with lithium aluminum hydride afforded two isomeric cyclohexenediols, **6a** and **6b**.



According to the nmr spectra, both of the cyclohexenediols contain the $-CH{=}\overset{|}{C}CH_3$, $>CHCH_2O-$, and $>CHO-$ groups establishing them as structural isomers. The C_4 methine protons were narrow ($w_{1/2}$ = 10 Hz) for **6a** and broad ($w_{1/2}$ = 22 Hz) for **6b** and were, therefore, assigned the pseudoequatorial (e′) and pseudoaxial (a′) configuration, while the C_4 hydroxyls are a′ and e′, respectively.

Results of our investigation to prepare substituted intermediates which would be suitable for polyene synthesis are shown in Charts I and II. An Oppenauer

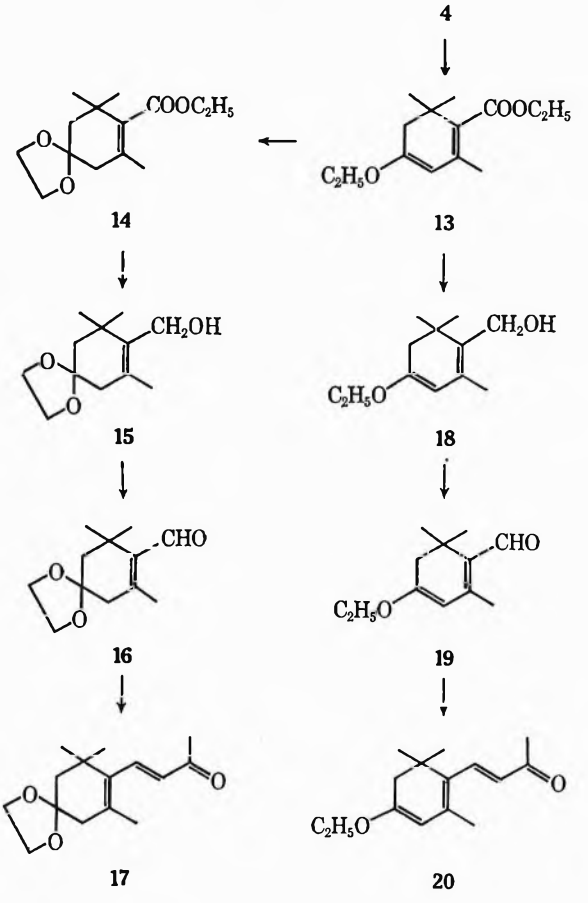
CHART I



oxidation of **6a** led to the keto alcohol (**7**), which, on condensation with triphenylphosphonium bromide in methylene chloride, afforded the phosphonium salt **8**. The product **8** failed to form a phosphorane on treatment with sodium methoxide, but cleaved instead to yield triphenylphosphine and the dienone **9**.

Condensation of **6a** with triphenylphosphonium bromide[4] in methylene chloride resulted in a dehydration affording the phosphonium salt **10**. When **6a** was stirred in methylene chloride containing a trace of hydrogen chloride, the bicyclic ether **11** was formed which rearranged to the dienol **12**. Condensation of compound **12** with triphenylphosphonium bromide resulted in a rearranged phosphonium salt (**10**). Treatment of **10** with sodium methoxide resulted in the corresponding phosphorane, which reacted with crocetindialdehyde to yield 3,4,3′,4′-bisdehydro-β-carotene. Preparation of this carotenoid will be discussed in a subsequent publication.

CHART II



The enol ether **13** was prepared in 70% yield by treating **4** with triethyl orthoformate and anhydrous ethyl alcohol in the presence of sulfuric acid catalyst. The reaction of **13** with ethylene glycol in benzene led to a 48% yield of the ketal **14**. An attempt at direct ketalization of **4** to **14** resulted in considerable resin formation. Reduction of **14** with lithium aluminum hydride resulted in the alcohol **15**. The aldehyde **16** was prepared by oxidation of **15** with manganese dioxide in methylene chloride. Condensation of **16** with acetone afforded the ionone **17**, mp 39°, after recrystallization from hexane.

The substituted ionone **20** was prepared from **13** by following the same sequence of reactions which were described for **17**. Reduction of **13** with lithium aluminum hydride led to the alcohol **18**, which, on oxidation with manganese dioxide, resulted in the aldehyde **19**. Condensation of **19** with acetone afforded the ionone **20**. The nmr, ir, and uv spectra and the analytical data were compatible with the structures assigned to the products shown by Charts I and II.

(4) J. D. Surmatis and A. Ofner, *J. Org. Chem.*, **28**, 2735 (1963).

Experimental Section[5]

3,5,5-Trimethyl-2-cyclohexen-1-one-4-carboxylic Acid Ethyl Ester (4).—A mixture of mesityl oxide (196 g), ethyl acetoacetate (260 g), $ZnCl_2$ (40 g), heptane (200 ml), and benzene (200 ml) was refluxed for 72 hr. The H_2O which was formed during the reaction was azeotropically distilled and collected in a separator. The cooled reaction mixture was washed with H_2O (500 ml), with 5% $NaHCO_3$ (500 ml), and again with H_2O (200 ml). The oil layer was dried over $CaCl_2$, and the solvent was removed under vacuum. The remaining oil was distilled in a packed column with an efficiency of approximately 10 theoretical plates. After a forecut consisting of unreacted mesityl oxide and ethyl acetoacetate, there was obtained 52.5 g (19%) of isophorone, 2,4-dinitrophenylhydrazone derivative, mp 191°, and 168 g (40%) of a condensation product distilling at 75–78° (0.2 mm), $n^{25}D$ 1.4771. The distillate contained two compounds, **4** and **5**, in a ratio of 4:1 as determined by vpc using a 0.5% Carbowax M-Chromosorb G column. An analytical sample of **4** was prepared by column chromatography on silica gel G using a solvent system consisting of hexane–ethyl ether in a ratio of 7:3: $n^{25}D$ 1.4763; uv max (EtOH) 235 mμ ($E^{1\%}_{1\,cm}$ 508); ir (film) 1735 (s), 1675 (s), 1645 cm^{-1} (m); nmr (CCl_4) δ 5.82 (m, 1, –CH=), 4.16 (quartet, 2, J = 7 Hz, $-OCH_2-$), 2.90 (s, 1, $=CHCOOC_2H_5$), 2.65, 1.93 (AB, 2, J = 16 Hz, $-CH_2-$), 1.90 (d, 3, J = 1.5 Hz, $=CHCH_3$), 1.28 (t, 3, J = 7 Hz, $-CH_2CH_3$), 1.05 (s, 6, $2CH_3$). *Anal.* Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.82; H, 8.69.

3,5,5-Trimethyl-2-cyclohexen-1-one-6-carboxylic Acid Ethyl Ester (5).—This isomer was eluted as the first fraction from the chromatogram of **4**: uv max (EtOH) 237 ($E^{1\%}_{1\,cm}$ 584); ir (film) 1740 (s), 1675 (s), 1640 cm^{-1} (m); nmr (CCl_4) δ 5.79 (m, 1, –CH=), 4.13 (quartet, 2, J = 7 Hz, OCH_2-), 2.97 (s, 1, $=CHCOOC_2H_5$), 2.50, 2.04 (AB, 2, J = 17 Hz, $-CH_2-$), 1.96 (broad s, 3, $=CHCH_3$), 1.26 (t, 3, J = 7 Hz, $-CH_2CH_3$), 1.10 (s, 3, CH_3), 1.05 (s, 3, CH_3). *Anal.* Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.65; H, 8.62.

Hydrolysis of 3,5,5-Trimethyl-2-cyclohexen-1-one-6-carboxylic Acid Ethyl Ester (5) to Isophorone (3).—The isomer **5** (12.0 g), H_2O (500 ml), and $ZnCl_2$ (3.0 g) were stirred on a steam bath for 24 hr. The cooled reaction mixture was extracted with hexane. The combined extracts were washed with 5% $NaHCO_3$ and H_2O and the solvent was removed under vacuum. The resulting oil, 6.1 g (92.8%), was identified as isophorone by the 2,4-dinitrophenylhydrazone derivative, mp and mmp 191°. One peak was obtained by vpc which was identical with an authentic sample of isophorone.

Purification of 3,5,5-Trimethyl-2-cyclohexen-1-one-4-carboxylic Acid Ethyl Ester (4) by Selective Hydrolysis of the Isomer Mixture.—A distilled mixture of **4** and **5** (1650 g) was placed in a flask with H_2O (5.0 l.), 95% C_2H_5OH (500 ml), and $ZnCl_2$ (50 g) and stirred on a steam bath for 24 hr. The cooled reaction mixture was extracted with benzene, and the combined extracts were washed with H_2O (2 l.), with 5% $NaHCO_3$ (2 l.), and finally with H_2O (2 l.). The benzene was removed under vacuum and the residue was distilled through a Vigreux column. The main fraction, which consisted of **4** as determined by vpc, weighed 1300 g (78.7%) and distilled at 77–78° (0.2 mm), $n^{25}D$ 1.4764.

4-Hydroxy-2,6,6-trimethyl-2-cyclohexene-1-methanol (6).—3,5,5-Trimethyl-2-cyclohexen-1-one-4-carboxylic acid ethyl ester (**4**, 25 g) was reduced by adding it to a suspension of $LiAlH_4$ (4.3 g) in ethyl ether (200 ml) at such a rate as to maintain a gentle refluxing. The stirring and refluxing were then continued for an additional 4 hr. H_2O (22 ml) was added to the cold reaction mixture (5°) drop by drop; then the inorganic precipitate was filtered off by suction. The filtrate was dried over Na_2SO_4, and the solvent was removed under vacuum. The crude diol **6**, 19.5 g (96.4%), was obtained as a viscous oil. *Anal.* Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.27; H, 10.45.

The Separation of Isomers 6a and 6b.—The isomer mixture **6** (19.0 g) was chromatographed on 300 g of silica gel G with 10% acetone and 90% hexane. The acetone content was gradually increased to 25% during the elution of the product. The first isomer (**6a**), which was obtained from the column crystallized from ethyl ether (2.0 g): mp 95–96°; nmr ($CDCl_3$) δ 0.92 (3, s, CH_3), 0.97 (3, s, CH_3), 1.63 (3, m, $J \sim 1$ Hz, CH_3), 3.38 (2, s, OH), 3.83 (2, d, J = 6.5 Hz, $-CH_2O-$), 4.48 (1, m, $w_{1/2}$ = 10 Hz, =CHO–), 5.43 (1, m, –CH=). *Anal.* Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.39; H, 10.60. The more strongly absorbed isomer (**6b**) was obtained as a viscous oil: nmr ($CDCl_3$) δ 0.85 (3, s, CH_3), 1.00 (3, s, CH_3), 1.72 (3, m, $J \sim 1$ Hz, CH_3), 2.45 (2, s, OH), 3.72 (2, d, J = 4 Hz, $-CH_2O-$), 4.13 (1, m, $w_{1/2}$ = 22 Hz, –CHO–). *Anal.* Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.71; H, 10.56.

3,5,5-Trimethyl-2-cyclohexen-1-one-4-methanol (7).—The cyclohexenediol (**6**, 19 g) was refluxed for 20 hr with aluminum isopropoxide (11.0 g) in acetone (150 ml). Most of the solvent was removed by distilling under reduced pressure. The residue was transferred to a separator with 5% H_2SO_4 (500 ml) and extracted with ethyl ether. The ether extract was washed with $NaHCO_3$ (5%), and dried over Na_2SO_4, and the solvent was removed under vacuum. The residue which crystallized from ethyl ether–hexane afforded 6.2 g (33.0%) of **7**: mp 63–65°; uv max (EtOH) 238 mμ ($E^{1\%}_{1\,cm}$ 722); ir (KBr) 3350 (s), 1660 cm^{-1} (s). *Anal.* Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.55; H, 9.50.

(4-Oxo-2,6,6-trimethyl-2-cyclohexen-1-yl)methyltriphenylphosphonium Bromide (8).—3,5,5-Trimethyl-2-cyclohexen-1-one-4-methanol (**7**, 16.8 g) and triphenylphosphonium bromide (36 g) in CH_2Cl_2 (200 ml) were stirred for 20 hr at room temperature. The solution was washed with H_2O and dried over Na_2SO_4, and the solvent was removed under vacuum. The crystalline residue which was obtained was recrystallized from methyl alcohol–ethyl acetate to afford 39.5 g (80%) of **8**: mp 192–194°; ir (KBr) 1660 (s), 1590 (m), 1440 (s), 750 s, 690 cm^{-1} (s). *Anal.* Calcd for $C_{28}H_{30}OPBr$: C, 68.16; H, 6.13. Found: C, 68.14; H, 6.17.

3,5,5-Trimethyl-4-methylene-2-cyclohexen-1-one (9).—Sodium methoxide (4 g) was added to a solution of **8** (39.5 g) in CH_3OH (100 ml) and the reaction was stirred for 1 hr at room temperature. The crystalline triphenylphosphine which was formed was filtered off and the filtrate was diluted with H_2O (200 ml) and extracted with hexane (200 ml). The solvent layer was dried over anhydrous Na_2SO_4 and fractionated to yield 10.0 g (82.5%) of **9**: bp 64–66° (0.75 mm); $n^{25}D$ 1.5173; uv (EtOH) 272 mμ ($E^{1\%}_{1\,cm}$ 1007); ir (film) 1840 (w), 1770 (w), 1680 cm^{-1} (s); nmr (CCl_4) δ 2.50 (m, 1, –CH=), 2.90 and 2.83 (s and d, respectively, 2, $=CH_2$), 2.25 (s, 2, $-CH_2-$), 2.07 (d, 3, J = 1 Hz, CH_3), 1.20 [s, 6, $=C(CH_3)_2$]. *Anal.* Calcd for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 80.15; H, 9.44.

(2,6,6-Trimethyl-1,3-cyclohexadien-1-yl)methyltriphenylphosphonium Bromide (10).—Compound **6a** (15 g) and triphenylphosphonium bromide (39 g) were stirred in CH_2Cl_2 (200 ml) for 24 hr. The solution was washed with H_2O and dried over Na_2SO_4, and the solvent was removed under vacuum. The resulting residue was crystallized from acetone–ethyl ether to yield 33 g (78.5%) of **10**, mp 124–125°. *Anal.* Calcd for $C_{28}H_{30}PBr$: C, 70.44; H, 6.33; Br, 16.74. Found: C, 70.14; H, 6.11; Br, 16.64.

5,8,8-Trimethyl-2-oxabicyclo[2.2.2]oct-5-ene (11) and 2-Methylene-6,6-dimethyl-3-cyclohexene-1-methanol (12).—A trace of hydrogen chloride was introduced into a methylene chloride solution (200 ml) of **6a** (40 g), and the reaction was stirred for 2 hr. The contents of the flask were neutralized with NH_4OH and dried over Na_2SO_4, and the solvent was removed under vacuum. Fractionation through a Vigreux column yielded a forecut, 3.0 g (8.4%), which, after purification by chromatography on aluminum oxide with ethyl ether, was assigned the structure **11**: $n^{25}D$ 1.4663; ir (film) 1050 (s), 1025 (s), 970 (s), 820 cm^{-1} (s); nmr (CCl_4) δ 5.90 (m, 1, –CH=), 4.08 (m, 1, =CHO–) 3.94 and 2.94 (two d of d, 2, J_{gem} = 8 Hz, OCH_2), 1.87 (d, 3, CH_3), 1.83 (m, 1, CH), 165 and 1.05 (two d of d, 2, J_{gem} 12 Hz, CH_2), 1.11 (s, 3, CH_3), 0.84 (s, 3, CH_3). *Anal.* Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.80; H, 10.57.

The main fraction from the distillation, 15.0 g (41.9%), bp 58–61° (0.3 mm), $n^{25}D$ 1.506, was assigned structure **12**. An analytical sample was purified by chromatography on silica gel G with hexane–ethyl ether (4:1): uv max (EtOH) 231 mμ ($E^{1\%}_{1\,cm}$ 1114); ir (film) 3400 (s), 1640 (m), 1600 (m), 1060 (m), 1030 (s), 880 (m), 850 cm^{-1} (w); nmr (CCl_4) δ 6.03 (d, 1, J = 10 Hz, =CH–), 5.62 (m, 1, –CH=), 4.94 and 4.87 (singlets, 2, $=CH_2$), 3.55 and 3.25 (m, 2, $-CH_2OH$), 2.20–1.65 (m, 4, $-CH_2-$, =CH–, OH), 1.00 (s, 3, CH_3), 0.87 (s, 3, CH_3). *Anal.* Calcd for $C_{10}H_{16}O$: C, 78.70; H, 10.59. Found: C, 78.65; H, 10.55.

(5) Melting points were determined in vacuum capillaries and are uncorrected. Nuclear magnetic resonance (nmr) spectra were obtained with a Varian A-60 spectrometer.

Preparation of 2-Methylene-6,6-dimethyl-3-cyclohexene-1-methanol (12) from 11.—An analytical sample of **11** which was purified by chromatography (4.0 g) was stirred for 4 hr in CH_2Cl_2 (50 ml) containing a catalytic quantity of hydrogen chloride. The reaction mixture was neutralized with NH_4OH and the solvent was removed under vacuum to yield 3.6 g (90.0%) of residue. The ir, uv, and nmr spectra of the product were identical with the spectra which were obtained for **12**.

Preparation of the Wittig Salt (10) from 2-Methylene-6,6-dimethyl-3-cyclohexene-1-methanol (12).—Compound **12** (3.0 g) and triphenylphosphonium bromide (8.0 g) were stirred in CH_2Cl_2 (40 ml) for 24 hr. The reaction was worked up by the same procedure described for the preparation of **10** from **6a**. The product consisted of 6.5 g (68.9%) of **10**, mp and mmp 124–125°.

2,6,6-Trimethyl-4-ethoxy-1,3-cyclohexadiene-1-carboxylic Acid Ethyl Ester (13).—A solution of 3,5,5-triethyl-2-cyclohexen-1-one-4-carboxylic acid ethyl ester (4,800 g), trimethyl orthoformate (720 g), absolute C_2H_5OH (1.5 l.), and concentrated H_2SO_4 (4 ml) was allowed to stand at room temperature overnight. The dark blue solution was poured into a separator containing hexane (2 l.) and saturated $NaHCO_3$ solution (2 l.). The hexane layer was separated, washed with H_2O, and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was distilled to yield 600 g (66.0%) of **13**: bp 84–86° (0.3 mm); $n^{25}D$ 1.4885; uv max (EtOH) 397 mμ ($E^{1\%}_{1\,cm}$ 315); ir (film) 1710 1630 (s), 1580 cm^{-1} (s). *Anal.* Calcd for $C_{14}H_{22}O_3$: C, 70.55; H, 9.30. Found: C, 70.30; H, 9.26.

7,9,9-Trimethyl-1,4-dioxaspiro[4.5]dec-7-ene-8-carboxylic Acid Ether Ester (14).—2,6,6-Trimethyl-4-ethoxy-1,3-cyclohexadiene-1-carboxylic acid ethyl ester (**13**, 680 g) and ethylene glycol (185 g) were heated for 2 hr in benzene (3 l.) in the presence of *p*-toluenesulfonic acid (3.0 g). The reaction was stopped when 1.5 l. of benzene was distilled off. The cooled reaction mixture was washed with $NaHCO_3$ solution (5%) and H_2O, and the benzene was removed under vacuum. The product, 320 g (44.1%), distilled at 92–94° (0.1 mm); $n^{25}D$ 1.4788; ir (film) 1715 (s), 1090 cm^{-1} (s). *Anal.* Calcd for $C_{14}H_{22}O_4$: C, 66.12; H, 8.72. Found: C, 66.42; H, 8.92.

7,9,9-Trimethyl-1,4-dioxaspiro[4.5]dec-7-ene-8-methanol (15).—A solution of 7,9,9-trimethyl-1,4-dioxasporo[4.5]dec-7-ene-8-carboxylic acid ethyl ester (**14**, 300 g) in ethyl ether (1 l.) was added slowly to a stirred suspension of $LiAlH_4$ (50 g) in ethyl ether (1 l.). The temperature was maintained at 15° during the addition. The stirring then was continued for 4 hr at 20–25° under an atmosphere of N_2. The reaction mixture was decomposed by the addition of H_2O (250 ml) drop by drop at 5–10°. The inorganic salt was filtered off and the product was dried over Na_2SO_4. The ether was removed by distillation and the residue was crystallized from hexane–ethyl ether to yield 270 g (80.3%) of **15**, mp 35°. *Anal.* Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.74; H, 9.67.

7,9,9-Trimethyl-1,4-dioxaspiro[4.5]dec-7-ene-8-carboxaldehyde (16).—7,9,9-Trimethyl-1,4-dioxaspiro[4.5]dec-7-ene-8-methanol (**15**, 150 g) was oxidized with MnO_2[6] (3.0 kg) in CH_2Cl_2 (3 l.) by stirring for 3 days under an atmosphere of N_2. The spent MnO_2 was filtered off and the solvent was removed under vacuum. The product **16**, 120 g (80.8%), distilled at 80–82° (0.1 mm): $n^{25}D$ 1.5060; uv max (EtOH) 246 mμ ($E^{1\%}_{1\,cm}$ 524); ir (film) 1670 (s), 1615 (w), 1085 cm^{-1} (s); nmr (CCl_4) δ 10.1 (s, 1, CHO), 3.87 (s, 4, CH_2CH_2), 2.38 (m, 2, J = 1 Hz, CH_2), 2.10 (m, 3, J = 1 Hz, CH_3), 1.59 (m, 2, J = 1 Hz, CH_2), 1.22 [s, 6, $C(CH_3)_2$]. *Anal.* Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.46; H, 9.00.

3-Ethylenedioxy-β-ionone (17).—A mixture of 7,9,9-trimethyl-1,4-dioxaspiro[4.5]dec-7-ene-8-carboxaldehyde (120 g), acetone (500 ml), and 10% aqueous KOH (60 ml) was refluxed under an atmosphere of N_2 for 16 hr. Most of the solvent was distilled off, and the residue was added to hexane (500 ml) and washed neutral with H_2O. After removal of the solvent under vacuum, the product crystallized from low-boiling petroleum ether (30–60°) at −10° to afford 60 g (41.8%) of **17**: mp 38–39°; uv max (EtOH) 291 mμ ($E^{1\%}_{1\,cm}$ 383); ir (KBr) 1670 (s), 1605 (s), 1085 cm^{-1} (s); nmr (CCl_4) δ 7.10 and 6.05 (AB, 2, J = 16.5 Hz, –CH=CH–), 3.88 (s, 4, CH_2CH_2), 2.24 (s, 2, CH_2), 2.20 (s, 3, CH_3CO), 1.76 (s, 3, CH_3), 1.63 (s, 2, CH_2), 1.12 [s, 6, $C(CH_3)_2$]. *Anal.* Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.16; H, 8.55.

2,6,6-Trimethyl-4-ethoxy-1,3-cyclohexadiene-1-methanol (18).—2,6,6-Trimethyl-4-ethoxy-1,3-cyclohexadiene-1-carboxylic acid ethyl ester (**13**, 250 g) was reduced with $LiAlH_4$ (50 g) by the same procedure used for the preparation of **15**. The product **18**, 165 g (80.2%), distilled at 60–62° (0.2 mm). *Anal.* Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.26. Found: C, 73.22; H, 10.35.

2,6,6-Trimethyl-4-ethoxy-1,3-cyclohexadiene-1-carboxaldehyde (19).—Product **18** (150 g) was oxidized with MnO_2 (3 kg) by the same procedure used to prepare **16**. The resulting aldehyde (**19**), 76 g (51.2%), distilled at 88° (0.3 mm); $n^{25}D$ 1.5487; uv max (EtOH) 342 mμ ($E^{1\%}_{1\,cm}$ 692); ir (film) 1660 (s), 1622 (s), 1550 cm^{-1} (s). *Anal.* Calcd for $C_{12}H_{18}O_2$: C, 74.19; H, 9.33. Found: C, 74.02; H, 9.30.

3-Ethoxy-3,4-dehydro-β-ionone (20).—2,6,6-Trimethyl-1,3-cyclohexadiene-1-carboxaldehyde (**19**, 40 g), acetone (400 ml), and a 10% aqueous solution of KOH (80 ml) was refluxed to prepare compound **20** by the same procedure described for **17**. The ionone **20** was obtained as crystals from CH_3OH: 23 g (47.4%); mp 43–45°; uv max (EtOH) 383 mμ ($E^{1\%}_{1\,cm}$ 670); ir (KBr) 1655 (s), 1595 (s), 1540 cm^{-1} (s); nmr (CCl_4) δ 7.25 and 6.03 (AB, 2, J = 16.5 Hz, –CH=CH–), 4.92 (s, 1, –CH=), 3.83 (quartet, 2, OCH_2), 2.57 (s, 3, CH_3), 2.12 (s, 2, CH_2), 1.92 (s, 3, CH_3CO), 1.32 (t, 3, CH_3CH_2), 1.17 [s, 6, $C(CH_3)_2$]. *Anal.* Calcd for $C_{15}H_{22}O_2$: 76.89; H, 9.46. Found: C, 76.80; H, 9.35.

Registry No.—**4**, 23068-96-4; **5**, 23068-97-5; **6a**, 23068-98-6; **6b**, 23068-99-7; **7**, 23069-00-3; **8**, 23069-01-4; **9**, 20548-00-9; **10**, 23069-03-6; **11**, 23069-04-7; **12**, 23069-05-8; **13**, 23115-91-5; **14**, 23069-06-9; **15**, 23069-07-0; **16**, 23069-08-1; **17**, 23069-09-2; **18**, 23069-10-5; **19**, 23069-11-6; **20**, 23069-12-7.

Acknowledgment.—We wish to thank Dr. T. Williams for the nmr spectra, Dr. F. Forrester for the ir and uv spectra, and Dr. A. Steyermark for the microanalyses.

(6) Available from General Metallics Oxides Corp., Jersey City, N. J. (manganese hydrate no. 37).

Base-Induced Reactions of Phenacyl Chloride

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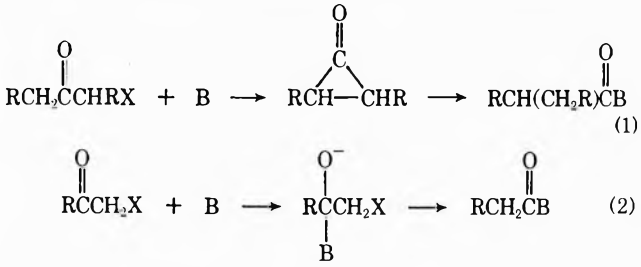
Received January 17, 1969

In benzene at reflux temperature, the reaction between phenacyl chloride and excess sodium hydride affords *trans*-1,2,3-tribenzoylcyclopropane and 3-chloro-2,4-diphenylfuran. With potassium *t*-butoxide at room temperature, acetophenone, diphenacyl, and phenacyl chloride are recovered after hydrolysis; the product ratio is sensitive to the mode of hydrolysis. Heating the butoxide reaction mixture prior to hydrolysis gives four rearranged products: *t*-butyl phenylacetate, phenylacetic acid, dibenzyl ketone, and ω-benzylacetophenone.

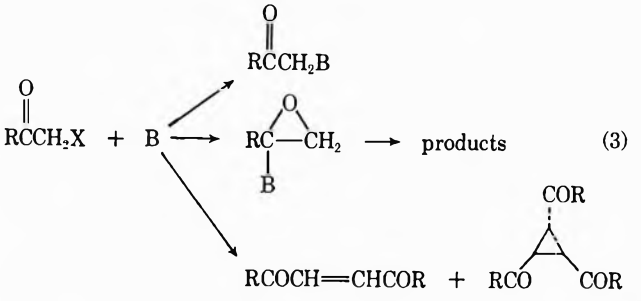
The reactions of α-halo ketones with alkoxides or hydroxides leads to both rearranged and unrearranged products.[2] Rearranged products[3] can be produced by both Favorskii (eq 1) and semibenzylic (eq 2) processes for α-halo ketones with and without α′ hydrogens.



(1)

(2)

Unrearranged products include α-hydroxy or alkoxy ketones,[4] epoxides or products derived from them,[5] 1,2-diacylethylenes, and 1,2,3-triacylcyclopropanes (eq 3).[6] Alternate routes involving keto carbenoids[7] and



(3)

their anionic precursors[8] have been proposed for the formation of acylethylenes and cyclopropanes.

This paper deals with the reactions between phenacyl halides and sodium hydride or potassium *t*-butoxide in cyclohexene and benzene. Phenacyl halides were used since they have no α′ hydrogens and cannot undergo Favorskii rearrangement.

Results and Discussion

Sodium Hydride Reactions.—The reaction between phenacyl chloride and excess sodium hydride in refluxing cyclohexene or benzene gives *trans*-1,2,3-tribenzoylcyclopropane (I) and 3-chloro-2,4-diphenyl furan (II). The reaction with phenacyl bromide gives the cyclopropane derivative and the corresponding bromofuran. The products yields as a function of the reaction conditions are summarized in Table I.

TABLE I

REACTION OF PHENYL HALIDES WITH SODIUM HYDRIDE AT SOLVENT REFLUX TEMPERATURE

$NaH/C_6H_5CO-CH_2Cl(Br)$ mole ratio	Phenacyl halide addition time and solvent	Yield of halofuran, cyclopropane, and acetophenone, %
	Phenacyl Chloride	
15:1	1 hr, C_6H_6	16.8, 17.2, 0.0
15:1	2 hr, C_6H_6	13.2, 14.0, 0.0
15:1	4 hr, C_6H_6	7.8, 11.0, 0.0
9:1	1 hr, C_6H_6 or cyclohexene	20–21, 20–21, 0.0
	Phenacyl Bromide	
15:1	1 hr, C_6H_6 or cyclohexene	6–7.5, 21–22, 4.0
15:1	4 hr, cyclohexene	0–1, 2.6, 0.0

When cyclohexene was used as a solvent, neither phenacyl chloride nor bromide gave any *cis*- or *trans*-dibenzoylethylene or 7-benzoylnorcarane. The chlorofuran, tribenzoylcyclopropane, and 7-benzoylnorcarane do not decompose or isomerize under simulated reaction conditions.

A mechanistic scheme compatible with these results follows (p 1058).

In path A the phenacyl halide enolate anion displaces halide from the phenacyl halide eventually leading to the cyclopropane. In path B the enolate anion adds to the carbonyl group of the phenacyl halide and ultimately provides the furan derivatives. The formation of halo furans in this scheme resembles the Feist–Bernary synthesis.[9]

It is plausible that the cyclopropane derivative (I) could arise from the reaction between a ketocarbene (*via* α elimination) and its dimer dibenzoylethylene. Previous workers have shown that divalent carbon fragments can be trapped with alkenes and cycloalkenes.[10,11] The photochemical decomposition of diazo ketones is thought to involve both triplet (primarily) and singlet carbenes, whereas the base-induced α-elimination reactions of diphenyldibromethane presumably involve a carbene–metal halide complex. These results suggest that under our conditions, cyclohexene, the solvent, should compete favorably with dibenzoylethylene for a keto carbene intermediate

(1) To whom inquiries should be addressed: Shell Development Co., Emeryville, Calif. 94608.

(2) (a) W. McPhee and E. Klingsberg, *J. Amer. Chem. Soc.*, **66**, 1132 (1944); (b) J. Harley-Mason, *J. Chem. Soc.*, 518 (1949).

(3) A. S. Kende and R. Adams, *Org. Reactions*, **11**, 261 (1960).

(4) A. A. Sacks and J. G. Aston, *J. Amer. Chem. Soc.*, **73**, 3902 (1951).

(5) A. M. Ward, *J. Chem. Soc.*, 1541 (1929).

(6) M. Charpentier-Morize and P. Colard, *Bull. Soc. Chim. Fr.*, 1982 (1962).

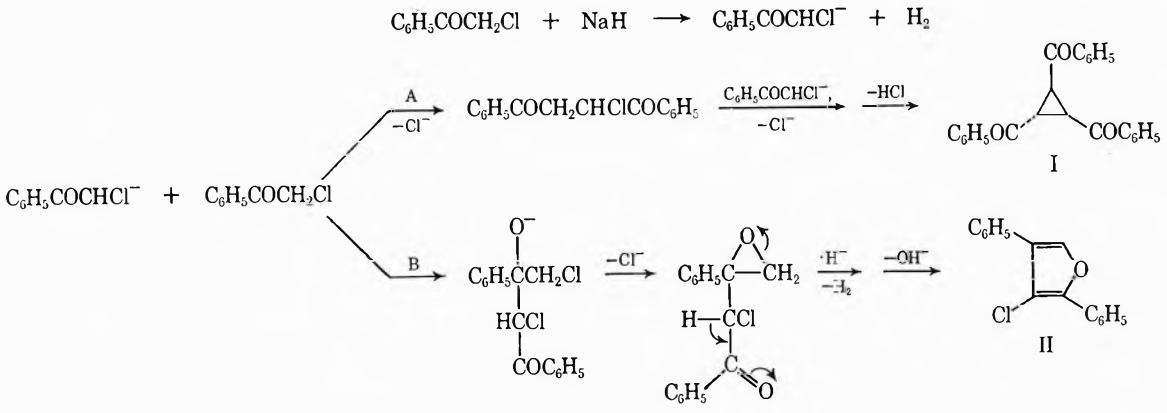
(7) (a) M. Siemiatycki and H. Strezelecka, *Compt. Rend.*, **250**, 3489 (1960); (b) V. Horak and L. Kohout, *Chem. Ind.* (London), 978 (1964).

(8) (a) G. Bonavent, M. Causse, and M. Guitard, *Bull. Soc. Chim. Fr.*, 2462 (1964); (b) H. Nozaki, K. Kondo, and M. Takaku, *Tetrahedron Lett.*, 251 (1965).

(9) A. F. Feist, *Chem. Ber.*, **35**, 1545 (1902).

(10) (a) D. O. Cowan, M. M. Couch, and G. S. Hammond, *J. Org. Chem.*, **29**, 1922 (1964); (b) M. Jones, Jr., and W. Ando, *J. Amer. Chem. Soc.*, **90**, 2200 (1968); (c) A. Padwa and R. Layton, *Tetrahedron Lett.*, 2167 (1967).

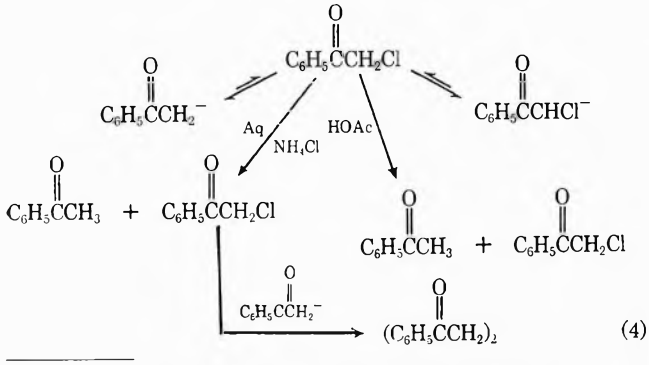
(11) G. L. Closs and L. E. Closs, *Angew. Chem.*, **74**, 431 (1962).



regardless of the fragment's multiplicity or degree of complexation. In the sodium hydride–phenacyl chloride–cyclohexene reaction, the absence of 7-benzoylnorcarane and the presence of *trans*-1,2,3-tribenzoylcyclopropane in the product mixture indicate that a phenacylidene fragment is an unlikely intermediate.

Potassium–*t*-Butoxide Reactions.—The addition of phenacyl chloride to fivefold excess potassium *t*-butoxide in benzene at room temperature results in the formation of a deep red solution. The solution gradually turns yellow on hydrolysis with aqueous ammonium chloride. Work-up affords diphenacyl (III) in 40–60% yield and acetophenone (IV) in 10% yield. When the red solution is hydrolyzed with acetic acid, it turns yellow rapidly and yields acetophenone (39%), phenacyl chloride (32%), and diphenacyl (<5%). An nmr spectrum of the initial red solution indicated that there was no phenacyl chloride, diphenacyl, or monoanion of diphenacyl in solution. An absorption at 5.5 ppm (singlet, phenacyl chloride or acetophenone enolate), which disappeared on hydrolysis, was observed.

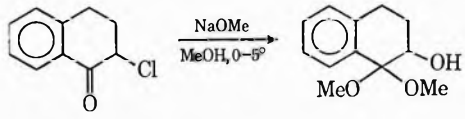
These results suggest that at the completion of the base addition only the enolate anions of phenacyl chloride and acetophenone, which are unreactive toward each other, remain. The presence of acetophenone enolate is likely because acetophenone is isolated after hydrolysis. Diphenacyl is apparently being formed during the subsequent neutralization step. The phenacyl chloride–acetophenone–diphenacyl distribution after hydrolysis depends on the neutralizing agent. It seems reasonable that the enolates are neutralized faster and more completely in the homogeneous acetic acid quench than in the heterogeneous aqueous ammonium chloride quench. In the ammonium chloride quench, diphenacyl formation[12] becomes important.



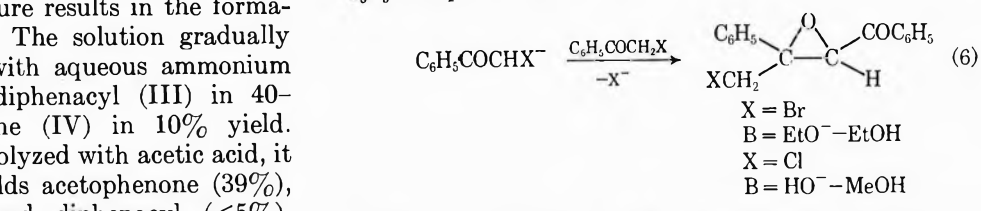
(4)

(12) Diphenacyl has been isolated previously in similar reactions: (a) O. Widman, *Chem. Ber.*, **42**, 3264 (1909); (b) P. R. Jones and J. R. Young, *J. Org. Chem.*, **33**, 1675 (1968).

Halo ketones without α' hydrogens react with alkoxides under mild conditions to provide alkoxy ethers and compounds derived from them[13] (eq 5) or



(5)



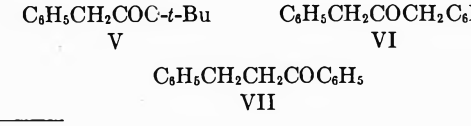
(6)

dimeric epoxides[14] (eq 6). Moreover, it has been reported that epoxyether formation competes with normal Favorskii rearrangement.[15] Cases have been reported[16] where tertiary α-halo ketones gave rise to rearranged acids on treatment with sodium hydroxide in refluxing xylene. This rearrangement is probably related to the benzylic acid rearrangement.

In our experiments, potassium *t*-butoxide was used as a base. In the experiments cited, hydroxide, methoxide, and ethoxide ions were employed. *t*-Butoxide is the strongest, most hindered, and least nucleophilic of the four bases. In the halo ketone–potassium *t*-butoxide reaction these properties favor deprotonation of the halo ketone by alkoxide over any reaction involving addition to the carbonyl group.

Evidence regarding the mode of formation of acetophenone is scant. However, subsequent experiments suggest that this enolate is reversibly formed from phenacyl chloride, presumably by transfer of positive chlorine to some acceptor.

If the reaction mixture is refluxed prior to neutralization, *t*-butylphenylacetate (V), dibenzyl ketone (VI), ω-benzylacetophenone (VII), and phenylacetic acid (VIII) are formed. The yields of the four products V, VI, VII, and VIII were 30, 15, 5, and 21%, respec-



(13) (a) C. L. Stevens, J. J. Beereboom, Jr., and K. G. Rutherford, *J. Amer. Chem. Soc.*, **77**, 4590 (1955); (b) C. L. Stevens, W. L. Malik, and R. Pratt, *ibid.*, **72**, 4758 (1950).

(14) H. H. Wasserman, N. E. Aubery, and H. E. Zimmerman, *ibid.*, **75**, 96 (1953).

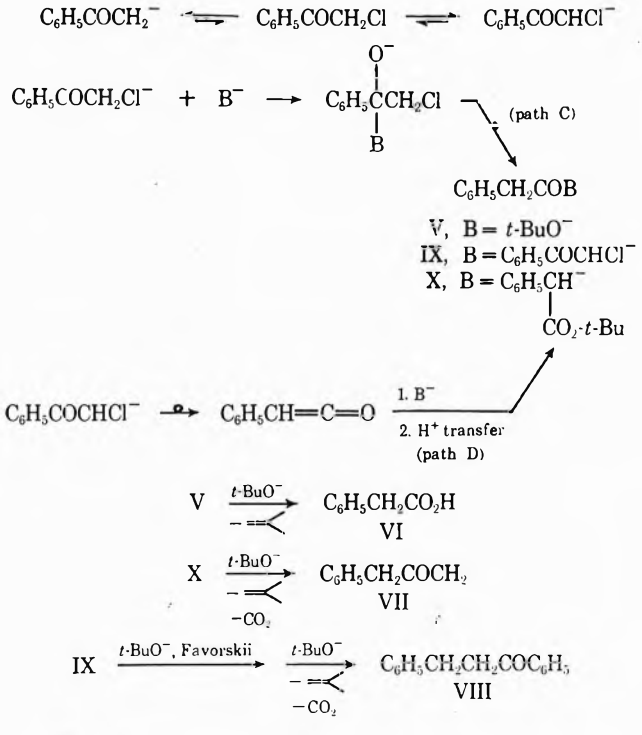
(15) C. L. Stevens and E. Farkas, *ibid.*, **74**, 618 (1952).

(16) (a) E. E. Smissman and G. Hite, *ibid.*, **81**, 2101 (1959); (b) B. Tchoubar, *Bull. Soc. Chim. Fr.*, **22**, 1363 (1955).

tively. The ratio of V to VI to VII was 6:3:1 regardless of the reflux time. Changing the solvent to cyclohexene gave the same products in approximately the same yields; 7-benzoylnorcarane was absent from the reaction mixture. The observed products are rearranged. To our knowledge, this is the first reported reaction in which alkoxide treatment of α-halo ketones without α' hydrogens provides rearranged products.

Possibly *t*-butyl phenylacetate could afford dibenzyl ketone *via* Claisen condensation followed by elimination of isobutylene and CO_2. However, when *t*-butyl ester V was treated with potassium *t*-butoxide under benzene reflux, no dibenzyl ketone was isolated. Only phenylacetic acid (21%) and unreacted ester (73%) were recovered. Isobutylene elimination must be the source of most of the phenylacetic acid in the phenacyl chloride–potassium *t*-butoxide reflux reaction.

Alternate paths leading to the rearranged products are suggested below.



Path C involves appreciable buildup of the phenacyl chloride concentration. If this is the case, it is surprising that other products, *e.g.*, diphenacyl, I, II, alkoxy ethers (as eq 5), etc., were not observed. In path D the concerted[17] rearrangement of phenacyl chloride anion to phenylketene is analogous to the nitrogen analog[18] in the Hofmann rearrangement. It is reasonable that $C_6H_5COCH_2COCH_2$ resulting from reaction of acetophenone anion by either path C or D is not detected. This β diketone should readily cleave with *t*-butoxide,[19] affording V and regenerating acetophenone anion. Products resulting from the direct reaction of acetophenone anion (including acetophenone) were not observed after hydrolysis. This is consistent with a rapid acetophenone anion–phenacyl chloride equilibrium which shifts to the right as the reaction proceeds.

(17) The results do not exclude a stepwise ionization of phenacyl chloride anion to a keto carbene followed by rapid rearrangement to phenylketene. In the absence of further data, the concerted rearrangement is offered for simplicity.

(18) C. R. Hauser and W. B. Renfrow, Jr., *J. Amer. Chem. Soc.*, **59**, 121 (1937).

(19) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., Inc., New York, N. Y., 1959, p 339.

Experimental Section

All reactions were carried out in a nitrogen atmosphere. Vapor phase chromatography analysis was done on an F & M Model 500 instrument using a 10 ft × 0.25 in. 12% QF-1 on Anakrom ABS 70–80 mesh column. Infrared spectra were recorded on a Perkin-Elmer Infracord and a Beckman IR-5A spectrometer. Nuclear magnetic resonance spectra were recorded in carbon tetrachloride with tetramethylsilane as an internal standard on a Varian A-60 spectrometer. Capillary melting points were determined using a Mel-Temp apparatus and are uncorrected.

Reaction of Phenacyl Chloride with Sodium Hydride in Cyclohexene.—Sodium hydride–mineral oil dispersion (34.7 g, 0.810 mol) was washed with 300 ml of benzene. Cyclohexene (100 ml) was added to the sodium hydride and the stirred mixture was maintained at reflux while phenaycl chloride (13.9 g, 0.0900 mol) dissolved in 200 ml of cyclohexene was added dropwise over a 1-hr period. The red mixture was refluxed for an additional 15 min, allowed to cool, and rapidly filtered under vacuum. The solution was extracted with saturated aqueous ammonium chloride. A white solid (1.0 g) precipitated from the organic layer and was removed and recrystallized from benzene, mp 218–220° (lit.[8b] mp 218°). Its nmr spectrum was identical with that of *trans*-1,2,3-tribenzoylcyclopropane (I).

The cyclohexene layer was dried (Na_2SO_4) and concentrated *in vacuo*, leaving 7.2 g of tarry resin.

Elution of this material from neutral alumina with hexane afforded 2.4 g (23%) of 3-chloro-2,4-diphenylfuran (II), which was recrystallized from 95% ethanol, leaving white plates, mp 110°.

Anal. Calcd for $C_{16}H_{11}OCl$: C, 75.44; H, 4.32; Cl, 13.95. Found: C, 75.29; H, 4.47; Cl, 13.96.

The nmr spectrum of II showed two multiplets centered at 7.40 and 7.95 ppm (area 9:2) with a singlet at 7.47 ppm (the 5 proton). The infrared spectrum of II displayed major absorptions at 6.2, 6.75, 6.95, 9.5, and 11.0 μ; uv max (95% EtOH) 283 mμ (log ϵ 4.38).

An additional 0.3 g (21% overall) of I was eluted with methylene chloride. Analysis of the reaction mixture by vpc showed no detectable amounts of 7-benzoylnorcarane or *cis*- or *trans*-dibenzoylethylene by comparison with authentic samples. The reaction was repeated in benzene with similar results.

Reaction of Phenacyl Bromide with Sodium Hydride.—The procedure was the same as the previous one except that bromofuran was eluted from alumina with 90:10 hexane–benzene, yielding 1.1 g (7%) of 3-bromo-2,4-diphenylfuran, mp 122° (lit.[20] mp 122°).

Anal. Calcd for $C_{16}H_{11}OBr$: C, 64.24; H, 3.68; Br, 26.73. Found: C, 63.83; H, 3.77; Br, 27.27.

Its infrared and nmr spectra were very similar to those of II, uv max (95% EtOH) 286 mμ (log ϵ 4.49).

trans-1,2,3-Tribenzoylcyclopropane (2.3 g, 23%) and acetophenone (0.4 g, 4%) were also isolated.

Control Experiments.—In three separate experiments, 7-benzoylnorcarane, *trans*-1,2,3-tribenzoylcyclopropane, and 3-chloro-2,4-diphenylfuran were refluxed in benzene for 1.5 hr in the presence of a tenfold excess of sodium hydride. Following the general work-up, the three compounds were recovered in virtually quantitative yields.

Reaction of Phenacyl Chloride with Potassium *t*-Butoxide at Room Temperature.—Potassium *t*-butoxide (34.6 g, 0.300 mol) was added to 100 ml of anhydrous benzene. A solution of phenacyl chloride (9.24 g, 0.0600 mol) dissolved in 100 ml of benzene was added dropwise to the stirred slurry over a 1-hr period. An nmr spectrum of the red solution showed that phenacyl chloride had been consumed. After an additional 15 min of stirring, neutralization with saturated aqueous ammonium chloride (50 ml) followed by conventional work-up afforded 3.0–4.2 g (40–65%) of crude diphenacyl (III). Recrystallization from ethanol

(20) This compound has been previously isolated. However, it was not fully characterized: H. A. Weidlich and G. H. Daniels, *Chem. Ber.*, **72**, 1590 (1939).

afforded a pure sample, mp 145–146° (lit.[21] mp 145°). Analysis of the crude reaction mixture by vpc revealed only two major products (*ca.* 1:7 ratio) which were identified as acetophenone (10%) and diphenacyl; traces of phenacyl chloride and *t*-butylphenylacetate were also detected. Traces of benzoic acid were isolated from the aqueous extracts.

The previous reaction was repeated at one-twelfth the scale. The reaction was quenched with 6 ml of glacial acetic acid in *ca.* 1 sec. Conventional work-up afforded a 0.46-g mixture of diphenacyl–phenacyl chloride–acetophenone (*ca.* 1:7:7, vpc). A 39 and 32% yield of acetophenone and phenacyl chloride, respectively, were obtained by nmr integration.

Reaction of Phenacyl Chloride with Potassium *t*-Butoxide at Benzene Reflux.—The procedure was identical with that of the previous large-scale, room temperature experiment up to the termination of the addition of the phenacyl chloride–benzene solution. At this point, the benzene mixture was refluxed for 1.5 hr with stirring. The reaction mixture was worked up as usual leaving an oily residue.

Vpc showed three major components in a 6:3:1 ratio. These were collected by vpc and identified as *t*-butyl phenylacetate (V), dibenzyl ketone (VI), and ω-benzylacetophenone (VII), respectively, by comparison of their physical and spectral properties with independently synthesized samples. Phenacyl chloride and acetophenone were minor components (<5%) in the residue. Acidification of the aqueous extracts afforded 0.84 g (21%) of phenylacetic acid, mp 74–76° (lit.[22] mp 77°).

(21) C. Weygand and W. Meusel, *Chem. Ber.*, **76**, 498 (1943).
(22) B. Sobin and G. B. Bachman, *J. Amer. Chem. Soc.*, **57**, 2458 (1935).

The reaction was conducted several times on a smaller scale. From the vpc and nmr spectrum of these crude reaction mixtures, the yield of V (30%), VI (15%), and VII (5%) was calculated. The V:VI:VII product ratio was identical after either 0.5- or 1.5-hr reflux.

Changing the solvent to cyclohexene gave the same products with slightly different ratios; the absence of 7-benzoylnorcarane was confirmed by vpc of the reaction mixture and synthetic norcaryl ketone.

Control Experiments.—In separate experiments, dibenzyl ketone, ω-benzylacetophenone, 7-benzoylnorcarane, and diphenacyl were reacted with a fourfold excess of potassium *t*-butoxide at benzene reflux for 1.5 hr. After work-up, all were recovered in quantitative or near quantitative yield.

Reaction of *t*-Butylphenylacetate with Potassium *t*-Butoxide.—Potassium *t*-butoxide (0.535 g, 5.00 mmol) was added to 8 ml of anhydrous benzene. To this stirred slurry, *t*-butylphenylacetate (0.30 g, 1.6 mmol) was added and the mixture was refluxed for 1.5 hr and worked up in the usual manner.

Unreacted starting material (0.218 g, 73%) was obtained from the organic phase. From the combined aqueous extracts, a white, crystalline acid, mp 74–76°, was isolated (0.08 g, 21%), whose nmr and ir spectra were identical with the spectra of phenylacetic acid.

Registry No.—Phenacyl chloride, 532-27-4; 3-bromo-2,4-diphenylfuran, 23346-66-9; II, 23346-65-8.

Acknowledgment—R. J. D. P. thanks Colgate Palmolive Co. and the Wright Fund for financial assistance.

Methylenation of Unsaturated Ketones. VIII.[1] Reaction of $\Delta^{1,4}$-, $\Delta^{1,4,6}$-, and $\Delta^{4,6}$-3-Keto Steroids with Phenyl(trichloromethyl)mercury[2]

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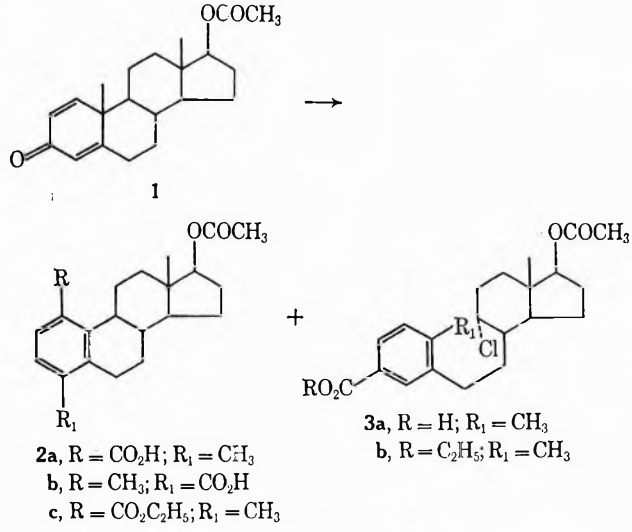
Received September 24, 1969

The $\Delta^{1,4}$- and $\Delta^{1,4,6}$-3-keto steroids **1** and **4** undergo dienol–benzene-type rearrangements on exposure to phenyl(trichloromethyl)mercury in benzene to yield ring-A aromatic carboxylic acids (**2a** and **3a** from **1**) and **5** from **4**. Although the $\Delta^{4,6}$-3 ketone **8a** is apparently resistant to attack by the mercurial reagent in boiling benzene, the corresponding 3β-acetoxy and 3-cycloethylenedioxy derivatives **8b** and **8c** are converted into the 6α,7α-dichloromethylene adducts **10a** and **10b** (plus **10d**), respectively, under the same conditions.

Phenyl(trichloromethyl)mercury is an exceptionally effective reagent for the dichloromethylenation of carbon–carbon double bonds. In an extensive series of investigations, Seyferth and coworkers showed that various olefins, as well as aliphatic α,β-unsaturated ketones, esters, and nitriles, react with the organomercurial in boiling benzene to afford the corresponding dichlorocyclopropanes in good yield.[3] This paper describes the results of an investigation aimed at evaluating phenyl(trichloromethyl)mercury as a reagent for preparing dichloromethylene steroids from linear and cross-conjugated dienone and trienone precursors.

Treatment of 17β-acetoxyandrosta-1,4-dien-3-one (**1**)[4] with 20 equiv of phenyl(trichloromethyl)mercury in boiling benzene followed by chromatography of the crude reaction mixture afforded the ring-A aromatic



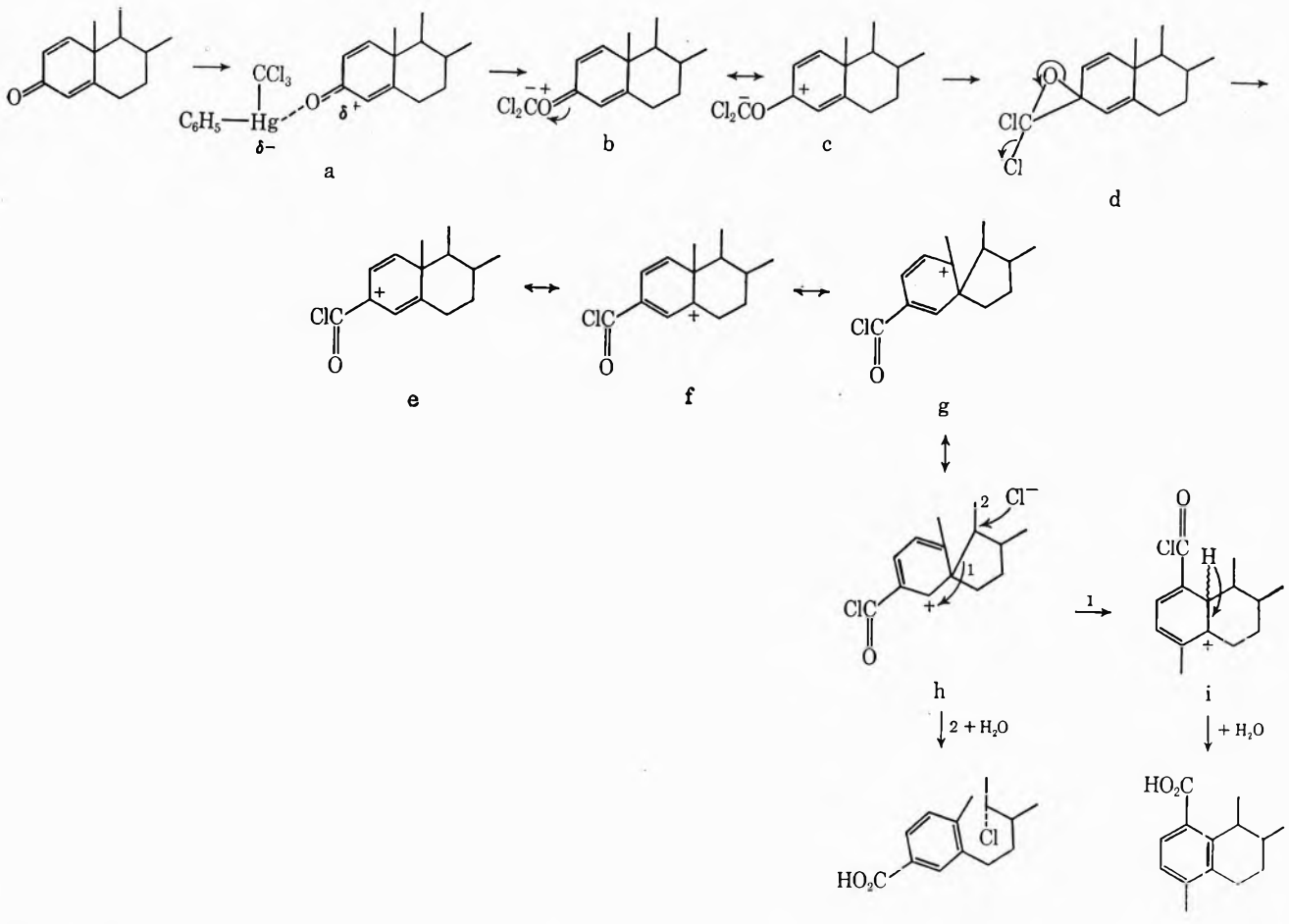
2a, R = CO_2H; $R_1 = CH_3$
b, R = CH_3; $R_1 = CO_2H$
c, R = $CO_2C_2H_5$; $R_1 = CH_3$

3a, R = H; $R_1 = CH_3$
b, R = C_2H_5; $R_1 = CH_3$

acids **2a** (12%) and **3a** (13%).[5] The structure of the seco acid **3** follows from its elemental analysis and

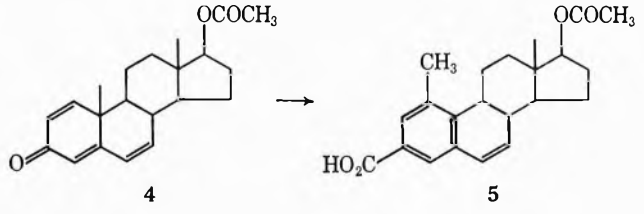
(1) Part VII: C. Beard, B. Berkoz, N. H. Dyson, I. T. Harrison, P. Hodge, L. H. Kirkham, G. S. Lewis, D. Giannini, B. Lewis, J. A. Edwards, and J. H. Fried, *Tetrahedron*, **25**, 1219 (1969).
(2) Publication 363 from the Syntex Institute of Organic Chemistry.
(3) D. Seyferth, J. M. Burlitch, R. J. Minasz, J. Y.-P. Mui, H. D. Simmons, Jr., A. J. H. Trieber, and S. R. Dowd, *J. Amer. Chem. Soc.*, **87**, 4259 (1965).
(4) R. B. Woodward, H. H. Inhoffen, H. O. Larson, and K. Menzel, *Chem. Ber.*, **86**, 594 (1953).
(5) Some difficulty was experienced with the removal of phenylmercuric chloride from the reaction mixture. In this experiment the isolated yield proved to be a poor measure of reaction efficiency, since substantial product losses were incurred during chromatographic purification.

SCHEME I



infrared, mass, and proton magnetic resonance spectroscopy. The latter determination shows an aromatic methyl proton resonance at 2.38 ppm in addition to three aromatic protons consisting of a singlet at 2.38 ppm (H-4) and an AB pattern centered at 7.56 ppm (J = 8.0 Hz, H-1 and H-2). The C-9 chloro substituent of **3a** is assigned the axial (α) stereochemistry, since the H-9 signal (broad singlet, $W_{1/2}$ = 0.07 ppm at 100 MHz) of the ethyl ester **3b** exhibits the splitting pattern typical of an equatorial proton coupled to several vicinal protons.[6] The tetracyclic carboxylic acid bears methyl and carboxyl substituents at the C-1 and C-4 positions of the A ring, as judged by the presence of signals for an aromatic methyl group (singlet at 2.22 ppm) and two aromatic (*ortho*) protons (AB pattern centered at 6.95 ppm, J = 8.0 Hz). The 1-carboxy-4-methyl structure **2a** is tentatively assigned to this product by analogy to the established course of the dienol–benzene rearrangement.[7a] However, the 1-methyl-4-carboxy substitution pattern **2b** cannot be ruled out on the basis of the available evidence.

17β-Acetoxyandrosta-1,4,6-trien-3-one (**4**)[8] was readily aromatized by heating with 1.1 equiv of the mercurial reagent in boiling benzene to give 1-methyl-3-carboxy-



estra-1,3,5(10),6-tetraene (**5**) in 56% yield. The pmr spectrum of this substance exhibits a singlet at 2.60 ppm (aromatic methyl), an AB pattern centered at 6.23 ppm ($J_{6,7}$ = 10.0 Hz, H-6 and H-7), and two doublets at 7.60 and 7.70 ppm ($J_{2,4}$ = 2.0 Hz, H-2 and H-4) in agreement with the 1,3-disubstituted estratetraene system present in **5**.

The ease with which phenyl(trichloromethyl)mercury induces the $\Delta^{1,4}$-3-ketone system to undergo a dienol–benzene-type rearrangement prompted a study of the reaction of **1** with sodium trichloroacetate, an alternate source of dichlorocarbene.[9] In this case treatment of **1** with 29 equiv of the sodium salt in boiling diglyme afforded a complex mixture of products from which a low yield (3.8%) of the seco acid **3a** was obtained after repeated chromatography. A similar result has been reported for the reaction of **1** with difluorocarbene (generated from sodium difluorochloroacetate in boiling diglyme), the only aromatic product of this reaction being 4-methylestra-1,3,5(10)-trien-17β-ol acetate (obtained in 2.5% yield).[1]

The foregoing results suggest that the aromatization reactions of **1** and **4** are assisted by participation of

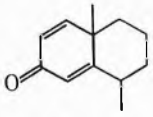
(6) For examples illustrating the use of band width at half-height in determining the axial or equatorial orientation of an alicyclic methine proton, see A. Hassner and C. Heathcock, *J. Org. Chem.*, **29**, 1350 (1964), and references cited therein.

(7) For comprehensive reviews, see (a) N. L. Wendler in "Molecular Rearrangements," Part 2, P. de Mayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, Chapter 16; (b) B. Miller in "Mechanism of Molecular Migrations," Vol. 1, B. S. Thyagarajan, Ed., Interscience Publishers, Inc., New York, N. Y., 1968, pp 275–285.

(8) G. Rosenkranz, C. Djerassi, S. Kaufmann, J. Pataki, and J. Romo, *Nature*, **165**, 814 (1950).

(9) W. M. Wagner, *Proc. Chem. Soc.*, 229 (1956).

mercury, with the rearrangement possibly being initiated by association of the carbonyl group with the mercurial reagent rather than a free carbene[10] (see a, Scheme I). Loss of phenylmercuric chloride leads, *via* the resonance-stabilized zwitterions b and c, to the intermediate oxide d. Lewis acid promoted opening of the oxide d followed by loss of chloride ion generates the chloroformyl mesomeric cation species e–i, which give rise to the aromatic acids **2a** and **3a** after hydrolysis of the intermediate acid chloride. Evidence for the existence of the acid chloride as the initial product follows from the isolation of the ethyl ester **2c** when the crude product obtained from reaction of **1** with the mercurial is allowed to stand in chloroform solution containing ethanol. Support for the intermediacy of the dichloro epoxide d is also provided by the recent observations of Seyferth and Tronich, which show that perchlorothiiranes are formed by reaction of thiophosgene and thiobenzophenone with phenyl(dichlorobromomethyl)mercury.[11] As in the case of dienol–benzene and dienone–phenol rearrangements,[7] the presence of a 6,7 double bond alters the course of the mercurial-promoted rearrangement of the $\Delta^{1,4,6}$-3 ketone **4**, the product **5** being formed by a methyl migration to the C-1 position. The isolation of the seco acid **3a** is of interest, since this is the first product of C_9–C_{10} bond cleavage to be identified from dienone–phenol- or dienol–benzene-type rearrangements in the steroid series.[7] However, Kropp has shown that the bicyclic dienone **6** rearranges in part to the monocyclic phenol **7** by acid catalysis.[12]



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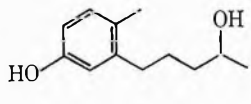
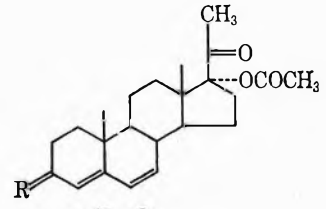
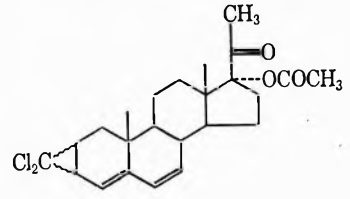


7

The reaction of the $\Delta^{4,6}$-pregnadienes **8a**,[13] **8b**,[14] and **8c**[15] with phenyl(trichloromethyl)mercury was next investigated, since these substances are not susceptible to the aromatization process. The $\Delta^{4,6}$-3 ketone **8a** appeared to be resistant to attack by the mercurial in boiling benzene. Under essentially the same conditions the allylic acetate **8b** yielded two products identified as 17α-acetoxy-2ξ,3ξ-dichloromethylenepregna-4,6-dien-20-one (**9**, 26%) and the noncrystalline 3β,17α-diacetoxy-6α,7α-dichloromethylenepregn-4-en-20-one (**10a**, 30%). The latter substance was characterized as 17α-acetoxy-6α,7α-dichloromethylenepregn-4-ene-3,20-dione (**10b**) by selective hydrolysis of the 3-acetate of **10a** followed by oxidation of the resulting allylic alcohol with manganese dioxide. The formation of 17α-acetoxypregna-2,4,6-trien-20-one (**11**),



8a, R = O
b, R = β-OCOCH$_3$; α-H
c, R = cycloethylenedioxy



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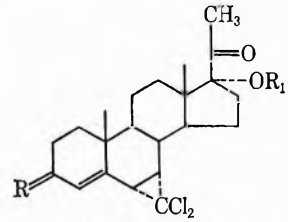
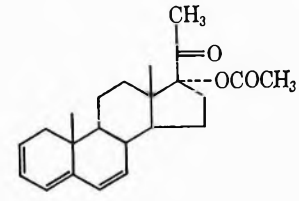


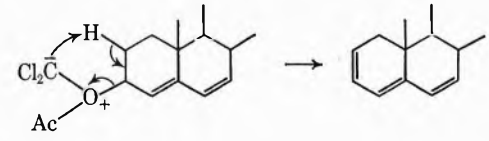


11

10a, R = β-OCOCH$_3$, α-H; R_1 = COCH$_3$
b, R = O; R_1 = COCH$_3$
c, R = O; R_1 = H
d, R = cycloethylenedioxy; R_1 = COCH$_3$

the precursor of the 2ξ,3ξ-dichloromethylene adduct **9**, is attributed to the action of the electrophilic mercurial reagent or dichlorocarbene on the allylic acetoxy group rather than phenylmercuric chloride, since **8b** was recovered unchanged after prolonged treatment with the latter substance in boiling benzene.

A possible mechanism to account for the formation of the intermediate **11** is as follows.



The assignment of the 6α,7α stereochemistry to the dichloromethylene group of adducts **10a–10d** is supported by the rotatory dispersion curve of **10b**, which is in good agreement with the curves reported for various 6α,7α-methylene- and 6α,7α-difluoromethylene-Δ^4-3 ketones.[1]

The ketal derivative **8c** is the most suitable starting material for the synthesis of the 6α,7α-dichloromethylene-Δ^4-3 ketone **10b**. Thus reaction of **8c** with an excess of the mercurial for 8 days in boiling benzene afforded directly the Δ^4-3-keto adduct **10b** in 40% yield *via* mercury salt catalyzed cleavage of the intermediate Δ^4-3-ketal adduct **10d**.[16] The latter substance was also obtained in 15% yield from this reaction.

(10) W. E. Parham and J. R. Potoski have suggested that the cleavage of certain allylamines by phenyl(trichloromethyl)mercury is initiated by attack of the mercurial reagent on the nitrogen atom instead of dichlorocarbene. See *J. Org. Chem.*, **32**, 278 (1967). See also D. Seyferth, M. E. Gordon, and R. Damrauer, *ibid.*, **32**, 496 (1967).

(11) D. Seyferth and W. Tronich, *J. Amer. Chem. Soc.*, **91**, 2138 (1969).

(12) P. J. Kropp, *ibid.*, **85**, 3280 (1963).

(13) R. Sciaky, *Gazz. Chim. Ital.*, **91**, 545 (1961).

(14) D. J. Marshall, P. F. Morand, C. Revesz, and R. Gaudry, *J. Med. Chem.*, **7**, 355 (1964).

(15) M. J. Weiss, J. F. Poletto, G. R. Allen, Jr., R. F. Schaub, and I. Ringler, *ibid.*, **7**, 804 (1964).

(16) The use of metal salts (*e.g.*, magnesium sulfate) for the cleavage of Δ^4-3 ketals to the corresponding Δ^4-3 ketones has been reported: J. J. Brown, R. H. Lenhard, and S. Bernstein, *Experientia*, **18**, 309 (1962).

Experimental Section[17]

Preparation of Phenyl(trichloromethyl)mercury.—The procedure of Seyferth and Burlitch[18] was modified as follows. A solution of phenylmercuric bromide (15.0 g) in dry tetrahydrofuran (300 ml) and chloroform (30.0 g) was cooled to −80° in acetone–Dry Ice and treated portionwise with stirring with 15.0 g of freshly prepared potassium *t*-butoxide (containing 1 molar equiv of *t*-butanol) during 20 min. The reaction mixture was stirred at −80° for 2 hr and then allowed to warm to room temperature. Water (500 ml) was added and the product was isolated by extraction with methylene dichloride. The crystalline residue (19.2 g), containing unreacted phenylmercuric bromide, was dissolved in benzene and percolated through a column of neutral alumina (200 g) to give 15.0 g of phenyl(trichloromethyl)mercury, mp 117–119° (lit.[18] mp 116.5–118°).

Reaction of 17β-Acetoxyandrosta-1,4-dien-3-one (1) with Phenyl(trichloromethyl)mercury.—A solution of **1** (2.0 g) and phenyl(trichloromethyl)mercury (2.8 g) in benzene was heated under reflux with stirring for 84 hr with further additions of 1.40 g and 0.70 g of mercurial reagent being made at 24- and 48-hr intervals. The precipitated phenylmercuric chloride was removed by filtration of the cooled reaction mixture and the resulting solution was evaporated to dryness. The residue was dissolved in ethyl acetate and chromatographed on 150 g of silica gel. Elution with ethyl acetate–acetic acid (200:1) provided a series of crystalline fractions from which the following compounds were obtained by preparative tlc[19] with benzene–acetic acid (49:1).

Compound **2a** (264 mg) gave the following data: mp 208–210° (from acetone–hexane); $[\alpha]_D$ +247°; λ_{max} 242 mμ (log ε 3.78); ν_{max} 3400, 1730, 1700, 1680, 1585, and 1245 cm^{-1}; nmr 0.83 (s, H-18), 1.98 (s, H-17β-acetoxy), 2.22 (s, CH_3-4), and 6.85 and 7.05 ppm (AB pattern, $J_{2,3}$ = 8.0 Hz, H-3 and H-2, respectively).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 73.76; H, 8.11.

Compound **3a** (310 mg) gave the following data: mp 133–136° (from hexane); $[\alpha]_D$ −9°; λ_{max} 238 mμ (log ε 4.14) and 270 (sh, 2.99); ν_{max} 3430, 1740, 1690, 1620, 1580, and 1250 cm^{-1}; nmr 0.83 (H-18), 2.03 (s, H-17β-acetoxy), 2.38 (s, aromatic CH_3), 4.3–4.9 (m, H-9β and H-17α), 7.25, 7.89 (AB pattern, $J_{2,3}$ = 8.0 Hz, H-3 and H-2, respectively), and 7.92 ppm (s, H-4); mass spectrum *m/e* 292 (M^+ for ^{35}Cl) and 294 (M^+ for ^{37}Cl).

Anal. Calcd for $C_{22}H_{29}O_4Cl$: C, 67.25; H, 7.44; Cl, 9.02. Found: C, 67.43; H, 7.41; Cl, 8.86.

The ethyl ester **3b** was prepared as follows. A solution of **3a** (130 mg) in dry benzene (5 ml) and thionyl chloride (1 ml) was heated under reflux for 2 hr and the solvents were evaporated to dryness. The residue was dissolved in 8 ml of benzene–pyridine (3:1) containing ethanol (2 ml) and after 2 hr the solvents were evaporated and the resulting oil was purified by preparative tlc with ethyl acetate–hexane (1:9). The pmr spectrum (100 MHz) of the resulting noncrystalline ethyl ester **3b** shows resonances at 0.84 (s, H-18), 1.38 (t, J = 7 Hz, CH_3CH_2O), 2.04 (s, H-17β-acetoxy), 2.37 (s, aromatic CH_3), 4.31 and 4.43 (AB pattern, J = 7.0 Hz, CH_3CH_2O), 4.57 (broad s, $W_{1/2}$ = 0.07 ppm, H-9β), 4.73 (ill-resolved m, H-17α), 7.19 and 7.78 (AB pattern, J = 8.0 Hz, H-1 and H-2, respectively), and 7.83 ppm (s, H-4). When the crude reaction mixture, obtained by treating **1** (2.0 g) with phenyl(trichloromethyl)mercury as described above, was allowed to stand for 7 days in chloroform (500 ml) containing ethanol, purification by preparative tlc yielded **2a** (84 mg), **3a** (350 mg), and the tetracyclic ethyl ester **2c** (190 mg): mp 116–118°; $[\alpha]_D$ +226°; λ_{max} 243 mμ (log ε 3.87) and 285 (3.13); ν_{max} 1740, 1715, 1590, 1280, and 1250 cm^{-1}; nmr 0.83 (s, H-18), 1.18 (t, J = 7 Hz, CH_3CH_2O), 2.02 (s, H-17β-acetoxy), 2.23 (s, CH_3-4), 4.22 and 4.42 (AB pattern, J = 7.0 Hz, CH_3CH_2O), 4.5–5.0 (m, H-17α), and 7.01 and 7.42 ppm (AB pattern, $J_{2,3}$ = 8.0 Hz, H-3 and H-2, respectively).

Anal. Calcd for $C_{24}H_{32}O_4$: C, 74.96; H, 8.39; O, 16.64. Found: C, 74.92; H, 8.34; O, 16.75.

Reaction of 17β-Acetoxyandrosta-1,4,6-trien-3-one (4) with Phenyl(trichloromethyl)mercury.—A solution of **4** (5.0 g) and phenyl(trichloromethyl)mercury (6.6 g) in benzene (700 ml) was heated under reflux for 26 hr. The precipitated phenylmercuric chloride was removed by filtration and the solvent was evaporated to yield an oil which was dissolved in ethyl acetate and adsorbed on a column of silica gel (400 g). Elution with ethyl acetate provided 2.6 g of a mixture of starting **4** and phenylmercuric chloride. Further purification by preparative tlc with ethyl acetate–benzene (1:49) yielded pure **4** (740 mg). Continued elution of the column with ethyl acetate–acetic acid (49:1) gave 17β-acetoxy-1-methylestra-1,3,5(10),6-tetraene-3-carboxylic acid (**5**, 2.4 g): mp 272–275° (from acetone); $[\alpha]_D$ −143°; λ_{max} 235 mμ (log ε 4.62), 260 (sh, 3.81) and 310 (3.12); ν_{max} 1740, 1685, and 1245 cm^{-1}; nmr (100 mHz) 0.85 (s, H-18), 2.05 (s, H-17β-acetoxy), 2.60 (s, CH_3-1), 5.90, 6.49 (pair of d with additional splitting, $J_{6,7}$ = 10.0 Hz, H-6 and H-7), and 7.60 and 7.70 ppm (pair of d, $J_{2,4}$ = 2.0 Hz, H-2 and H-4).

Anal. Calcd for $C_{22}H_{26}O_4$: C, 74.12; H, 7.35. Found: C, 73.81; H, 7.25.

Reaction of 17β-Acetoxyandrosta-1,4-dien-3-one (1) with Sodium Trichloroacetate.—A solution of **1** (660 mg) and sodium trichloroacetate (11.0 g) dissolved in 75 ml of dry diglyme was added dropwise during 1.5 hr to 50 ml of diglyme maintained at 130–140°. The reaction mixture was kept at 140° for 15 min after completion of the addition, then cooled, filtered, and evaporated to dryness under reduced pressure. The resulting brown oil was dissolved in methylene chloride and adsorbed on a column of 100 g of silica gel. Elution with methylene chloride–ethyl acetate (1:1) gave impure **1**. Continued elution with ethyl acetate–acetic acid (49:1) gave 150 mg of acidic mixture, which was purified by preparative tlc with ethyl acetate–acetic acid (49:1) to give the secoacid **3a** (30 mg), mp 130–131°, identical by mixture melting point and infrared spectral comparison with seco acid obtained by reaction of **1** with phenyl(trichloromethyl)-mercury.

Reaction of 3β,17α-Diacetoxypregna-4,6-dien-20-one (8b) with Phenyl(trichloromethyl)mercury.—A solution of **8b** (960 mg) and phenyl(trichloromethyl)mercury (1.14 g) in benzene (240 ml) was heated under reflux for 5 days. Removal of the solvent followed by purification of the resulting product by preparative tlc with ethyl acetate–hexane (3:7) afforded the following compounds.

The 2ξ,3-ξ-dichloromethylene adduct (**9**, 330 mg) gave the following data: mp 215° dec (from methanol); λ_{max} 251 mμ (log ε 4.32); ν_{max} 1720, 1710, and 1260 cm^{-1}; nmr 0.68 (s, H-18), 0.97 (s, H-19), 2.02 (s, H-17α-acetoxy), 2.06 (s, H-21), 5.45 (broad s, H-4), and 5.63 and 5.96 ppm (AB pattern, J = 11.0 Hz, H-6 and H-7).

Anal. Calcd for $C_{24}H_{30}O_3Cl_2$: C, 65.90; H, 6.91; Cl, 16.21. Found: C, 65.96; H, 7.28; Cl, 16.39.

The 6α,7α-dichloromethylene adduct **10a** (358 mg) was obtained as an oil.

17α-Acetoxy-6α,7α-dichloromethylenepregn-4-ene-3,20-dione (10b).—Adduct **10a** (358 mg) was dissolved in methanol–water (5:1, 30 ml) containing sodium hydroxide (0.2 g) and the resulting solution was kept at room temperature for 4 hr. Acetic acid (0.2 ml) and water (200 ml) were added and the product was isolated by extraction with diethyl ether. The resulting oil (300 mg) was oxidized by stirring with manganese dioxide (3.6 g) in chloroform (20 ml) for 2 hr to yield a mixture of two products separable by preparative tlc with ethyl acetate–hexane (3:7) into the following compounds.

The 17-acetate **10b** (100 mg) gave the following data: mp 188° (from acetone–hexane); $[\alpha]_D$ +81°; RD $[\Phi]_{600}$ +270°, $[\Phi]_{386}$ +3380°, $[\Phi]_{376}$ +3110°, $[\Phi]_{369}$ +3560°, $[\Phi]_{359}$ +3160°, $[\Phi]_{353}$ +2525°, $[\Phi]_{345}$ +1625°, $[\Phi]_{336}$ +2615°, $[\Phi]_{307}$ +8340°, $[\Phi]_{298}$ +6630°, $[\Phi]_{289}$ +3970°, $[\Phi]_{283}$ +3605°, $[\Phi]_{267}$ +14,960°, $[\Phi]_{262}$ +15,190°, $[\Phi]_{252}$ 0°, $[\Phi]_{284}$ −12,795°, $[\Phi]_{279}$ −7075°, and

(17) Melting points are corrected and were taken on a Fisher-Johns apparatus or a Thomas–Hoover capillary apparatus. Optical rotations were measured in chloroform solution at 27° and infrared spectra were determined in KBr discs unless otherwise specified. Ultraviolet spectra were measured on a Cary Model 14 spectrometer. We wish to thank Dr. L. Throop and his staff for these measurements. Pmr spectra were recorded for 5–10% solutions (w/v) in deuteriochloroform containing tetramethylsilane as internal reference on Varian A-60 and HA-100 spectrometers. Chemical shifts are reported as parts per million on the δ scale to the nearest 0.01 ppm. Coupling constants are reported in cycles per second to the nearest 0.5 Hz. We thank Mr. J. W. Murphy and Miss J. Tremble for assistance with these measurements. Mass spectra were obtained with an Atlas werke CH-4 spectrometer equipped with a direct inlet system. Spectra were measured at an ionizing potential of 70 eV and an acceleration voltage of 3 kV. We wish to thank Dr. L. Tökes and Mr. J. Smith for assistance with these measurements. Microanalyses were performed by Dr. A. Bernhardt, Mülheim (Ruhr), West Germany.

(18) D. Seyferth and J. M. Burlitch, *J. Organometal. Chem.*, **4**, 127 (1965).

(19) Preparative tlc was conducted using silica gels GF and HF (from Brinkmann Instruments, Inc., N. Y.) at thicknesses of 1.3 mm and steroid loadings of 2 mg/cm.

$[\Phi]_{208}$ 0°; λ_{max} 252 mμ (log ε 4.16); ν_{max} 1740, 1720, 1680, and 1250 cm^{-1}; nmr 0.70 (s, H-18), 1.11 (s, H-19), 2.03 (s, H-17α-acetoxy), 2.11 (s, H-21), and 6.14 ppm (s, H-4).

Anal. Calcd for $C_{24}H_{30}O_4Cl_2$: C, 63.57; H, 6.67; Cl, 15.64. Found: C, 63.50; H, 6.72; Cl, 15.70.

The 17 alcohol **10c** (50 mg) gave the following data: mp 259–260° (from acetone); $[\alpha]_D$ +107°; λ_{max} 251 mμ (log ε 4.09); ν_{max} 3460, 1710, 1670, and 1660 cm^{-1}; nmr 0.56 (s, H-18), 1.07 (s, H-19), 2.09 (s, H-21), and 6.00 ppm (s, H-4).

Anal. Calcd for $C_{22}H_{28}O_3Cl_2$: C, 64.23; H, 6.86. Found: C, 64.37; H, 6.91.

Reaction of 17α-Acetoxy-3,3-cycloethylenedioxypregna-4,6-dien-20-one (8c) with Phenyl(trichloromethyl)mercury.—A solution of **8c** (830 mg) and phenyl(trichloromethyl)mercury (950 mg) in benzene (210 ml) was heated under reflux for 120 hr. Since tlc analysis showed the presence of starting **8c**, an additional 950 mg of the mercurial reagent was added and the solution was boiled again for 72 hr. Purification of the crude product by preparative tlc afforded **10b** (360 mg), mp 188°, identical in all respects with a sample of **10b** obtained from the preceding experiment, and the ketal adduct **10d** (235 mg): mp 166–167° (from acetone–hexane); $[\alpha]_D$ +58°; ν_{max} 1740, 1720, and 1250 cm^{-1}; nmr 0.67 (s, H-18), 0.95 (s, H-19), 2.01 (s, H-17α-acetoxy), 2.06 (s, H-21), 4.01 (s, cycloethylenedioxy H), and 5.71 ppm (s, H-4).

Anal. Calcd for $C_{26}H_{34}O_5Cl_2$: C, 62.77; H, 6.89; Cl, 14.25. Found: C, 62.54; H, 7.16; Cl, 14.08.

Treatment of ketal **10d** with methanol containing concentrated hydrochloric acid for 15 min at room temperature furnished the Δ^4-3 ketone **10b**.

Registry No.—Phenyl(trichloromethyl)mercury, 3294-57-3; **2a**, 23367-44-4; **2c**, 23330-50-9; **3a**, 23367-45-5; **3b**, 23330-51-0; **5**, 23330-52-1; **9**, 23330-53-2; **10b**, 23157-28-0; **10c**, 23330-55-4; **10d**, 23330-56-5.

Acknowledgment.—The authors wish to thank Dr. J. H. Fried for helpful discussions.

Steroidal β-Lactams

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Received September 16, 1969

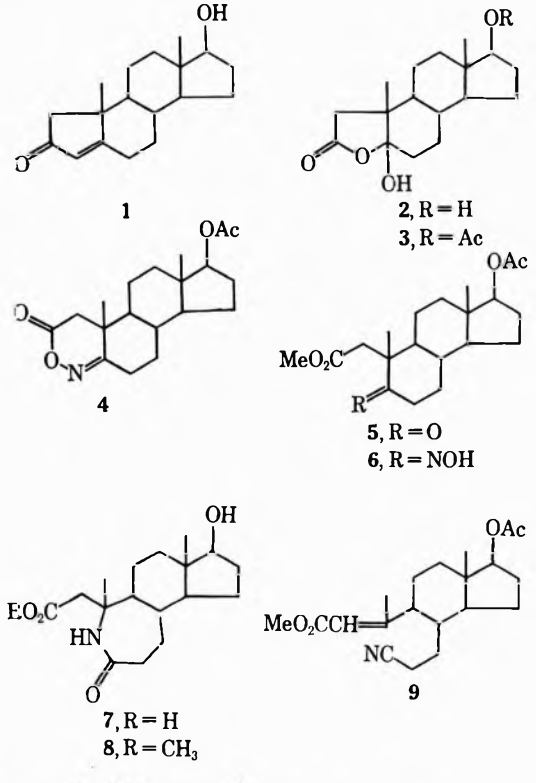
The multistep conversion of A-nortestosterone into a new B-homo steroidal ring system possessing a fused β-lactam as ring A is described. The deshielding effect of the nitrogen atom on the C-19 methyl signal in the nmr spectra of the 5-aza steroidal compounds prepared in this study is discussed briefly.

In this paper, the conversion of A-nortestosterone (**1**)[1] into a new steroidal ring system possessing a fused β-lactam as ring A[2] will be described.[3] The synthesis of this novel structure was of interest to us from both a chemical and biological point of view.

The synthetic scheme for the preparation of the steroidal β-lactam can be divided into three parts. The first stage involves the removal of a carbon atom from ring A of **1** to give a seco compound bearing a two-carbon side chain attached to C-10, the terminal carbon atom of the side chain being oxygenated. The next problem concerns the positioning of a nitrogen atom into ring B in a β relationship to the oxygen-bearing carbon atom of the side chain. Lastly, the modified steroid skeleton must be transformed into a β-amino acid that can then be cyclized to the β-lactam.

The removal of carbon atom 3 from **1** could be achieved by hydroxylation of the conjugated double bond with osmium tetroxide, followed by oxidative cleavage with periodic acid to afford the lactonol **2**.[4] Our synthesis required large amounts of **2**, and it was more conveniently prepared in one step by use of the periodate–permanganate combination.[5] Reaction of **2** with acetic anhydride in pyridine at room temperature resulted in selective acetylation at C-17 to give **3**. Acetylation of the hydroxyl at C-5 is possible, if this reaction is conducted at reflux temperature.

In our initial attempt to introduce the nitrogen atom into ring B in the form of an oxime, we treated **3** with hydroxylamine hydrochloride in pyridine at reflux temperature. The product did not exhibit any hydroxyl or carboxyl bands in the ir spectrum, but showed two carbonyl bands at 5.68 and 5.80 μ. This compound was assigned the cyclic structure **4**, which was confirmed by elemental analysis and the presence of an AB quartet at τ 7.26 and 7.76 (J = 16 cps) in the nmr spectrum for the C-1 methylene hydrogens. In order to circumvent the undesired cyclization of the oximino



(1) F. L. Weisenborn and H. E. Applegate, *J. Amer. Chem. Soc.*, **81**, 1960 (1959).

(2) A ring-A γ-lactam was an intermediate in the synthesis of A-nor-B-homo-5-aza cholestane: W. J. Rodewald and J. Wicha, *Rocz. Chem.*, **40**, 837 (1966).

(3) Presented in part at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., March 1968. A preliminary communication has appeared: S. D. Levine, *Chem. Commun.*, 580 (1968).

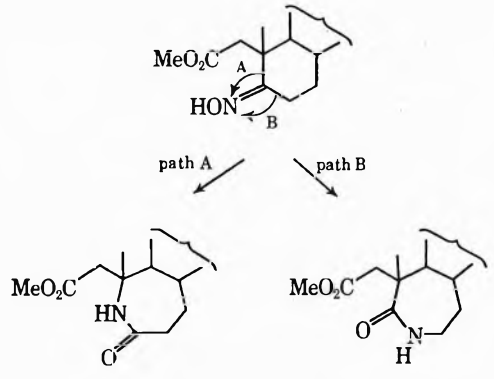
(4) S. D. Levine, *J. Med. Chem.*, **8**, 537 (1965).

(5) M. E. Wall and S. Serota, *J. Org. Chem.*, **24**, 741 (1959).

acid, we treated **3** with diazomethane to open the lactonol and form the keto ester **5**. This oily product was then treated with hydroxylamine hydrochloride in pyridine at room temperature to yield an oxime (**6**) in quantitative yield. Evidence that **6** was actually a single compound, and not a mixture of oxime isomers, was based on the following observations: (a) the nmr spectrum exhibited only one signal for the C-19 methyl group; and (b) tlc revealed only one spot. The orientation of the oxime will be discussed in more detail later.

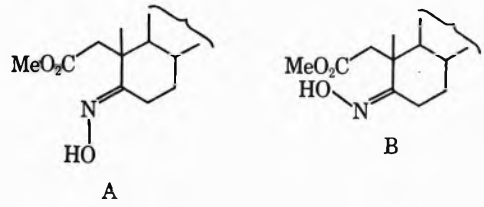
The Beckmann rearrangement of **6** was then investigated under various conditions to find the most efficient route to a ring-B lactam. Among the experimental conditions examined were the use of thionyl chloride as both the solvent and acid catalyst at temperatures of 0 to −20°, and thionyl chloride in dioxane at 10° for varying time intervals. The condition of choice was the addition of thionyl chloride to the oxime in dioxane at 10° and a reaction time of 7–10 min. After hydrolysis with aqueous potassium hydroxide solution, the lactam acid **7** was obtained in 70–80% yield. This compound was characterized by elemental analysis and its ir spectrum, which showed broad bands in the hydroxyl region, a band at 5.86 μ (–CO_2H), and a band at 6.09 μ (–NHCO). The insolubility of **7** in $CDCl_3$ precluded an nmr spectrum in that solvent. Methylation of **7** with diazomethane gave the oily ester **8**, the purity and structure of which were confirmed by tlc and nmr. The C-19 methyl signal appeared at τ 8.58, and this pronounced downfield shift will be discussed further in a separate section.

That the Beckmann rearrangement product resulted from migration of the more substituted α-carbon atom (path A), rather than one in which the less substituted α-carbon atom migrated (path B), was in accord with the results of Rodewald and Wicha for the rearrangement of a related system.[2] Additional evidence for the operation of this pathway was the ultimate formation of the β-lactam.



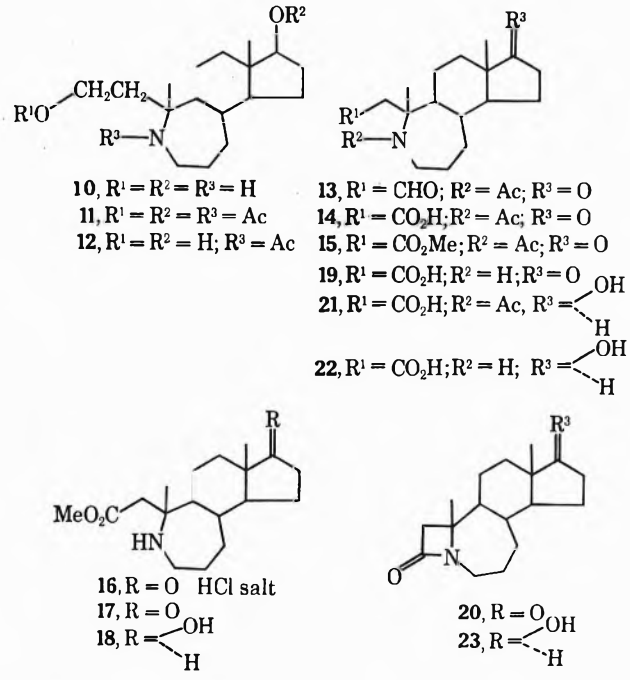
We were unable to isolate any cyclic lactam from the reaction mixture, which would have formed *via* path B; however, a small amount of an oily product was isolated after chromatography of the neutral fraction on alumina. The ir spectrum did not show any hydroxyl bands, but exhibited a peak at 4.45 μ (–CN), a broad carbonyl band at 5.80 μ (–OAc, –CO_2Me), and a band at 6.10 μ (conjugated double bond). The only structure compatible with these results was **9**, which would be formed as a result of an abnormal Beckmann rearrangement. In accord with this structure, the nmr spectrum exhibited the C-18 methyl at τ 9.13, but did not exhibit a signal for the C-19 methyl group. Instead, there were signals at τ 7.84 and 8.12 that could be assigned to vinyl methyl groups, two signals at *ca.* τ 6.3 for methoxyl groups, and a broad signal at τ 4.27 for vinyl protons. Thus it would appear that **9** was a mixture of *cis* and *trans* isomers.

Based on the results from the Beckmann rearrangement, it is tempting to assign oxime **6** the *syn*[6] stereochemistry, as shown in A, rather than the *anti* form depicted in B.



Mazur, in his work on the Beckmann rearrangement of oximes of testosterone derivatives,[7] showed, however, that under these reaction conditions (thionyl chloride in dioxane) the products obtained were not necessarily related to the stereochemistry of the initial oxime. Hence we refrain from making a definite assignment based on the evidence available in our case.

The next step required reduction of the lactam carbonyl. Attempted lithium aluminum hydride reduction of the free acid **7** in tetrahydrofuran led to a poor yield of the dihydroxy amine **10**. Further investigation revealed that this was due to the poor



solubility of **7** in tetrahydrofuran. This was obviated by conducting the reduction on the methyl ester **8** instead, and in this case the reduction product **10** could be obtained in 60–70% yield. Since the presence of nitrogen in a molecule as an amine usually leads to difficulties when attempting oxidations with chromium trioxide,[8] the amine nitrogen was protected as an

(6) In this case, *syn* and *anti* refers to the relationship of the oxime hydroxyl to the C_6–C_7 bond.

(7) R. H. Mazur, *J. Org. Chem.*, **28**, 248 (1963).

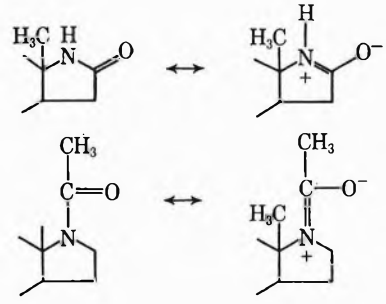
(8) M. Heller and S. Bernstein, *ibid.*, **32**, 3978 (1967).

amide.[9] This was accomplished by first preparing the N-acetyl diacetate **11** under normal acetylation conditions. Selective room-temperature hydrolysis of **11** with potassium carbonate in methanol gave the N-acetyldiol **12**. We next turned our attention to the oxidation of the C-2 hydroxyl group to a carboxylic acid. Oxidation of **12** with Jones reagent led to smooth oxidation of the hydroxyls at both C-2 and C-17; however, the oxidation of the primary alcohol proceeded only to the aldehyde stage. This was quite apparent from the nmr spectrum of the product **13**, which displayed a signal for the aldehyde proton at τ 0.28 (J = 1.8 cps). Treatment of **13** with silver oxide in the dark at room temperature for 4 hr gave the N-acetyl amino acid **14** in 50% yield, and additional oxidation product could be obtained in the form of its methyl ester **15** after treatment of the mother liquor with diazomethane and subsequent chromatography on alumina.

The penultimate synthetic step required hydrolysis of the N-acetyl group of **14** to afford an amino acid. The pilot experiments were conducted on the ester **15** and indicated that acid hydrolysis at room temperature (HCl–methanol or HCl–ethanol) did not cleave the amide bond. After **15** was refluxed overnight in 10% methanolic HCl, evaporation of the solvents gave a chloroform-soluble amine hydrochloride **16** as an oil which was conveniently purified and converted into the free amine **17** as an oil by chromatography on alumina. In an attempt to obtain a crystalline derivative, **17** was reduced with sodium borohydride to the 17β-hydroxy compound **18**, but this too was obtained as an oil. Hydrolysis of the methyl ester of **17** with sodium hydroxide in ethanol and removal of the solvent gave an amino acid containing residue. Electrophoresis indicated that the amino acid **19** was essentially neutral at pH 4.5–6.0.[10] Attempts to extract **19** into organic solvents from aqueous solutions at pH levels within this range were unsuccessful; this behavior could be explained by assuming that the amino acid was very soluble in water. In the next experiment, the free acid **14** was refluxed in acidic dioxane. After removal of the solvents, the aqueous phase was adjusted to pH 5.1 and extracted with chloroform to remove organic material other than the amino acid. The aqueous phase was then brought to pH 5.5 and evaporated, and the white residue was extracted with chloroform to afford, after removal of the solvent, the oily amino acid **19**, identified by ir and nmr. The cyclization of **19** was conducted at room temperature in nitromethane employing dicyclohexylcarbodiimide (DCC). At the end of the reaction, the bulk of the dicyclohexylurea was removed by filtration. Alumina chromatography easily removed excess DCC, but the remaining dicyclohexylurea had an R_f value similar to that of the β-lactam **20**, and it was necessary to repeat the chromatography to achieve good separation. The β-lactam structure was supported by microanalysis, its molecular ion (m/e 275), and the following spectral data. The carbonyl region in the infrared spectrum exhibited a peak at 5.74 μ (17-one) with a shoulder at 5.70 μ (β-lactam carbonyl), while the nmr spectrum showed the following diagnostic signals: τ 9.09 (C-18 Me), 8.56 (C-19 Me), 7.35 (C-1 CH_2), and 6.66 (C-6 CH_2).

A β-lactam bearing a hydroxyl group at C-17 was prepared in the following manner. Sodium borohydride reduction of **14** gave the 17β-hydroxy compound **21**, which was hydrolyzed and the resultant amino acid isolated in the same manner as described previously for **19**. In this case, the amino acid **22** was obtained as a high-melting, crystalline material, which was quite insoluble in nitromethane and other organic solvents; therefore, the cyclization of **22** was carried out in aqueous dioxane using diisopropylcarbodiimide,[11] and the β-lactam **23** was isolated in low yield after chromatography on alumina.

Nmr Spectra.—The nmr spectra of some 17-aza steroids have been discussed recently.[12] The observed deshielding effect of the nitrogen atom on the C-18 methyl protons was close to that predicted when the substituent on nitrogen was either hydrogen or alkyl. When a carbonyl group was present adjacent to the C-17 nitrogen atom, however, the observed deshielding became greater than that predicted. The authors explained these results on the basis of the contribution of charged species as shown below. The charged nitrogen atom would be expected to deshield the adjacent angular methyl group. The 5-aza steroids prepared in this investigation showed a similar pattern. For compounds in which a carbonyl group was adjacent to the C-5 nitrogen atom, the observed chemical shift of the C-19 methyl group was in the τ 8.4–8.6 range, while for those in which the nitrogen atom was not flanked by a carbonyl the signal appeared at τ >8.8. It would appear that charged species analogous to those shown above satisfactorily explain the results obtained in our study.



Experimental Section

Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Values of $[\alpha]D$ have been approximated to the nearest degree and were taken on a Perkin-Elmer Model 141 polarimeter in 95% ethanol. Infrared spectra were determined on a Perkin-Elmer Model 21 spectrometer in pressed potassium bromide pellets (unless otherwise indicated), and nmr spectra were determined on a Varian A-60 spectrometer in $CDCl_3$ (unless otherwise indicated) with $(CH_3)_4Si$ as internal standard. All evaporations were carried out *in vacuo*, and organic solutions were dried over sodium sulfate. Alumina refers to neutral alumina, activity V. Tlc was carried out on alumina and the compounds were detected with iodine vapor.

3-Oxa-5β,17β-dihydroxy-A-norandrostan-2-one (2)[4].—A suspension of potassium carbonate (10 g), potassium permanganate (1.3

(9) In a subsequent experiment, oxidation of **12** with Jones reagent gave a crude reaction product which showed the presence of at least five components (tlc). This justifies the necessity of protecting the amino group prior to oxidation.

(10) The author wishes to thank Mr. O. Kocy for this determination.

(11) J. C. Sheehan and K. R. Henery-Logan, *J. Amer. Chem. Soc.*, **84**, 2983 (1962).

(12) S. Rakhit, T. Wittstruck, and M. Gut, *Steroids*, 135 (1967).

g), and sodium periodate (41 g) in water (1 l.) was added to a solution of A-nortestosterone (6.6 g)[1] in *t*-butyl alcohol (1 l.) and stirred at room temperature for 1 day. The mixture was filtered, and the filtrate was diluted with water and acidified to pH 2 with concentrated HCl. The acidic solution was extracted with chloroform. The chloroform extracts were washed with water and 8% salt solution, dried, and evaporated. Crystallization of the residue from ethyl acetate–isopropyl ether gave **2** (4.5 g), mp 177–178°).

3-Oxa-5β-hydroxy-17β-acetoxy-A-norandrostan-2-one (3).—A solution of **2** (100 mg) in pyridine (1.6 ml) and acetic anhydride (0.8 ml) was left at room temperature for 4 hr. The reaction mixture was diluted with water and the product was collected by filtration to give **3** (73 mg), mp 183–185°. Recrystallization from chloroform–isopropyl ether gave the analytical sample: mp 187.5–188.5°; $[\alpha]^{25}D$ +24°; λ 3.07, 5.69, and 5.79 μ; nmr τ 9.18 (s, 18-Me), 8.87 (s, 19-Me), 7.97 (s, 17β-acetate), and 5.48 (m, 17α-H).

Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.65; H, 8.41.

3-Oxa-4-aza-17β-acetoxy-4-androsten-2-one (4).—A solution of **3** (500 mg) and hydroxylamine hydrochloride (500 mg) in pyridine (15 ml) was refluxed for 2.5 hr. Dilution with water gave a precipitate which was collected by filtration to yield **4** (248 mg), mp 186–188°. Recrystallization from chloroform–isopropyl ether gave the analytical sample: mp 203–205°; $[\alpha]^{27}D$ +51°; λ 5.68 and 5.80 μ; nmr τ 9.16 (s, 18-Me), 8.85 (s, 19-Me), 7.94 (s, 17β-OAc), 7.76 and 7.26 (q, J = 16 cps, 2-CH_2), and 5.41 (m, 17α-H).

Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16. Found: C, 68.37; H, 8.25.

5-Oxo-17β-acetoxy-2,5-seco-3,4-bisnorandrostan-2-oic Acid 2-Methyl Ester (5).—A solution of **3** (1.0 g) in methanol (10 ml) and ether (25 ml) was treated with an excess of diazomethane in ether. After 45 min at room temperature, acetic acid was added and the solvents were evaporated. The residue was dissolved in chloroform and this solution was washed with 8% salt solution, dried, and evaporated to afford **5** (1.0 g) as a homogeneous oil (tlc): λ^{CHCl_3} 5.80 μ; nmr τ 9.15 (s, 18-Me), 8.8 4(s, 19-Me), 7.97 (s, 17β-acetate), 6.38 (s, 2-OCH_3), and 5.39 (m, 17α-H).

5-Oximino-17β-acetoxy-2,5-seco-3,4-bisnorandrostan-2-oic Acid 2-Methyl Ester (6).—A solution of **5** (1.0 g) and hydroxylamine hydrochloride (1 g) in pyridine (20 ml) was left at room temperature for 3 days. The reaction mixture was diluted with ice–water and the product was collected by filtration to give **6** (860 mg), mp 150–152.5°. Recrystallization from chloroform–isopropyl ether gave the analytical sample: mp 155–157°; λ^{CHCl_3} 2.95 and 5.80 μ; nmr τ 9.18 (s, 18-Me), 8.81 (s, 19-Me), 7.97 (s, 17β-acetate), 6.38 (s, 2-OCH_3), and 5.39 (m, 17α-H).

Anal. Calcd for $C_{20}H_{31}NO_5$: C, 65.73; H, 8.55. Found: C, 65.93; H, 8.59.

6-Oxo-17β-hydroxy-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-oic Acid (7).—A solution of **6** (9.2 g) in dioxane (130 ml) was cooled to 10° in an ice bath. Thionyl chloride (9.2 ml) was added, the ice bath was removed, and the reaction mixture was stirred for 7 min. The reaction mixture was then added to 25% aqueous potassium hydroxide solution (725 ml), stirred and heated to 80°. After cooling, the reaction mixture was extracted with ether. The aqueous layer was acidified with concentrated HCl and diluted with ice–water. The precipitate was collected by filtration to give **7** (1.28 g), mp 268.5–269.5°. The filtrate was extracted with chloroform. The chloroform extracts were washed with 8% salt solution, dried, and evaporated. The residue was crystallized from methanol–isopropyl ether to give additional **7** (5.12 g), mp 271–272.5°. Recrystallization from methanol–isopropyl ether gave the analytical sample: mp 275–276°; $[\alpha]^{28}D$ +30°; λ 3.00, 3.08, 5.86, and 6.09 μ.

Anal. Calcd for $C_{17}H_{27}NO_4$: C, 65.99; H, 8.80; N, 4.53. Found: C, 66.10; H, 8.82; N, 4.63.

The ether extract from the Beckmann rearrangement of **6** (800 mg) was washed with water, dried, and evaporated to give a 113-mg residue. Plate chromatography on alumina using chloroform–hexane (3:1) as the developing solvent and elution of the least polar band with ethyl acetate gave, after evaporation, **9**: λ^{CHCl_3} 4.45, 5.80, and 6.10 μ; τ nmr 9.13 (s, 18-Me), 8.12, 7.84 (s, 10-Me), 7.97 (s, 17β-acetate), 6.33, 6.31 (s, 2-OCH_3), 5.39 (m, 17α-H), and 4.27 (s, 1-H).

6-Oxo-17β-hydroxy-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-oic Acid 2-Methyl Ester (8).—A solution of **7** (3.1 g) in methanol (100 ml) and ether (360 ml) was treated with an excess of diazomethane in ether. After 45 min at room temperature, acetic acid was added and the reaction mixture was evaporated. The residue was dissolved in chloroform, washed with water, dried, and evaporated to afford **8** as a homogeneous oil (tlc): λ^{CHCl_3} 2.75, 2.95, 5.78, and 6.08 μ; nmr τ 9.23 (s, 18-Me), 8.58 (s, 19-Me), 6.4 (m, 17α-H), and 6.38 (s, 2-OCH_3).

2,17β-Dihydroxy-2,5-seco-3,4-bisnor-5-aza-B-homoandrostane (10).—A solution of **8** (1.29 g) in tetrahydrofuran (150 ml) was treated with lithium aluminum hydride (2 g) and refluxed for 60 hr. Excess hydride was destroyed with ethyl acetate. The reaction mixture was treated with 25% aqueous sodium hydroxide solution and the layers were separated. The aqueous phase was extracted with additional chloroform. The combined organic fractions were washed with 8% salt solution, dried, and evaporated. The residue was crystallized from chloroform–isopropyl ether to give **10** (617 mg), mp 168–169.5°. Recrystallization from chloroform–isopropyl ether gave the analytical sample: mp 170.5–171°; $[\alpha]^{25}D$ −16°; λ 3.02 μ; nmr τ 9.25 (s, 18-Me) and 8.82 (s, 19-Me).

Anal. Calcd for $C_{17}H_{31}NO_2$: C, 72.55; H, 11.10; N, 4.98. Found: C, 72.65; H, 11.08; N, 4.98.

N-Acetyl-2,17β-diacetoxy-2,5-seco-3,4-bisnor-5-aza-B-homoandrostane (11).—A solution of **10** (2.56 g) in acetic anhydride (17 ml) and pyridine (17 ml) was left at room temperature overnight. The reaction mixture was diluted with water and the product was collected by filtration to give **11** (3.40 g), mp 136–137°. Recrystallization from isopropyl ether gave the analytical sample: mp 139–140°; $[\alpha]^{26}D$ −41°; λ 5.78 and 6.11 μ; nmr τ 9.20 (s, 18-Me), 8.63 (s, 19-Me), 7.97 (s, 17β-acetate and 2-acetate), 7.93 (s, 5-N-acetyl), and 5.42 (m, 17α-H).

Anal. Calcd for $C_{23}H_{37}NO_5$: C, 67.78; H, 9.15; N, 3.44. Found: C, 67.70; H, 9.16; N, 3.35.

N-Acetyl-2,17β-dihydroxy-2,5-seco-3,4-bisnor-5-aza-B-homoandrostane (12).—A solution of **11** (4.55 g) in methanol (550 ml) was treated with 10% potassium carbonate solution (90 ml) and stirred overnight at room temperature. The solution was concentrated, diluted with water, and neutralized with acetic acid. The product was collected by filtration to give **12** (0.93 g), mp 166.5–167.5°. The aqueous phase was extracted with chloroform and the chloroform extracts were washed with 8% salt solution, dried, and evaporated. The residue was crystallized from acetone–isopropyl ether to give additional **12** (1.97 g), mp 169–170°. Recrystallization from acetone–isopropyl ether gave the analytical sample: mp 172–172.5°; $[\alpha]^{23}D$ −47°; λ 2.93, 3.12, and 6.23 μ; nmr τ 9.25 (s, 18-Me), 8.60 (s, 19-Me), 7.93 (s, 5-N-acetyl) and 6.5 (m, 2-CH_2, 6-CH_2, and 17α-H).

Anal. Calcd for $C_{19}H_{33}NO_3$: C, 70.55; H, 10.28; N, 4.33. Found: C, 70.31; H, 10.29; N, 4.43.

N-Acetyl-17-oxo-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-al (13).—A solution of **12** (1.0 g) in acetone (100 ml) was cooled to 3.5° and treated with an excess of Jones reagent. After 2 hr at 3.5°, methanol was added to decompose excess oxidant and water was added. The organic solvents were evaporated and the aqueous phase was extracted with chloroform. The chloroform extracts were washed with water and 8% salt solution, dried, and evaporated. The residue was crystallized from ethyl acetate–isopropyl ether to give **13** (590 mg), mp 171.5–172.5°. Recrystallization from ethyl acetate–isopropyl ether gave the analytical sample: mp 172–173°; $[\alpha]^{24}D$ +60°; λ 3.55, 3.68, 5.75, 5.84, and 6.07 μ; nmr τ 9.12 (s, 18-Me), 8.54 (s, 19-Me), 7.92 (s, 5-N-acetyl), and 0.28 (t, J = 1.3 cps, 2-CHO).

Anal. Calcd for $C_{19}H_{29}NO_3$: C, 71.44; H, 9.15; N, 4.39. Found: C, 71.22; H, 8.96; N, 4.67.

N-Acetyl-17-oxo-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-oic Acid (14).—A solution of silver nitrate (725 mg) in water (7.5 ml) was added to a solution of **12** (695 mg) in 95% ethanol (15 ml). This solution was treated dropwise with a solution of sodium hydroxide (700 mg) in water (12.5 ml) and the resulting suspension was stirred in the dark for 4 hr. The precipitate was removed by filtration and washed with water, and the filtrate was extracted with chloroform. The aqueous phase was acidified and extracted with chloroform. The chloroform extracts were washed with 8% salt solution, dried, and evaporated. The residue was crystallized from acetone–isopropyl ether to give **14** (348 mg), mp 178.5–179.5. Recrystallization from acetone–isopropyl ether gave the analytical sample: mp 180.5–181.5°; $[\alpha]^{23}D$ −2°; λ 2.8–3.2, 5.78, and 6.28 μ; nmr τ 9.12 (s, 18-Me), 8.44 (s, 19-Me), and 7.91 (s, 5-N-acetyl).

Anal. Calcd for $C_{19}H_{29}NO_4$: C, 68.05; H, 8.71; N, 4.18. Found: C, 68.29; H, 8.42; N, 4.28.

N-Acetyl-17-oxo-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-oic Acid 2-Methyl Ester (15).—The mother liquor from the crystallization of **14** in the previous example was dissolved in ether (5 ml) and methanol (2 ml) and treated with an excess of diazomethane for 10 min. Acetic acid was added, and the solution was evaporated. Plate chromatography of the residue on alumina using chloroform as the developing solvent gave a major band which was eluted with ethyl acetate. Evaporation and crystallization from isopropyl ether gave **15** (81 mg), mp 131–132°. Recrystallization from isopropyl ether gave the analytical sample: mp 131.5–132.5°; λ 5.79 and 6.15 μ; nmr τ 9.12 (s, 18-Me), 8.46 (s, 19-Me), 7.94 (s, 5-N-acetyl), and 6.41(s, 2-OCH_3).

Anal. Calcd for $C_{20}H_{31}NO_4$: C, 68.74; H, 8.94; N, 4.01. Found: C, 68.69; H, 8.78; N, 3.77.

Hydrolysis and Reduction of 15.—A solution of **15** (80 mg) in water (0.5 ml) and 10% methanolic HCl (10 ml) was refluxed overnight and then evaporated to give crude 17-oxo-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-oic acid 2-methyl ester hydrochloride (**16**) as an oil: nmr τ 9.13 (s, 18-Me), 8.48 (broad s, 19-Me), and 6.25 (s, 2-OCH_3).

Plate chromatography of **16** on alumina using chloroform as the developing solvent gave a major band which was eluted with ethyl acetate. Evaporation gave 17-oxo-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-oic acid 2-methyl ester as an oil (**17**, 44 mg): nmr τ 9.13 (s, 17-Me), 8.82 (s, 19-Me), and 6.36 (s, 2-OCH_3); λ^{CHCl_3} 3.0 and 5.78 μ.

A solution of **17** (40 mg) was dissolved in methanol (3 ml), treated with sodium borohydride (30 mg), and stirred at room temperature for 35 min. The methanol was evaporated and the residue was diluted with water and extracted with chloroform. The chloroform extracts were washed with 8% salt solution, dried, and evaporated. The residue was plate chromatographed on alumina using chloroform–methanol (99:1) as the developing solvent. Elution of the major band with ethyl acetate and evaporation gave 17β-hydroxy-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-oic acid 2-methyl ester as an oil (**18**, 24 mg): nmr τ 9.26 (s, 18-Me), 8.84 (s, 19-Me), 6.4 (m, 17α-H), and 6.33 (s, 2-OCH_3).

17-Oxo-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-oic Acid (19).—A solution of **14** (200 mg) in water (0.3 ml), concentrated HCl (5 ml), and dioxane (15.5 ml) was refluxed for 17 hr and then evaporated. The residue was dissolved in water, the pH of the solution was adjusted to 5.1 with sodium bicarbonate solution, and 8% salt solution was added. This aqueous solution was extracted with chloroform. The aqueous layer was then adjusted to pH 5.5 and evaporated. The residue was treated with several portions of chloroform. The chloroform layers were dried and evaporated to give **19** (150 mg) as an oil: nmr τ 9.14 (s, 18-Me) and 8.63 (s, 19-Me); λ^{CHCl_3} 2.92, 5.78, and 6.23 μ.

3,4-Bisnor-5-aza-B-homoandrostane-2,17-dione (20).—A solution of **19** (452 mg) in nitromethane (15 ml) was treated with dicyclohexylcarbodiimide (270 mg) and stirred at room temperature or 45 hr. The N,N′-dicyclohexylurea was removed by filtration and the filtrate was evaporated. The residue was plate chromatographed on alumina, using chloroform–hexane (1:1) as the developing solvent. The plate was developed twice and the major band was eluted with ethyl acetate. Evaporation and crystallization from ethyl acetate–isopropyl ether gave **20** (181 mg), mp 157.5–158.5°. Recrystallization from acetone–isopropyl ether gave the analytical sample: mp 158–159°; $[\alpha]^{24}D$ + 117°; λ 5.70 (sh) and 5.75 μ; nmr τ 9.09 (s, 18-Me), 8.56 (s, 19-Me), 7.35 (s, 1-CH_2), and 6.66 (m, 6-CH_2).

Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.38; H, 9.35; N, 5.08.

N-Acetyl-17β-hydroxy-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-oic Acid (21).—A solution of **14** (50 mg) in methanol (5 ml) was treated with sodium borohydride (30 mg) and stirred at room temperature for 1 hr. The reaction mixture was concentrated, diluted with water, acidified to pH 2, and extracted with chloroform. The chloroform extracts were washed with 8% salt solution, dried, and evaporated. The residue was crystallized from acetone–isopropyl ether to give **21** (43 mg), mp 186–187°. Recrystallization from acetone–isopropyl ether gave the analytical sample: mp 188–188.5°; $[\alpha]^{24}D$ −71°; λ 2.8–4.0 (br), 5.83, and 6.20 μ.

Anal. Calcd for $C_{19}H_{31}NO_4$: 67.62; H, 9.26; N, 4.15. Found: C, 67.91; H, 9.44; N, 4.06.

17β-Hydroxy-2,5-seco-3,4-bisnor-5-aza-B-homoandrostan-2-oic Acid (22).—A solution of **21** (275 mg) in water (0.3 ml), concentrated HCl (4 ml), and dioxane (15 ml) was refluxed overnight. The same procedure described for the isolation of **19** was followed. Crystallization of the residue from methanol–ethyl acetate gave **22** (100 mg), mp 233–234°. Recrystallization from methanol–ethyl acetate gave the analytical sample: mp 233.5–234.5°; $[\alpha]^{23}D$ 0°; λ 2.85–2.95, 6.17, and 6.25 μ; nmr (DMSO) τ 9.35 (s, 18-Me) and 8.82 (s, 19-Me).

Anal. Calcd for $C_{17}H_{29}NO_3$: C, 69.11; H, 9.90. Found: C, 69.09; H, 9.81.

17β-Hydroxy-3,4-bisnor-5-aza-B-homoandrostan-2-one (23).—A solution of **22** (143 mg) in water (1 ml) and dioxane (2 ml) was treated with a solution of diisopropylcarbodiimide (0.085 ml) in dioxane (1 ml). The mixture was stirred at room temperature for 3 days. The mixture was evaporated and the residue was treated with water and extracted with chloroform. The chloroform extracts were washed with 8% salt solution, dried, and evaporated. The residue was treated with ethyl acetate and filtered to remove N,N′-diisopropylurea, and the filtrate was plated on alumina using chloroform as the developing solvent. The major steroid band was eluted with ethyl acetate and evaporated to give **23** (9 mg). Recrystallization from acetone–isopropyl ether gave the analytical sample: mp 208–209°; λ 2.90 and 5.78 μ; nmr τ 9.21 (s, 18-Me), 8.58 (s, 19-Me), 7.37 (s, 2-CH_2), and 6.35 (s, 17α-H).

Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.60; H, 9.81. Found: C, 73.99; H, 9.72.

Registry No.—**1**, 1154-01-4; **2**, 23327-88-0; **3**, 19508-55-5; **4**, 23327-90-4; **5**, 19508-56-6; **6**, 19508-57-7; **7**, 19508-58-8; **8**, 23327-94-8; **9**, 23327-95-9; **10**, 20711-47-1; **11**, 20711-48-2; **12**, 20711-49-3; **13**, 19508-62-4; **14**, 19508-63-5; **15**, 19508-64-6; **16**, 23328-02-1; **17**, 23328-03-2; **18**, 23367-39-7; **19**, 19508-65-7; **20**, 19746-47-5; **21**, 23330-26-9; **22**, 23330-27-0; **23**, 23330-28-1.

Acknowledgment.—The author wishes to thank Dr. A. I. Cohen for the nmr spectra and Mr. J. Alicino and his staff for the microanalyses.

Alumina-Catalyzed Reactions of Hydroxyarenes and Hydroaromatic Ketones. IV. Products and Mechanism of Reaction of 2-Naphthol with Methanol[1]

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Received March 17, 1969

The alumina-catalyzed reaction of 2-naphthol (**2**) with excess methanol was studied as a function of catalyst acidity and temperature (275–470°). At 350–470° **2** undergoes mainly (45–96 mol % on converted naphthol) ring methylation with concurrent elimination of the arenolic group to give the following specifically substituted naphthalenes as principal products: 1,2-dimethyl-, 1,2,3-trimethyl-, 1,2,3,4-tetramethyl-, and 1,2,3,4,6-pentamethylnaphthalene. Yields of 1,2,4-trimethyl- and 1,2,3,4,6,7-hexamethylnaphthalene become significant at higher temperatures (420–470°), with a sodium-free catalyst (A). At 275–300°, with sodium-containing catalysts (C, D), the product consists mainly (57–75 mol % on converted **2**) of the oxygen-containing precursors 1-methyl-2-naphthol, 1,1-dimethyl-2-oxo-1,2-dihydronaphthalene (**6**), and 1,1,3-trimethyl-2-tetralone (**7**). At 275°, with C, **6** reacts with methanol to yield 1,2-dimethylnaphthalene (60%) and **7** (36%). At 300°, with A, **7** plus methanol give 1,2,3-trimethylnaphthalene in 94% yield. The preferential methylation of **2** at C-1 and the methylation of **6** at C-3, observed at 275–300°, are consistent with calculated simple Hückel molecular orbital reactivity indices for electrophilic attack on the corresponding systems. Mechanistic and stereochemical aspects of the reactions are discussed.

It was found previously[2] that the alumina-catalyzed reaction of 1-naphthol (**1**) with methanol, to form polymethylnaphthalenes containing two to six substituents, occurs with a high degree of positional selectivity. It was proposed (on the basis of quantum mechanical calculations, isolation and identification of oxygen-bearing intermediates, and observed specific structures of the final products) that ring methylation involves electrophilic attack preferentially at C-2, C-4, and C-7. Dimethylation at C-4 and C-7 is followed by rearrangement of a methyl group to C-3 and C-6, respectively, while dimethylation at C-2 is followed by reduction–rearrangement, whereby migration of a methyl group to C-1 occurs with attendant loss of the oxygen function and termination of the overall process.[3] As a continuation of this study, the reaction of 2-naphthol (**2**) with methanol was investigated. The direction of ring methylation in this case is of particular interest in view of the reported low reactivity of the C-3 position (as compared with the C-1 position) in **2** in a number of electrophilic substitutions.[4]

The apparatus and procedure were essentially the same as employed in the study of **1**.[2] Experiments were carried out at 275–470° and alumina catalysts used were A, sodium-free, prepared by hydrolysis of aluminum isopropoxide; C, Houdry hard alumina, containing *ca.* 0.4% of sodium; and D, from sodium aluminate, containing *ca.* 0.5% sodium.[2,3,5] Individual compounds were isolated from the total products by preparative gas chromatography and were identified by a combination of infrared and nmr spectral methods, and, in some cases, by conversion into derivatives. Quantitative analyses were carried out by gas chromatography.

Results

Results obtained are summarized in Table I. As in the case of 1-naphthol,[2] the reaction of 2-naphthol with methanol yields four types of products in the temperature range studied, *i.e.*, methyl naphthyl ethers (**3**, **4**), methylated naphthols (almost entirely **5**), methylated oxo compounds (**6**, **7**), and methylnaphthalenes (**8**–**17**). The change in the relative yields of these types of products as a function of temperature and catalyst acidity follows a pattern similar to that observed in the reaction of 1-naphthol. Formation of ethers **3** and **4** occurs mainly at the lower temperatures (275–300°), and the relative importance of this reaction decreases with increased catalyst acidity (*cf.* expt 1–6; catalyst acidity A > C > D). The main reaction at 275–300° over the weakly acidic catalysts C and D (expt 1, 2, 4, 5) is ring methylation of **2** to give oxygen-bearing compounds **5**–**7** (combined yield 57–75 mol % on converted **2**). Only small amounts of methylnaphthalenes, mainly **11** and **12**, are formed in these experiments. However, the yields of **11** and **12** plus **14** and other polymethylnaphthalenes are markedly higher with the strongly acidic catalyst A (expt 3, 6). The combined yield of the oxygen-bearing compounds **5**–**7** with catalyst C or D passes through a maximum at *ca.* 300°. There is a gradual decrease in the yield of these components and a concomitant increase in the yield of methylnaphthalenes as the temperature is raised. These trends are consistent with the previously established role of methylated naphthols and oxo compounds as intermediates in the formation of methylnaphthalenes from 1-naphthol.[2,3,6] More facile conversion of the intermediate compounds occurs with catalyst A than with catalyst C or D. It is found that the combined yields of methylnaphthalenes from 2-naphthol with A at 275° (33 mol %) and at 300° (51 mol %) are considerably higher than those from 1-naphthol under identical conditions (13 and 28 mol %, respectively).

(1) This investigation was carried out in the Department of Chemistry, University of Oregon, and was supported by Research Grants CA-5969 from the National Cancer Institute and GM 12730 from the National Institute of General Medical Sciences, U. S. Public Health Service.

(2) Part I: L. H. Klemm, J. Shabtai, and D. R. Taylor, *J. Org. Chem.*, **33**, 1480 (1968).

(3) Part II: J. Shabtai, L. H. Klemm, and D. R. Taylor, *ibid.*, **33**, 1489 (1968). Note that catalyst D was from potassium aluminate (instead of from sodium aluminate) in this earlier study.

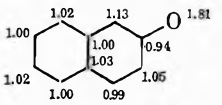
(4) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold Publishing Corp., New York, N. Y., 1961, pp 880–883.

(5) H. Pines and W. O. Haag, *J. Amer. Chem. Soc.*, **82**, 2471 (1960).

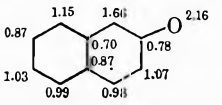
(6) Part III: J. Shabtai, L. H. Klemm, and D. R. Taylor, *J. Org. Chem.*, **33**, 1494 (1968).

CHART I

MOLECULAR DIAGRAMS OF 2-NAPHTHOXY ANION. π-ELECTRON DENSITIES (q_r) AND SUPERDELOCALIZABILITIES FOR ELECTROPHILIC ATTACK (S_r^{elec}, IN UNITS OF β_0^{-1})



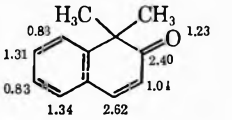
q_r



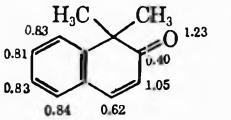
S_r^{elec}

CHART II

SUPERDELOCALIZABILITIES FOR NUCLEOPHILIC ATTACK (S_r^{nuc}) AND FOR ELECTROPHILIC ATTACK (S_r^{elec}) IN 6 (IN UNITS OF β_0^{-1})



S_r^{nuc}



S_r^{elec}

TABLE I

ALUMINA-CATALYZED REACTIONS OF 2-NAPHTHOL (2) WITH METHANOL[a]

Expt. no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Catalyst	D	C	A	D	C	A	D	C	A	D	C	A	D	C	A
Reaction temp, °C	275	275	275	300	300	300	350	350	350	420	420	420	470	470	470
Conversion of 2, mol %	38	40	71	51	52	78	84	87	92	89	95	100	93	100	100
Product component,[b] mol %															
2-Methoxynaphthalene (3)	10.8	4.9	0.5	10.3	4.5	0.3	5.3	Trace	...	0.9	Trace	...	...	...	...
1-Methyl-2-methoxynaphthalene (4)	2.0	1.2	Trace	3.4	1.2	Trace	2.8	Trace	...	0.8	Trace	...	...	...	...
1-Methyl-2-naphthol (5)	19.3	26.0	28.5	25.3	32.3	19.0	15.0	13.2	7.5	6.5	1.2	...	...	...	...
1,1-Dimethyl-2-oxo-1,2-dihydronaphthalene (6)	2.1	3.0	1.3	2.6	2.5	0.6	5.2	0.5	<0.1	0.9	0.4	...	...	...	...
1,1,3-Trimethyl-2-tetralone (7)	0.4	0.9	1.7	1.3	2.0	1.1	2.9	0.9	<0.1	1.1	0.5	...	...	...	...
Naphthalene (8)	...	...	...	0.5	0.6	Trace	2.0	1.8	Trace	6.3	3.8	Trace	2.5	3.4	Trace
1-Methylnaphthalene (9)[c]	...	...	...	0.2	0.4	1.4	2.6	3.5	2.3	3.8	4.8	2.6	3.5	6.4	1.5
1,2-Dimethylnaphthalene (11)	1.3	1.4	12.5	4.2	4.5	16.3	20.2	21.5	17.5	19.0	22.7	18.0	19.7	21.9	13.8
1,2,3-Trimethylnaphthalene (12)	0.2	0.3	15.8	0.3	0.7	20.8	11.4	18.3	30.2	20.6	29.0	16.1	25.8	21.4	10.6
1,2,4-Trimethylnaphthalene (13)	Trace	Trace	1.5	Trace	0.1	2.7	2.0	2.6	6.5	3.2	5.8	12.0	6.7	6.0	15.9
1,2,3,4-Tetramethylnaphthalene (14)	...	...	3.0	...	...	6.5	1.8	6.2	12.7	6.8	9.5	20.2	15.4	25.5	18.3
1,2,3,4,6-Pentamethylnaphthalene (15)	...	...	Trace	...	...	2.1	...	1.0	6.4	1.4	3.0	14.0	4.0	4.7	24.6
Others[d]	...	...	0.9[e]	...	...	1.8[g]	...	0.7[e]	4.2	1.7	1.9	11.3[f]	2.0	5.0	11.6[g]
Unidentified[h]	(6.5)	(9.2)	(10.8)	(9.2)	(9.8)	(8.7)	(15.8)	(16.3)	(5.1)	(18.0)	(13.0)	(4.3)	(8.2)	(5.6)	(2.9)
Depth of ring methylation[i]	0.8	0.9	1.9	1.0	1.2	2.3	1.8	2.2	3.0	2.3	2.7	3.7	2.9	3.0	3.9

[a] A mixture of 14.4 g (0.1 mol) of 2 and 32 g (1 mol) of methanol was used as starting material in each experiment. [b] Calculated on the basis of 100 mol of starting 2 (including unreacted material). [c] 2-Methylnaphthalene (10) is formed in low yield (0.1–0.2 mol %) above 350°. [d] 1,2,3,4,6,7-Hexamethylnaphthalene (16) and a component tentatively assigned the structure of 1,2,6-trimethylnaphthalene (17) on the basis of vpc behavior (see Experimental Section) and mechanistic considerations; includes also (especially at 420–470°) small amounts of two tetramethylnaphthalenes of undetermined structure. Formaldehyde was detected (by means of 2,4-dinitrophenylhydrazine) in the gaseous products for all runs at 350° and above. [e] Mainly 17; includes 0.2–0.3 mol % of a dimethylnaphthol. [f] Includes 4.2 mol % of 16. [g] Includes 5 mol % of 16. [h] Percentage by weight of total product; for experiments up to 350°, mainly unidentified chromatographic peaks in a range characteristic for dihydronaphthalenes; for experiments at 420–470°, carbon deposits and nondistillable residues. [i] In average number of methyl groups per naphthalene or hydronaphthalene moiety for all identified products (exclusive of recovered 2).

The isomeric compositions of the trimethyl- and tetramethylnaphthalene fractions derived from 2-naphthol (**2**) are markedly different from those observed in the reaction of 1-naphthol (**1**) under identical experimental conditions.[2] 1,2,3-Trimethylnaphthalene (**12**), a minor isomeric product from **1**, is the predominant trimethylnaphthalene formed from **2** at temperatures up to 350° (82–99% of the isomeric fraction; expt 1–9). 1,2,4-Trimethylnaphthalene (**13**), normally a major component of the isomeric fraction from **1** at 275–350°, is formed as a minor component from **2** in the same temperature range. The relative importance of **13** increases, however, at 420–470° with catalyst A (expt 12, 15). Small amounts of a third isomer, tentatively assigned the structure of 1,2,6-trimethylnaphthalene, are also obtained with A (Table I, footnotes *d* and *e*). 1,2,3,4-Tetramethylnaphthalene (**14**), a relatively minor component from **1**, comprises 90–99% of the isomeric fraction obtained from **2**. Reaction of **2** also produces 1,2-dimethylnaphthalene (**11**), 1,2,3,4,6-pentamethylnaphthalene (**15**), and 1,2,3,4,6,7-hexamethylnaphthalene (**16**) as isomer-free components. 1-Methylnaphthalene is the predominant isomer in the monomethylnaphthalene fraction, in contrast to the formation of 2-methylnaphthalene as the main isomer from **1**. Calculations based on the composition of the total products from 2-naphthol (Table I) show that the average depth of ring methylation (average number of methyl groups per product molecule) increases with catalyst acidity (A > C > D) and with temperature, up to 470°.

Reactions of 1,1-Dimethyl-2-oxo-1,2-dihydronaphthalene (6) and of 1,1,3-Trimethyl-2-tetralone (7).—A solution of **6** in methanol (1:10 by weight) was passed over catalyst C at 275° to yield a product which contained 1,2-dimethylnaphthalene (**11**), 60 mol %; 1,1,3-trimethyl-2-tetralone (**7**), 36 mol %; and 1,2,3-trimethylnaphthalene (**12**), 3.5 mol % (total conversion 52%). In a parallel experiment with catalyst A the conversion of **6** was 85% and the product consisted of **11**, 41 mol %; **7**, 6 mol %; and **12**, 53 mol %. Passing a solution of **7** in methanol (1:10 by weight) over catalyst A at 300° gave isomerically pure 1,2,3-trimethylnaphthalene (**12**) in 94% yield.

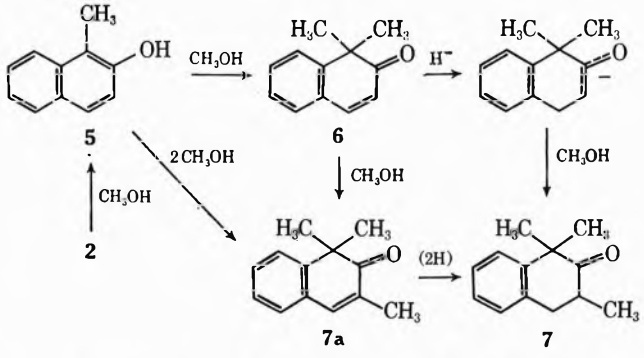
Discussion

Formation of Oxygen-Bearing Products.—A qualitative indication of the expected positions for methylation in **2** was obtained by simple Hückel molecular orbital calculations of π-electron densities (q_r) and of superdelocalizabilities for electrophilic attack (S_r^{elec}) on 2-naphthoxy anion. Chart I gives the molecular diagram obtained with the set of parameters $h_{(O)} = 1.0$ and $k_{(C=O)} = 1.0$.[7] The calculated values (in particular for S_r^{elec}) would indicate a strong preference for electrophilic attack at the oxygen atom and at C-1. Positions C-3, C-6, and C-8 should show lower, but still significant reactivity. Although O-methylation could be favored over ring methylation, the observed relatively low yield of 2-methoxynaphthalene (Table I, expt 1–7) may be due to reversibility of the ether-forming reaction (*cf.* study of 1-methoxynaphthalene)[3] and/or to shielding of the oxygen atom by the catalyst surface.[2,8]

From the oxygen-bearing products isolated it is apparent that in the temperature range of 275–300° the first step of ring methylation occurs with a very high degree of preference at C-1, though methylation at C-3 is also significant. Thus in expt 1–5 the major product formed is 1-methyl-2-naphthol (**5**), while other methylnaphthols are virtually absent. Compounds **4** and **6** also result from ring methylation at C-1, while formation of **7** requires methylation both at C-1 and C-3.

Scheme I depicts likely pathways from 2-naphthol (**2**) to 1,1-dimethyl-2-oxo-1,2-dihydronaphthalene (**6**) and 1,1,3-trimethyl-2-tetralone (**7**) *via* 1-methyl-2-naphthol (**5**). Introduction of a second methyl group

SCHEME I



at C-1 would give **6**, while dimethylation of **5** in the order C-1, C-3 or C-3, C-1 (*vide infra*) should form **7a**. Although **7a** was not isolated, its presence in the total product in concentrations below 2% is possible. Compound **7** might then result by reduction of the carbon–carbon double bond in **7a** or alternatively, by initial hydride attack[10] at C-4 in **6** followed by methylation at C-3 (*vide infra* for mechanistic details).

The plausibility of **6** as an intermediate on the route to **7** is provided by calculated superdelocalizabilities for electrophilic and nucleophilic attacks on the former compound (Chart II, parameters $h_{(O)} = 1.0$, $k_{(C=O)} = 1.0$).[7] If **6** is subjected to electrophilic attack by the methylating species, C-3 would be the preferred ring position for methylation. On the other hand, C-4 and (to a slightly lesser extent) C-2 would be the favored positions for hydride addition.

Formation of Methylnaphthalenes.—Ketones **6** and **7** (or **7a**) could serve as precursors of 1,2-dimethylnaphthalene (**11**) and 1,2,3-trimethylnaphthalene (**12**), respectively. This is fully supported by the smooth conversion of **6** and **7** into the corresponding naphthalenes under the experimental conditions (*vide supra*). The facile transformation **7** → **12** is consistent with the

(7) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, Inc., New York, N. Y., 1961, pp 123, 135. The parametric set for the 2-naphthoxy anion takes into account the expected decrease in the Coulomb integral which accompanies the increase in negative charge produced by ionization, but the molecular properties calculated from this set do not include the effects of *n* electrons on the oxygen atom.

(8) It is noteworthy that the preferential C-methylation (rather than O-methylation) of 2-naphthol, or a possible transformation 2-methoxynaphthalene → *x*-methyl-2-naphthol, is consistent with the Principle of Hard and Soft Acids and Bases (HSAB).[9]

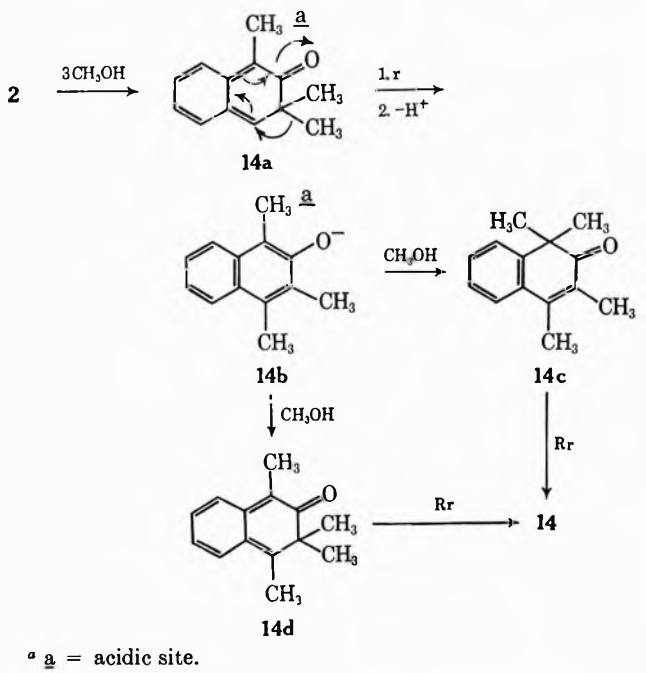
(9) R. G. Pearson, *Science*, **151**, 172 (1966); *J. Chem. Educ.*, **45**, 581, 643 (1968); R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, **89**, 1827 (1967).

(10) For further discussion of the mechanism of reducing activity of the methanol–alumina system, see part V: J. Shabtai, L. H. Klemm, and D. R. Taylor, *J. Org. Chem.*, **35**, 1075 (1969).

finding[10] that, under similar conditions, 2,2-dimethyl-1-tetralone and 2,2,4,7-tetramethyl-1-tetralone are converted into 1,2-dimethylnaphthalene and 1,2,4,7-tetramethylnaphthalene, respectively. As indicated in the following paper, these reactions proceed with the intermediate formation of the corresponding 1,2-dihydronaphthalenes. The formation of **12** could similarly involve a dihydronaphthalene intermediate (*cf.* Table I, footnote *h*).

The increased yields of tri-, tetra- and pentamethylnaphthalenes above 300° indicate that ring methylation of **2** at positions other than C-1 becomes increasingly significant with rise in temperature. Whereas monomethylation at C-1 probably remains the most facile step, the introduction of a second methyl substituent at the same carbon could be preceded by methylation(s) at C-3, or both at C-3 and C-6. As in the case of 1-naphthol, it is proposed that polymethylnaphthalenes are derived from **2** by sequential pathways which involve ring methylation, dienone–arenol rearrangement (r), and a terminal reduction–rearrangement step (Rr). The formation of 1,2,3,4-tetramethylnaphthalene (**14**), for instance, is visualized as proceeding by one or more of the plausible sequences (1,3),3,r,[1,3],Rr, where the parenthesized numbers refer to allowed permutations in the methylation sequence[6] and the bracketed numbers refer to alternative positions for methylation (*cf.* Scheme II). Analogously, the sequences (1,3,6),3,r,[1,3],Rr are suggested for the formation of 1,2,3,4,6-pentamethylnaphthalene (**15**). As noted in Scheme II, dimethylation at C-3 (see **14a** and **14d**) involves the formation of a nonaromatic intermediate ketone (*cf.* Scheme II, paper III).[6] It is suggested that such highly energetic intermediates are reasonable in view of the elevated reaction temperature used and the possibility that flatwise (or nearly flatwise) adsorption of the entire π system occurs to a significant extent. Such adsorption could in fact be requisite for methylation at C-6. For a simplified picture the increased combined yield of **14** and **15** in expt 10–15 may reflect an enhancement in the reactivity of the C-3 (relative to the C-1) position in **2** with increase in temperature and catalyst acidity.

SCHEME II[a]



[a] a = acidic site.

The lack of methylation at C-8 can be attributed to *peri* interference[11] by a methyl substituent introduced at C-1 in an earlier methylation step. A similar effect was considered to prevent methylation at C-5 in 1-naphthol through earlier introduction of a methyl group at C-4.[2,6]

The small amounts of naphthalene and 1-methylnaphthalene formed in the reaction (Table I) are probably derived by direct reduction of 2-naphthol and 1-methyl-2-naphthol, respectively. 1,2,4-Trimethylnaphthalene (**13**) might be produced in a similar way from the corresponding naphthol (Scheme II, **14b**).

Surface Ensembles and Stereochemical Mechanisms.—The generalized mechanistic schemes which have been presented in this and preceding papers[2,3,6] stressed mainly the chemical transformations of the naphthol reactants and of reaction intermediates, with little attention paid to the nature of the methylating agent, stereochemical requirements of the catalyst surface, and the catalytic function of the alumina *per se*. It seems pertinent at this time to present a more detailed picture of the interactions between the catalyst surface and the reacting molecules. This picture is based, in part, on the model for γ-alumina developed by Peri.[12]

The catalyst surface (Figure 1a) is represented as a defect lattice work of incompletely coordinated oxide ions (strong basic sites, designated simply as "basic sites") in the outermost, partially filled surface layer, a nearly regular array of incompletely coordinated, exposed aluminum ions (designated simply as "acidic sites") in the second (filled) layer, and alternating layers of catalytically inactive oxide and aluminum ions below. The outermost layer also contains some hydroxide groups (considered weak basic sites in the fresh catalyst and amphoteric sites during the reaction proper, *vide infra*). The strength and hardness[9] of acidic sites vary over wide ranges and increase with increasing numbers of incompletely coordinated neighboring aluminum ions. For simplicity of argument, in most cases one may consider that all of the catalysts used in these studies contain only two types of Lewis acidic sites, strong and weak ones. The relative acidities of the catalysts then depend largely on the relative concentrations of these two types of sites,[5] though certain catalytic steps may occur only on the more potent of the strong sites (*i.e.*, on "very strong" sites, *vide infra*). Fully coordinated aluminum ions would not function as acidic sites. Only the outermost layer of oxide ions and hydroxide groups is considered interchangeable with the reacting species.

Based on the studies of Greenler[13] and Kagel[14] on the nature of methanol adsorbed on alumina in an equilibrated system, a detailed mechanism for formation of oxygen-bearing adsorbed intermediates is proposed (Figure 1). In Figure 1a an ensemble of four sites (two acidic, two basic) is used to illustrate initial independent processes of dissociative chemisorption of

(11) V. Balasubramaniyan, *Chem. Rev.*, **66**, 567 (1966).
(12) J. B. Peri, *J. Phys. Chem.*, **69**, 220 (1965); **70**, 1482, 3168 (1966).
(13) R. C. Greenler, *J. Chem. Phys.*, **37**, 2094 (1962).
(14) R. O. Kagel, *J. Phys. Chem.*, **71**, 844 (1967).

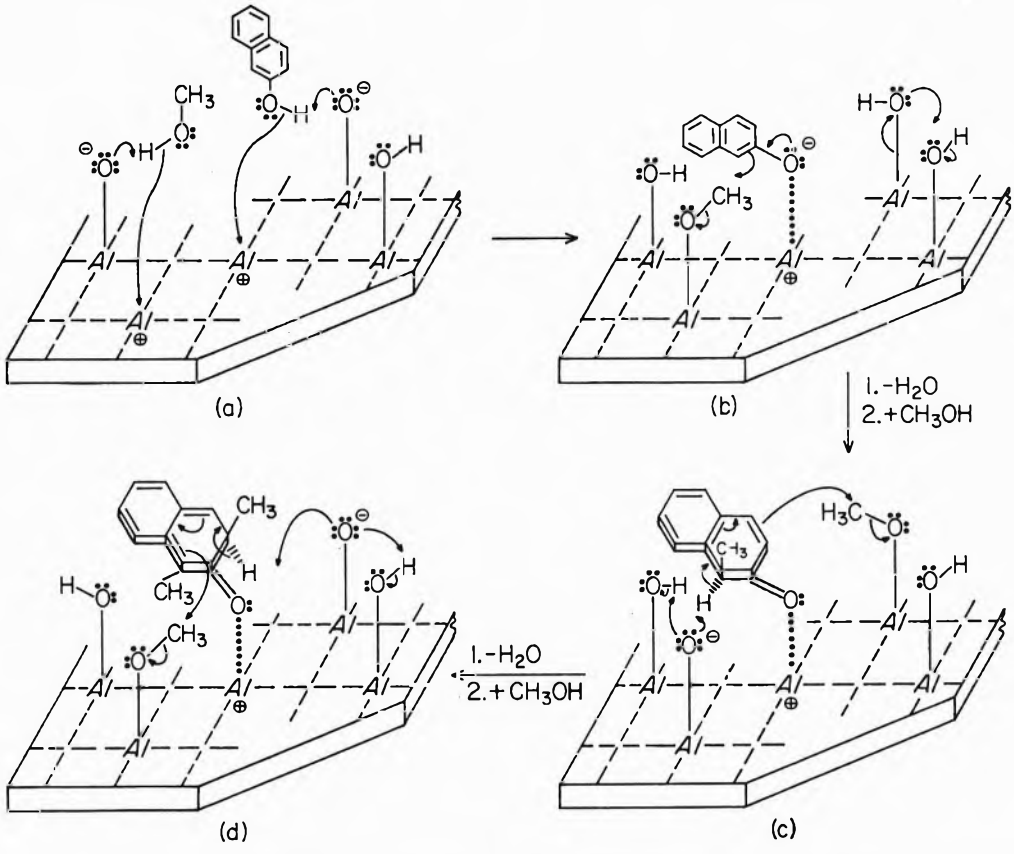


Figure 1.—Five-site ensemble for sequential methylation of 2 at C-1 and C-3.

2-naphthol[15] and methanol with formation of surface naphthoxide and methoxide[13,14,16] groups, respectively. Bonding occurs between the hard acidic site and the hard basic oxygen in both cases. However, the bonding is indicated as covalent for the methoxide and ionic (dotted line) for the naphthoxide, in accordance with the relative acidities of methanol and 2-naphthol (*i.e.*, with bonding to the proton, also a hard acid). Methylation of the adsorbed naphthoxide species at C-1 by a juxtaposed methoxide[16] is represented in Figure 1b as a concerted step, accompanied by regeneration of an oxide site (Figure 1c) at a different position on the surface. Repeated methylation of the adsorbed naphthoxide at C-1 would produce 1,1-dimethyl-2-oxo-1,2-dihydronaphthalene (**6**). On the other hand, if the second methyl substituent is introduced at C-3 (Figure 1c) and this step is followed by methylation at C-1 (Figure 1d), the product would be 1,1,3-trimethyl-2-oxo-1,2-dihydronaphthalene (**7a**, Scheme I). It is readily apparent from Figure 1 that geometric relationships of the adsorbed reactants should favor methylation at carbons vicinal to C-2, particularly if the naphthalene ring protrudes outward from the surface. At higher temperatures and/or with more acidic catalysts the ensemble of acidic sites may be more extensive in area and permit both flatwise adsorption of the naphthalene ring and access of surface methoxide groups to ring positions more distant from the oxygen function.

A fifth site (an hydroxide group) in the ensemble (Figure 1) serves to effect loss of water from the catalyst surface. This process involves proton transfer between adjacent hydroxide groups (amphoteric sites). Proton transfer may also occur from an hydroxide group to adsorbed arenoxide with the attendant loss of arenol, *e.g.*, 1-methyl-2-naphthol (**5**), from the surface. Other than in these desorption processes, however, Brönsted acidity of the catalyst surface (acquired principally during the reaction proper) is considered to be nonfunctional.[17]

A more detailed possible mechanism for the reduction–rearrangement of **6** is presented in Figures 2 and 3. In Figure 2a an ensemble of four sites (two acidic and two basic) serves to adsorb methanol and ketone **6**.[18] Adsorption is followed by hydride transfer from a methoxide group to the carbonyl function (Figure 2b) to produce formaldehyde (*cf.* Table I, footnote *d*) and a chemisorbed dihydronaphthoxide intermediate (Figure 2c). This intermediate subsequently undergoes loss of its oxygen function in the form of a surface oxide group, with concurrent neopentyl-type rearrangement of a methyl group.[10] As depicted in Figure 2c, the rearrangement involves anchimeric assistance by the migrating methyl group and γ participation[19] by proton extraction from the other methyl group to the surface. Hydrogen exchange between the surface and the unstable intermediate **11a** (Figure 2d) should occur rapidly (with or without intervening translation of **11a** upon the catalyst surface) on an ensemble of two sites (one

(15) This mechanism should also be applicable to the 1-naphthol system.[2]

(16) Since the system used in the present study is nonequilibrated, it is still possible that nondissociatively adsorbed methanol serves as a methylating agent; *cf.* J. R. Jain and C. N. Pillai, *Tetrahedron Lett.*, 675 (1965).

(17) H. P. Boehm, *Advan. Catal.*, **16**, 179 (1966); J. M. Parera and N. S. Figoli, *J. Catal.*, **14**, 303 (1969).

(18) In fact **6** might still be anchored to the site on which it was formed.

(19) H. Pines and J Manassen, *Advan. Catal.*, **16**, 80 (1966); C. N. Pillai and H. Pines, *J. Amer. Chem. Soc.*, **83**, 3274 (1961). Alternatively, rearrangement could occur without γ participation. A referee has suggested a third mechanism in which rearrangement is initiated by abstraction of the proton at C-2.

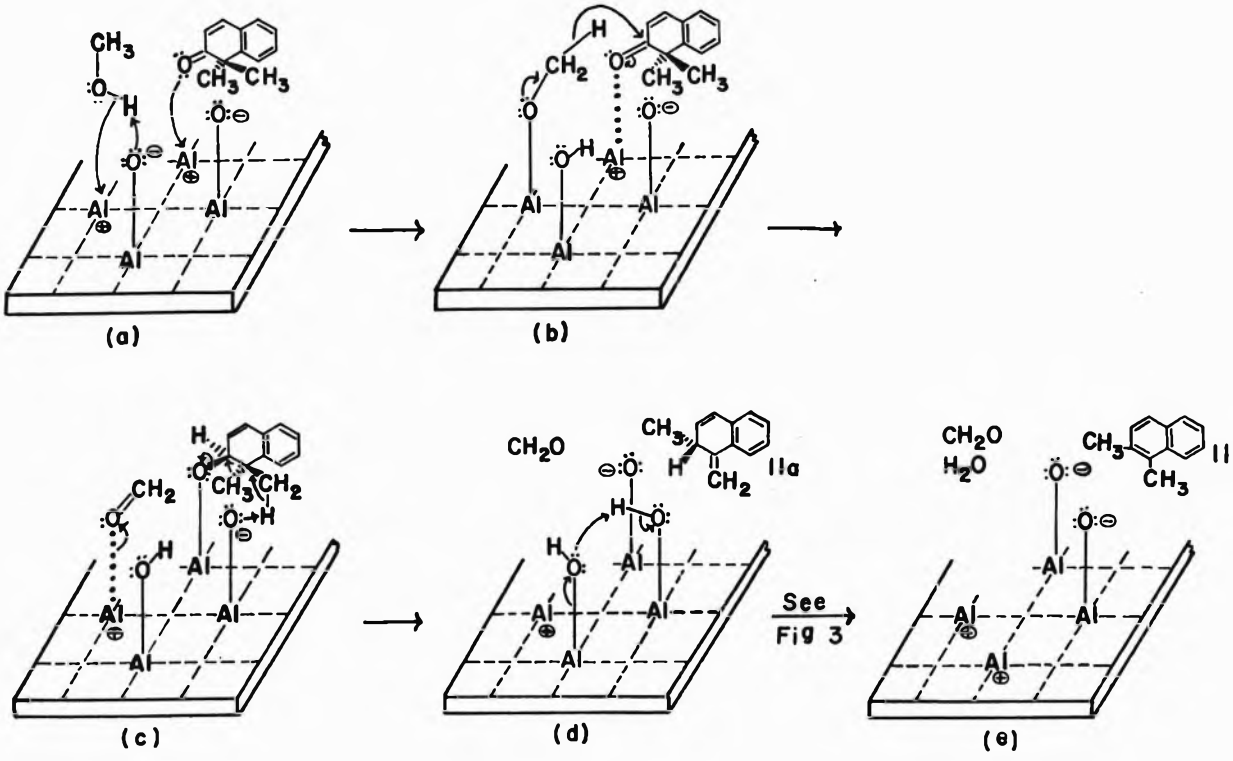


Figure 2.—Four-site ensemble for reduction–rearrangement of 6.

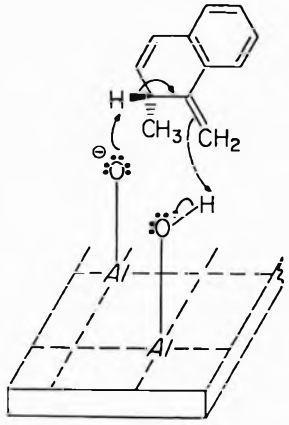


Figure 3.—Two-site ensemble for formation of 11 from 11a by hydrogen transfer.

basic and one hydroxide) to form 1,2-dimethylnaphthalene (11), as shown in Figure 3. Desorption of a molecule of water from the surface (Figure 2d), plus diffusion of water, formaldehyde, and 11 from the immediate vicinity would regenerate both ensembles of sites (but in slightly altered geometric arrangements).

Experimental Section

Apparatus, Catalysts, and Procedure.—The apparatus and experimental procedure were essentially the same as employed in the study of 1-naphthol.[2] The alumina catalysts A (from aluminum isoproproxide) and D (from sodium aluminate) were prepared according to methods described previously;[2,3,5] catalyst C (Houdry Process Corp., Philadelphia, hard alumina, Grade HA 100) was obtained commercially. A fresh portion of catalyst (80 g, 0.125-in. pellets) was used in each experiment after preliminary activation *in situ* by a standard procedure.[2] In all reactions with 2-naphthol the starting mixture of reactants (Table I, footnote *a*) was passed through the reactor (total addition time, 2 hr) at a constant liquid feed rate, in a stream of nitrogen (22 ml/min), at atmospheric pressure.

Reactions of 1,1-Dimethyl-2-oxo-1,2-dihydronaphthalene (6) and 1,1,3-Trimethyl-2-tetralone (7) in the Presence of Methanol.—In experiments with compounds 6 and 7 the starting mixture consisted of 1 g of the ketone in 10 g of methanol. The solution was passed through the catalyst (30 g) over a period of 45 min. At the end of the run the catalyst was washed first with methanol (5 ml), then with benzene (50 ml), and finally extracted with boiling acetone. The product was processed and analyzed as usual.[2,3]

Isolation and Identification of Reaction Products.—The methylnaphthalenes 9–16 were identified by comparison of nmr and infrared spectra, as well as vpc retention volumes, with those of authentic samples. 1-Methyl-2-naphthol (5), mp 110–111° (lit.[20] mp 110–111°), was isolated from the acidic fractions of expt 1–6, whereas 2-methoxynaphthalene (3) and 1-methyl-2-methoxynaphthalene (4) were isolated from the neutral products of expt 1, 2, and 4. Compounds 3–5 were identified by comparison of nmr and infrared spectra (also mixture melting point for 5) with those of reference samples (*vide infra*).

1,1-Dimethyl-2-oxo-1,2-dihydronaphthalene (6) was isolated in >99% purity by preparative vpc of the products from expt 2, 4, and 7: 2,4-dinitrophenylhydrazone mp 224–225° (lit.[21] mp 224.5–225.5°); nmr (CCl_4) δ 1.41 (s, 6, geminal CH_3 groups), 6.05 (d, 1, J = 10.0 Hz, =CH— at C-3), and 7.1–7.5 (m, 5, aromatic protons and —CH= at C-4); ir (neat) 764 (s), 839 (s), 1102 (m), 1216 (m), 1252 (m), 1298 (m), 1381 (w), 1399 (m), 1467 (m), 1566 (m), 1624 (w), 1670 (s), and 2990 cm^{-1} (m).

In the nmr spectrum the partial overlapping of the doublet which is due to the vinylic proton at C-4 with the multiplet arising from the aromatic protons is similar to that shown by the β-vinylic and aromatic protons in the cinnamic acids.[22] The frequency of the carbonyl absorption (1670 cm^{-1}) falls in the range characteristic of α,β-unsaturated ketones (1665–1685 cm^{-1}).[23a] The strong band at 839 cm^{-1} is assigned to CH out-of-plane deformation at the *cis* double bond (estimated frequency, 820 cm^{-1} for the *cis* CH=CH–C=O group[23b] plus 15–20 cm^{-1}

(20) E. Wenkert, R. D. Youssefyeh, and R. G. Lewis, *J. Amer. Chem. Soc.*, 82, 4675 (1960).

(21) E. N. Marvell and J. L. Stephenson, *ibid.*, 77, 5177 (1955).

(22) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "NMR Spectra Catalog," Varian Associates, Palo Alto, Calif., 1962, Spectrum No. 230; E. O. Bishop and R. E. Richards, *Mol. Phys.*, 3, 114 (1960).

(23) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1962: (a) p 132; (b) p 48; (c) p 77.

for phenyl conjugation[24]). The frequency of CH out-of-plane deformation of the four adjacent aromatic hydrogens (764 cm^{-1}) is close to that observed for *o*-methylstyrene (772 cm^{-1}).[25] The presence of geminal methyl groups is evidenced by splitting of the symmetric methyl (CH) bending vibration (doublet at 1381 and 1399 cm^{-1}).[26]

The nmr and infrared spectra of the product were identical with those of a sample of **6** synthesized by independent means (*vide infra*).

1,1,3-Trimethyl-2-tetralone (7) was isolated in 98% purity by vpc of the neutral products from expt 3, 5, and 7, and from a preparative experiment with compound **6** as starting material (275°, catalyst C): $n^{20}D$ 1.5440; nmr (CCl_4) δ 1.0–1.5 (m, 9, geminal CH_3 groups at C-1 and CH_3 at C-3), 2.4–3.2 (m, 3, CH at C-3 and CH_2 at C-4), and 6.9–7.5 (m, 4, aromatic protons); ir (neat) 768 (s), 1022 (m), 1054 (m), 1244 (m), 1315 (m), 1367 (w), 1386 (m), 1465 (s), 1725 (s), and 3000 cm^{-1} (s).

Anal. Calcd for $C_{13}H_{16}O$: C, 82.93; H, 8.57. Found: C, 83.32; H, 8.56.

The absence of methyl substitution in the aromatic ring is evidenced by the strong band at 768 cm^{-1}, which is assigned to the CH out-of-plane deformation of the four adjacent aromatic hydrogens (*ortho*-disubstituted structure).[23c,25] Again the symmetric bending vibration of the geminal methyl groups is split (bands at 1367 and 1386 cm^{-1}). However, the doublet is rather obscured (compared with that in the spectrum of **6**), apparently as a result of overlapping with a singlet arising from symmetric deformation of the methyl group at C-3. The frequency of the carbonyl absorption (1725 cm^{-1}) fits the range for an unconjugated, six-membered ring ketone (1705–1725 cm^{-1}).

The positions of the methyl groups in **7** were confirmed by subjecting a small sample (0.8 g) to reduction with sodium borohydride, followed by dehydration of the intermediate carbinol (ir band at 3610 cm^{-1}) with potassium bisulfate at 2 mm pressure. The dehydration product was collected in a cold trap and aromatized by means of 2,3-dichloro-5,6-dicyanobenzoquinone[27] to give 1,2,3-trimethylnaphthalene (0.43 g, 71% overall yield), free of isomers (*cf.* analogous case for conversion of 2,2,4,7-tetramethyl-1-tetralone into 1,2,4,7-tetramethylnaphthalene).[2]

Sources and Synthesis of Reference Compounds.—Pure samples of the methylnaphthalenes **9–16** were available from previous studies.[2,3,28] 1,1-Dimethyl-2-oxo-1,2-dihydronaphthalene (**6**) was prepared according to Marvell and Stephenson;[21] 1-methyl-2-naphthol (**5**) and 1-methyl-2-methoxynaphthalene (**4**), according to Wenkert, *et al.*[20] Pure 2-methoxynaphthalene (**3**) was obtained by recrystallization of a commercial product.

Analytical.—Vpc analysis of neutral products was carried out on an 8 ft × 0.375 in. (o.d.) column, filled with 10% Bentone 34 (modified with 5% Apiezon L) on 60–80 Chromosorb P. The same type of column was used for the isolation of individual compounds. Most of the unidentified components (Table I, footnote *h*) showed lower retention times than methylnaphthalenes and appeared in a range characteristic for dihydronaphthalenes.[29] The analysis and isolation of acidic products was carried out on a 5 ft × 0.375 in. column filled with 10% Carbowax 20M on Chromosorb W. A Varian A-60 spectrometer was employed for the measurement of the nmr spectra, with carbon tetrachloride as a solvent and tetramethylsilane as reference compound. Infrared spectral analyses were carried out with a Beckman IR 7 spectrophotometer. The spectra of compounds **6** and **7** were measured with the pure liquids in a microcell of capillary thickness. Elemental analysis of **7** was performed by Micro-Tech Laboratories, Skokie, Ill.

Registry No.—**2**, 135-19-3; **6**, 23230-52-6; **7**, 23230-53-7; methanol, 67-56-1.

Acknowledgment.—Thanks are due to Mr. K. C. Bodily for assistance in syntheses of reference compounds.

(24) *Cf.* 2,3-dichloro-*cis*-cinnamic acid: S. Lindenfors, *Ark. Kemi*, **13**, 127 (1959). Measurement in this laboratory shows that ethyl *cis*-cinnamate absorbs at 836 cm^{-1}.

(25) H. Pines and J. Shabtai, *J. Org. Chem.*, **26**, 4220 (1961).

(26) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Inc., Boston, Mass., 1966, p 94.

(27) E. A. Braude, L. M. Jackman, R. P. Linstead, and G. Lowe, *J. Chem. Soc.*, 3123 (1960).

(28) L. H. Klemm and A. J. Kohlik, *J. Org. Chem.*, **28**, 2044 (1963).

(29) L. H. Klemm, J. Shabtai, and K. C. Bodily, unpublished results.

Alumina-Catalyzed Reactions of Hydroxyarenes and Hydroaromatic Ketones. V. Mechanism of Reduction of 1-Tetralones to 1,2-Dihydronaphthalenes by Means of Methanol[1a]

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Received March 17, 1969

The alumina-catalyzed reactions of methanol with 1-tetralone (**1**), 2,2-dimethyl-1-tetralone (**2**), and 2,2,4,7-tetramethyl-1-tetralone (**3**) were studied as a function of temperature (220–420°) and catalyst acidity. At 220°, with sodium-containing catalysts (C, D), **1** yields 1,2-dihydronaphthalene (**4**) as the main product (59–91 mol %, based on converted **1**). At 250–275°, with C or A (sodium-free alumina), the reduction of **1** is accompanied by methylation to give 2-methyl-3,4-dihydronaphthalene (**5**) in 75–85 mol % yield (based on converted **1**). At 325°, with A, **2** undergoes reduction–rearrangement to give 1,2-dimethyl-3,4-dihydronaphthalene (**6**) in 51 mol % yield, while at 420° the main product is 1,2-dimethylnaphthalene (80 mol %), probably derived from **6** as a precursor. The one-step conversion of 1-tetralones into 1,2-dihydronaphthalenes appears to be of general synthetic applicability. At 375–420°, with A, **3** is transformed smoothly into 1,2,4,7-tetramethylnaphthalene in 76–89 mol % yield. It is proposed that the reductive action of the alumina–methanol system involves a surface process which is mechanistically analogous to the Meerwein–Ponndorf–Verley reaction. Spectral characteristics of **4**, **5**, and **6** are reported.

It was shown previously[2] that 1-oxo-2,2-dimethyl-1,2-dihydronaphthalene is smoothly converted into 1,2-dimethylnaphthalene (84–98% yield at 275–350°) in the presence of methanol as a reducing agent and of alumina as a catalyst. As an extension of this study, the alumina-catalyzed reactions of methanol with 1-tetralone (**1**), 2,2-dimethyl-1-tetralone (**2**), and 2,2,4,7-

(1) (a) This investigation was carried out in the Department of Chemistry, University of Oregon, and was supported by Research Grant CA-5969, U. S. Public Health Service; (b) to whom inquiries should be addressed; (c) Research Assistant, 1964–1967.

(2) Part II: J. Shabtai, L. H. Klemm, and D. R. Taylor, *J. Org. Chem.*, **33**, 1489 (1968).

TABLE I

ALUMINA-CATALYZED REACTIONS OF 1-TETRALONE (1) WITH METHANOL[a]

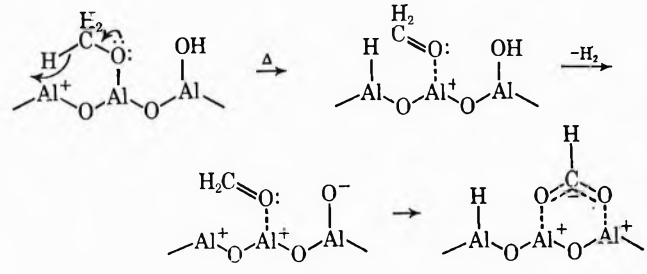
Expt no.	1	2	3	4	5	6
Catalyst	D	C	C	C	A	A
Reaction temp, °C	220	220	250	275	275	350
Conversion of 1, mol %	48	51	74	83	97	100
Product component,[b] mol %						
1,2-Dihydronaphthalene (4)	43.6	30.2	17.3	15.0	14.0	21.3
2-Methyl-3,4-dihydronaphthalene (5)	3.9	19.8	55.5	67.5	82.0	30.5
1,2-Dimethyl-3,4-dihydronaphthalene (6)	...	...	...	...	<0.1	15.4
2-Methylnaphthalene (7)	...	...	...	<0.1	0.2	13.9
1,2-Dimethylnaphthalene (8)	...	...	...	...	...	10.2[c,d]

[a] The starting mixture used in each experiment consisted of 2.92 g (0.02 mol) of 1 and 32 g (1 mol) of methanol. [b] Calculated on the basis of 100 mol of starting 1 (including unreacted material). Differences between conversion and total product figures represent losses owing to unrecovered deposits on the catalyst. [c] Plus 1.9% (by weight of total product) of 1,4-dihydronaphthalene and 3.5% of unidentified products. [d] In every case the total product also included water (which formed a separate phase) and probably formaldehyde (detected by means of 2,4-dinitrophenylhydrazine solution in expt 4–6; presence not checked in expt 1–3).

tetramethyl-1-tetralone (**3**) were investigated in order to determine whether the alumina–methanol reductive system can be used for conversion of 1-tetralones into 1,2-dihydronaphthalenes (or into naphthalenes). Catalysts employed in this study were A (sodium-free alumina, obtained by hydrolysis of aluminum isopropoxide), C (Houdry hard alumina, containing *ca.* 0.4% sodium), and D (from sodium aluminate, containing *ca.* 0.5% sodium).[2-6] The acidity of these catalysts decreases in the order A > C > D, as evaluated from their activities for ring methylation of hydroxyarenes,[3-5] for dienone–arenol rearrangement of 1-oxo-4,4-dimethyl-1,4-dihydronaphthalene,[2] and for dehydration and isomerization reactions.[6] The apparatus and procedure were similar to those used previously.[2-5] Reactions were carried out in a nitrogen atmosphere at temperatures of 220–420°. Individual compounds were isolated from product mixtures by preparative gas chromatography and identified by a combination of infrared, ultraviolet, and nmr spectral methods. The positions of methyl substituents in 1,2-dihydronaphthalene derivatives were confirmed by aromatization to the corresponding naphthalenes. Quantitative analysis of reaction products was performed by gas chromatography.

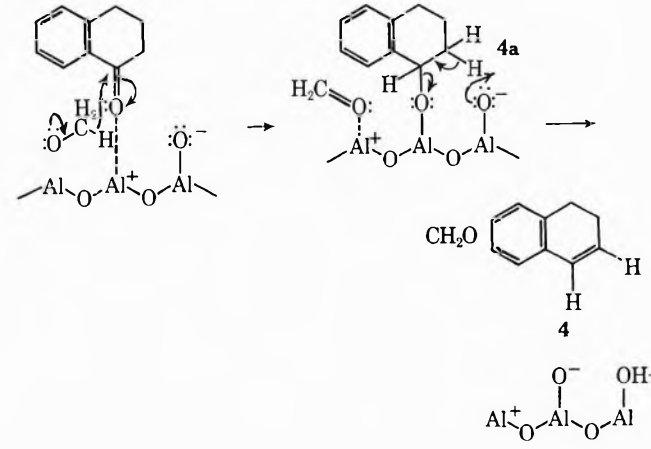
Reactions of 1-Tetralone (1).—As seen from Table I, only two products, *i.e.*, 1,2-dihydronaphthalene (**4**) and 2-methyl-3,4-dihydronaphthalene (**5**) (in addition to water and formaldehyde) are formed by reaction of **1** with methanol at 220–275° over the sodium-containing catalysts C and D. While compound **4** is a simple reduction product of **1**, formation of **5** involves methylation of **1** at C-2 as well as reduction of the carbonyl group (*vide infra*). A mechanism for the reductive action of the alumina–methanol system is suggested on the basis of infrared studies by Greenler[7] and Kagel[8] on the nature of surface species formed by methanol chemisorption on γ-alumina in the temperature range of 35–430° (in an equilibrated system). Their spectral measurements at 35–170° were consistent with the presence of surface methoxide groups, while increase in temperature above 170° caused gradual conversion of this species into a formatelike surface compound. Kagel[8] showed that this transformation is accompanied by evolution of hydrogen, which has been reported previously[9] as a major gaseous product from decomposition of methanol at 300–425° over alumina catalysts. Since formaldehyde is also produced from methanol under similar conditions,[3,5] it is likely that formation of hydrogen (from a surface methoxide) proceeds by a stepwise process, as suggested in Scheme I.[10]

SCHEME I



A possible mechanism for the formation of 1,2-dihydronaphthalene (**4**) from **1** is illustrated in Scheme II. Hydride transfer directly from a surface methoxide to the carbonyl group in **1** is assumed to produce formaldehyde and an alkoxide intermediate (**4a**). This intermediate is subsequently converted into **4** by loss of oxygen (as a surface oxide group) with concurrent elim-

SCHEME II



(3) Part I: L. H. Klemm, J. Shabtai, and D. R. Taylor, *J. Org. Chem.*, **33**, 1480 (1968).

(4) Part III: J. Shabtai, L. H. Klemm, and D. R. Taylor, *ibid.*, **33**, 1494 (1968).

(5) Part IV: L. H. Klemm, C. E. Klopfenstein, and J. Shabtai, *ibid.*, **35**, 1069 (1970).

(6) H. Pines and W. O. Haag, *J. Amer. Chem. Soc.*, **82**, 2471 (1960).

(7) R. C. Greenler, *J. Chem. Phys.*, **37**, 2094 (1962).

(8) R. O. Kagel, *J. Phys. Chem.*, **71**, 844 (1967).

(9) E. Briner, W. Plüss, and H. Paillard, *Helv. Chim. Acta*, **7**, 1046 (1924); K. V. Topchieva and A. P. Ballod, *Dokl. Akad. Nauk. SSSR*, **75**, 247 (1950).

(10) For simplicity, two-dimensional drawings (rather than three-dimensional ones presented previously[5]) are used in this paper.

ination of a proton at C-2.[11] Alternatively, hydride transfer from a methoxide group to the carbonyl group may occur indirectly *via* a surface aluminum hydride[12-14] (*cf.* Scheme I). It seems likely that surface formate is also produced[7,8] in the reaction, though no test for its presence was made.

The mechanism in Scheme II is similar to that proposed[15] for the Meerwein–Ponndorf–Verley reduction of ketones in the presence of aluminum alkoxides (*e.g.*, ethoxide and isopropoxide).[16] Although it appears that aluminum methoxide has not been used as a reducing agent in solution, it is presumed that surface aluminum methoxide can function as such an agent under the experimental conditions employed in this study. It is observed, however, that with the alumina–methanol system the reduction product is an alkene, rather than a carbinol. Indeed, alkenes have been reported as major products of Meerwein–Ponndorf–Verley reductions in solution at elevated temperature.[16]

The formation of the other major product in expt 1–5, *i.e.*, 2-methyl-3,4-dihydronaphthalene (**5**), could involve initial removal of a proton from **1** at C-2, followed by methylation at this position, and subsequent reduction as in Scheme II. Facile methylation of 1-tetralone at the 2 position is consistent with calculated superdelocalizabilities for electrophilic attack on the anion derived from **1** (Chart I, parameters[17] $h_{(O)} = 1.0$, $k_{(C=O)} = 1.0$). The calculated S_r values for the anion indicate the possibility of more facile electrophilic attack at C-2 than at the oxygen.

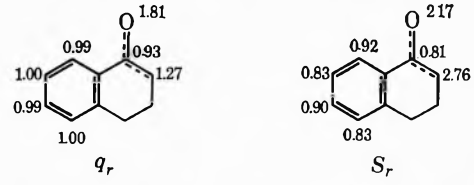
The formation of 1,2-dihydronaphthalene (**4**) as the main product in expt 1 (91 mol % on converted **1**) indicates that under conditions of very low acidity (catalyst D, 220°) methylation at C-2 is negligible, whereas reduction of the carbonyl group proceeds readily. The sharply increased yield of 2-methyl-3,4-dihydronaphthalene (**5**) in expt 3 and 4, however, indicates that in the presence of moderate acidity (catalyst C, 250–275°) methylation at C-2 commonly precedes the oxygen-eliminating step (*i.e.*, reduction). Support for such a sequence was obtained in a separate experiment (with a 1:10 by weight solution of **4** in methanol as starting material) which showed that **4** is not methylated under the conditions of expt 3. The previously observed conversion[2] of 1-oxo-4,4-dimethyl-1,4-dihydronaphthalene into 1,1,3-trimethyl-1,2-dihydronaphthalene by means of either C or D at 320° also involves ring methylation prior to oxygen elimination. The observed changes in the relative yields of **4** and **5** with a change in catalyst acidity could be explained by the effect of the acidic site on the position of bond cleavage in surface methoxide groups. For a strong acidic site the electron-withdrawing effect of the aluminum ion causes extensive polarization of the O–CH_3 bond and facilitates release of the electrophilic methylating species. For a weak acidic site, on the other hand, the polarization of the O–CH_3 bond should be relatively unimportant and ready transfer of hydride (see Scheme II) could occur in a cyclic process analogous to that envisaged in the Meerwein–Ponndorf–Verley reduction.[15] Accordingly, it is suggested that formation of **4** involves only catalysis by weak acidic sites, while that of **5** requires both weak and strong acidic sites. The relative yields of **4** and **5** would, therefore, depend on the distribution of weak and strong acidic sites in the catalysts used. Whereas weak acidic sites are present in all three catalysts, the concentration of strong acidic sites increases in the order A > C > D (where D has very few such sites, particularly at low temperature).[6]

Under conditions of both strong catalyst acidity and higher temperature (catalyst A, 350°) the reaction product (expt 6) contains, in addition to **4** and **5**, significant amounts of 1,2-dimethyl-3,4-dihydronaphthalene (**6**), 2-methylnaphthalene (**7**), and 1,2-dimethylnaphthalene (**8**). The formation of dimethyl products may be attributed to the presence of very strong acidic sites,[5] which will foster dimethylation of 1-tetralone at C-2 and (along with available weak acidic sites) will effect subsequent reduction–rearrangement. The formation of methylnaphthalenes, on the other hand, may be attributed to the effects of elevated temperature *per se* in fostering catalyzed dehydroaromatization of intermediates (*vide infra*, reactions of 2,2-dimethyl-1-tetralone).

The reaction of **1** under the conditions of expt 1 or 5 could be conveniently employed for the practical syn-

CHART I

MOLECULAR DIAGRAMS OF 1-TETRALONE ANION. π-ELECTRON DENSITIES (q_r) AND SUPERDELOCALIZABILITIES FOR ELECTROPHILIC ATTACK (S_r, IN UNITS OF β_0^{-1})



q_r S_r

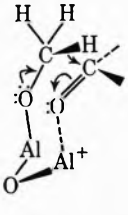
(11) For a stereochemical representation of such process in a similar ease, see ref 5, Figure 2.

(12) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 23–26.

(13) A surface aluminum hydride is probably more nearly like an $(RO)_3AlH^-$ ion than an AlH_4^- ion. See H. C. Brown and H. R. Deck [*J. Amer. Chem. Soc.*, **87**, 5620 (1965)] for reduction of ketones by these species.

(14) Molecular hydrogen formed in the system (as, for example, *via* Scheme I) could remain available for reduction by dissociative chemisorption on the catalyst. *Cf.* H. Pines and J. Ravoire, *J. Phys. Chem.*, **65**, 1859 (1961); M. J. D. Low and E. S. Argano, *ibid.*, **70**, 3115 (1966).

(15) J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, Inc., New York, N. Y., 1965, pp 456, 457; B. J. Yager and C. K. Hancock, *J. Org. Chem.*, **30**, 1174 (1965), and references cited therein. It might be noted that Scheme II depicts hydride transfer by means of a pseudocyclic eight-membered transition state involving two neighboring surface aluminum ions rather than by means of a six-membered cyclic transition state involving one coordinately bonded aluminum (as proposed for the Meerwein–Ponndorf–Verley reaction). While the latter type of transition state is not excluded for at least some surface sites, the stereochemistry of the alumina surface would seem to foster preferential formation of the former one, as indicated below. For a proposal on coordination of the



aluminum atom in a "melt" of aluminum isopropoxide, see V. J. Shiner and D. Whittaker, *J. Amer. Chem. Soc.*, **91**, 394 (1969); I. J. Worrall, *J. Chem. Educ.*, **46**, 510 (1969).

(16) A. L. Wilds, *Org. Reactions*, **2**, 178 (1944). NOTE ADDED IN PROOF.—D. V. Ramana and C. N. Pillai [*Can. J. Chem.*, **47**, 3705 (1960)] have recently described such reductions by alcohols and alumina.

(17) A. Streitwieser, "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, Inc., New York, N. Y., 1961, pp 123, 135. The parametric set for the anion derived from 1-tetralone takes into account the expected decrease in the Coulomb integral which accompanies the increase in negative charge, but the S_r values calculated from this set do not include the effects of n electrons on the oxygen atom.

TABLE II

ALUMINA-CATALYZED REACTIONS OF 2,2-DIMETHYL-1-TETRALONE (2) WITH METHANOL[a]

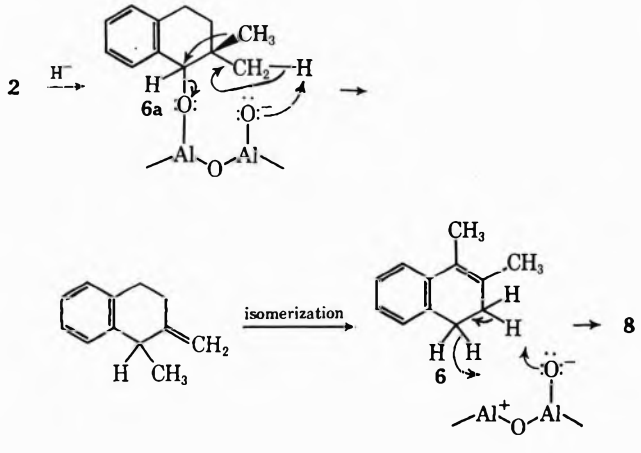
Expt no.	7	8	9	10	11
Catalyst	A	A	C	C	C
Reaction temp, °C	325	420	325	375	420
Conversion of 2, mol %	87	100	68	89	100
Product component,[b] mol %					
2-Methyl-3,4-dihydronaphthalene (5)	1.6	0.3	42.7	15.2	12.5
1,2-Dimethyl-3,4-dihydronaphthalene (6)	50.7	7.8	8.3	9.0	9.1
2-Methylnaphthalene (7)	1.2	5.0	10.2	40.3	37.5
1,2-Dimethylnaphthalene (8)	30.5	80.1	3.4	19.5	37.7
Unidentified[c]	(1.2)	(4.5)	(1.0)	(1.6)	(2.1)

[a] Total quantities of 1.74 g (0.01 mol) of 2 and 17.5 g (0.55 mol) of methanol were used as starting materials in each experiment. [b] See footnote *b*, Table I, but for starting 2 (rather than for 1). [c] Percentage by weight of total product.

thesis of 1,2-dihydronaphthalene or of 2-methyl-3,4-dihydronaphthalene, respectively. A decrease in the rate of addition of influent or an increase in the amount of catalyst (under conditions otherwise identical with those in expt 1) should improve the total conversion of 1. It is presumed that these conditions would also be applicable to the syntheses of homologs of 4 and 5 with substituents in the aromatic ring.

Reactions of 2,2-Dimethyl-1-tetralone (2).—As seen from Table II, 1,2-dimethyl-3,4-dihydronaphthalene (6) and 1,2-dimethylnaphthalene (8) are the main products formed by reaction of 2 in the presence of methanol at 325° over catalyst A (expt 7). When the temperature is increased to 420° (expt 8) there is a sharp increase in the yield of 8 and a corresponding decrease in the yield of 6. These results indicate that with A, 2 undergoes initial reduction–rearrangement to give 6, which is subsequently dehydrogenated to 1,2-dimethylnaphthalene to an extent largely dependent on temperature. A similar dehydrogenation step probably serves to convert 2-methyl-3,4-dihydronaphthalene (5) into 2-methylnaphthalene (7). Transformation of 2 into 8 (*via* the alkoxide intermediate 6a and the dihydronaphthalene 6) is depicted in Scheme III.

SCHEME III



Rearrangement of 6a may involve γ-participation (as shown) in a manner similar to that proposed by Sanderson and Mosher[18] for base-catalyzed dehydration of neopentyl alcohol, with bromoform in aqueous potassium hydroxide, to give 2-methyl-1-butene as principal product. It has been noted that γ participation is unlikely to occur in acid-catalyzed reactions in solution but may occur readily in the dehydration of neopentyl alcohol with sodium-containing alumina or with alumina treated with piperidine.[19]

With catalyst C (expt 9–11) two temperature-dependent processes are apparent in the reaction of 2. One is the aforementioned dehydroaromatization process, which becomes increasingly important as the temperature is raised (*cf.* total yield of 7 plus 8 with that of 5 plus 6 in each of the experiments). The other is loss of one of the geminal methyl groups, as indicated by the formation of 5 and 7. In contrast to the dehydrogenation case, however, the relative extent of reduction–demethylation *vs.* reduction–rearrangement decreases with increase in temperature (*cf.* total yield of 5 plus 7 with that of 6 plus 8). It is presumed that the latter temperature effect really operates through a change in the acidity of catalyst C (which increases with temperature in the range studied). Lending credence to this presumption is the fact that the strong acidic catalyst A fosters reduction–rearrangement (2 → 6 and 8), with very little attendant demethylation (*cf.* expt 7 and 9; 8 and 11). As noted before, it is believed that reduction–rearrangement occurs on (and presumably requires) a very strong acidic site (to which the substrate is bonded; *cf.* 6a, Scheme III). In the absence of a large concentration of strong acidic sites, the alternative process of reduction–demethylation becomes important. Such reaction may involve initial demethylation of 2 to 2-methyl-1-tetralone, followed by reduction (as in Scheme II).

Reactions of 2,2,4,7-Tetramethyl-1-tetralone (3).—As seen from Table III, compound 3 undergoes aromatization at 420° over catalyst A (expt 14) to give 1,2,4,7-tetramethylnaphthalene (10) in nearly 90% yield. A small amount of the expected precursor, 1,2,4,7-tetramethyl-3,4-dihydronaphthalene (9), is also formed. As temperature is decreased the yield of 10 decreases whereas that of 9 increases. The ratio of 9 to 10, however, is considerably lower than that of 6 to 8 under identical conditions (Table II, expt 7, 8). This would indicate that 9 undergoes dehydrogenation faster than 6, probably as a result of the presence in 9 of a methyl substituent at C-4, which facilitates the loss of a hydride ion from this position (*cf.* conversion of 6 to 8 in Scheme III). It might be noted in this regard that methyl substituents enhance the rate of aromatization of hydroaromatic hydrocarbons with chromia–

(18) W. A. Sanderson and H. S. Mosher, *J. Amer. Chem. Soc.*, 83, 5033 (1961). For consideration of alternative mechanisms for the rearrangement process, see the preceding paper.[5]

(19) H. Pines and J. Manassen, *Advan. Catal.*, 16, 49 (1966).

TABLE III
ALUMINA-CATALYZED REACTIONS OF 2,2,4,7-TETRAMETHYL-1-TETRALONE (3) WITH METHANOL[a]

Expt no.	12	13	14
Catalyst	A	A	A
Reaction temp, °C	325	375	420
Conversion of 3, mol %	93	96	100
Product component,[b] mol %			
1,2,4,7-Tetramethyl-3,4-dihydronaphthalene (9)	26.5	10.4	4.9
1,2,4,7-Tetramethylnaphthalene (10)	58.0	76.2	89.3
1,3,6-Trimethylnaphthalene (11)[c]	6.2	5.9	4.0
Unidentified[d]	(1.1)	(1.5)	(1.3)

[a] The starting mixture used in each experiment consisted of 2 g (0.01 mol) of 3 and 20 g (0.63 mol) of methanol. [b] See footnote *b*, Table I, but for starting 3 (rather than for 1). [c] Tentative structure, based on gas chromtographic behavior and mechanistic considerations only. [d] Percentage by weight of total product.

alumina catalysts.[20] Limited reduction–demethylation to a trimethylnaphthalene, probably **11**, is again found.

Experimental Section

Apparatus, Materials, and Procedure.—The apparatus and experimental procedure were essentially the same as previously used.[2-5] For each run 50 g of fresh alumina catalyst was employed in the form of a bed 25 cm long and situated in the isothermal section of the furnace. Catalysts A (from aluminum isopropoxide), C (Houdry hard alumina), and D (from sodium aluminate) were the same as used in previous studies.[2,5] The influent consisted of a solution of **1**, **2**, or **3** (0.02 mol) in methanol (1 mol) and was introduced into the reactor at a uniform rate (total addition time 1 hr 40 min) in a stream of nitrogen. Products were processed and analyzed as before.[3] Ultraviolet spectra were measured by means of a Cary Model 15 spectrophotometer. The nmr spectrum of **4** was measured with a Varian Associates HA-100 spectrometer.

Identification of Reaction Products.—2-Methylnaphthalene (**7**), 1,2-dimethylnaphthalene (**8**), and 1,2,4,7-tetramethylnaphthalene (**10**) were identified by comparison of infrared and nmr spectra, as well as vpc retention volumes, with those of authentic samples.[3] A minor product from **3** (Table III) was tentatively assigned the structure of 1,3,6-trimethylnaphthalene on the basis of gas chromatographic behavior on a Bentone-34 column.[21]

1,2-Dihydronaphthalene (**4**) was isolated in >99% purity by repeated vpc of products from expt 1, 2, and 6: bp 215–216° (760 mm) by micromethod;[22] n^{25}D 1.5716 (lit.[23] bp 84–85° (12 mm); $n^{18.2}$D 1.5832); uv max (95% EtOH) 258 mμ (ε 9590) and 264 (shoulder, 8960); ir (CS_2) 694 (*cis* CH=CH), 749, 785, 2840, 2895, 2950, and 3050 cm^{-1}; ir ($CHCl_3$) 1439, 1451, 1483, and 1640 cm^{-1} (C=C stretching); nmr (CCl_4) δ 6.7–7.3 (m, 4, aromatic protons at C-5 to C-8), ABC_2D_2 system (listed in order of decreasing δ values, where A = H-1, B = H-2, C = H-4, and D = H-3) 6.42 and 6.32 (d of t, 1, J_{AB} = 9.3 Hz, J_{AD} = 1.8 Hz, CH=CHCH$_2$), 5.90 (overlapping d of t, 1, J_{BD} = 4.3 Hz, CH=CHCH$_2$), 2.73 (unsymmetrical, partially split t, 2, J_{CD} = 8.3 Hz, protons at C-4), and 2.24 (m, 2, protons at C-3).

The absorption which is due to the C–H out-of-plane bending of the four vicinal aromatic hydrogens in **4** shows a characteristic splitting (bands at 749 and 785 cm^{-1}). A similar splitting is observed in the spectrum of 1,1,3-trimethyl-1,2-dihydronaphthalene[2] and in the spectra of 1,2,3,4-tetrahydronaphthalenes, which possess an unsubstituted aromatic ring.[24] The two sharp bands observed at 1451 and 1483 cm^{-1} could be tentatively assigned to the scissoring deformations of the two methylene groups in the hydroaromatic ring of **4**.[25]

2-Methyl-3,4-dihydronaphthalene (**5**) was isolated in >99% purity from the products of expt 6 and 7: bp 227–228° (760 mm) by micromethod; n^{25}D 1.5721 (lit.[23] bp 63–65° (0.6 mm); n^{20}D 1.5751); uv max (95% EtOH) 262 mμ (ε 12,000) and 268 (11,700); ir (CS_2) 726, 753, 842, 1653 (C=C stretching), 2830, 2880, 2930, and 3030 cm^{-1}; ir ($CHCl_3$) 1438 and 1485 cm^{-1}; nmr (CCl_4) δ 6.7–7.4 (m, 4, aromatic protons at C-5 to C-8), 6.14 (broad s, 1, CH=), A_2B_2 system 2.74 and 2.14 (two t, 2 each, J_{AB} = 8.0 Hz, CH$_2$ at C-4 and C-3, respectively), and 1.85 (s, 3, CH$_3$ at C-2).

Anal.[26] Calcd for $C_{11}H_{12}$: C, 91.61; H, 8.39. Found: C, 91.92; H, 8.54.

Compared with the uv absorption of **4**, the maxima shown by **5** at 262 and 268 mμ are better resolved and shifted bathochromically by *ca.* 4 mμ. This shift is consistent with the presence of the methyl group on the conjugated system. The splitting of the aromatic C–H out-of-plane bending signal is less symmetrical (strong band at 753 cm^{-1}, weak band at 726 cm^{-1}) compared with that of **4**. A sharp band at 842 cm^{-1} can be assigned to out-of-plane bending of the C–H at the trisubstituted double bond.[27a] The position of the C=C stretching band (1653 cm^{-1}) fits the anticipated one for a trisubstituted double bond (*ca.* 1670 cm^{-1}) with a shift to lower frequency of 17 cm^{-1} owing to conjugation with the benzenoid ring.[27b]

1,2-Dimethyl-3,4-dihydronaphthalene (**6**) was isolated in >99% purity from the products of expt 6 and 7: bp 245–246° (760 mm) by micromethod; n^{25}D 1.5750; uv max (95% EtOH) 263 mμ (ε 11,400) and 268 (11,300); ir (CS_2) 733, 760, 2835, 2885, and 2940 cm^{-1}; ir ($CHCl_3$) 1041, 1386, 1430, 1441, 1453, 1490, 1602, and 1645 cm^{-1} (C=C stretching); nmr (CCl_4) δ 6.8–7.3 (m, 4, aromatic protons at C-5 to C-8), A_2B_2 system 2.65 (t, 2, J_{AB} = 8.0 Hz, CH$_2$ at C-4), 2.13 (t partially overlapped by methyl signal, 2, CH$_2$ at C-3), 1.97 (s, 3, CH$_3$ at C-1), and 1.86 (s, 3, CH$_3$ at C-2).

Anal.[26] Calcd for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found: C, 90.90; H, 8.64.

As in the parent compound **4**, the aromatic C–H out-of-plane bending signal for **6** appears as a well-resolved doublet (strong bands at 733 and 760 cm^{-1}). The position of the C=C stretching band (1645 cm^{-1}) is normal for a conjugated, tetrasubstituted double bond.[27b]

An enriched (95% pure) sample of 1,2,4,7-tetramethyl-3,4-dihydronaphthalene (**9**) was obtained by vpc of the product from expt 12: uv max (95% EtOH) 263 mμ (ε 11,400) and 269 (11,300); ir ($CHCl_3$) 1648 cm^{-1} (C=C stretching, conjugated, tetrasubstituted double bond).[27b] The relative positions of the methyl substituents in **9** were confirmed by aromatization to 1,2,4,7-tetramethylnaphthalene (*vide infra*).

Aromatization of 4, 5, 6, and 9.—According to a standard procedure,[28] a solution of **4**, **5**, **6**, or **9** (1 mmol) and 0.5 g (2.2 mmol) of 2,3-dichloro-5,6-dicyanobenzoquinone in 50 ml of dry benzene was refluxed for 5 hr. The reaction mixture was diluted with petroleum ether (bp 30–60°), filtered, and chromatographed on Woelm neutral alumina with petroleum ether–benzene (1:1 by volume). The product was recovered by evaporation of the solvent. Compounds **4**, **5**, **6**, and **9** gave naphthalene, 2-methylnaphthalene, 1,2-dimethylnaphthalene, and 1,2,4,7-tetramethylnaphthalene, respectively, in 90–94% yields. The products were shown to be isomerically pure by vpc and infrared analysis.

Registry No.—**1**, 529-34-0; **2**, 2977-45-9; **3**, 23230-33-3; **4**, 447-53-0; **5**, 2717-44-4; **6**, 5195-39-1; methanol, 67-56-1.

Acknowledgment.—The authors wish to thank Dr. C. E. Klopfenstein for calculation of the Hückel molecular orbital reactivity indices in Chart I.

(20) A. A. Draeger, G. T. Gwin, and C. J. G. Leesemann in "Science of Petroleum," Vol. V, Part II, Oxford University Press, London, 1953, p 266.

(21) L. H. Klemm, J. Shabtai, and K. C. Bodily, unpublished results.

(22) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, John Wiley & Sons, Inc., New York, N. Y., 1967, pp 37, 38.

(23) "Dictionary of Organic Compounds," Vol. 2, Oxford University Press, New York, N. Y., 1965, p 1040. The reported value ($n^{18.2}$D 1.58317) for **4** seems to refer to an impure sample. *Cf.* F. Straus and L. Lemmel, *Chem. Ber.*, **54**, 25 (1921).

(24) "Sadtler Standard Infrared Spectra Catalog," Spectra No. 8215, 8217, 8219, 8221.

(25) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Inc., Boston, Mass., 1966, p 94.

(26) Analyzed by Micro-Tech Laboratories, Skokie, Ill.

(27) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Methuen and Co., Ltd., London, 1962: (a) pp 51, 52; (b) pp 34–41.

(28) E. A. Braude, L. M. Jackman, R. P. Linstead, and G. Lowe, *J. Chem. Soc.*, 3123 (1960).

Conformational Equilibria and Stereochemical Relationships among Carboxylic Acids[1]

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Received August 18, 1969

The circular dichroism spectra of certain acyclic carboxylic acids have been surveyed in an effort to study their conformation in solution. In aqueous solution the spectra of many α-hydroxy acids were characterized by two overlapping ellipticity bands: a weak one in the 240-mμ spectral region and a more intense one of opposite sign near 210 mμ. At elevated temperatures or in solvents of low dielectric constant, the band of longer wavelength increased in intensity with an attendant decrease in the short-wavelength band. These properties are compatible with the presence of two structural species in equilibrium, and could be related to the contributions of specific rotational isomers of the acids. Conformations with the hydroxyl and carbonyl groups in an eclipsed alignment are designated as preferred. In contrast to the α-hydroxy acids, carboxylic acids with α-alkyl substituents generally showed only a single dichroic band centered near 210 mμ. In general, coplanarity of the carboxyl group and α substituents has been assumed, and interpretations in terms of the preferred orientation of substituents adjacent to the carboxyl group are suggested. The proposed population of rotational isomers was consistent with the observed effects of solvent polarity, temperature, polarity of substituents, and predicted steric interactions. An empirical rule relating the sign of ellipticity and the conformation of these classes of carboxylic acids has been applied.

Studies using simple α-hydroxy acids such as lactic, malic, and tartaric acid led to some of the early theories of optical activity[3] and to assignments of absolute configurations for a variety of compounds. Recently, a number of investigators have reexamined the optical rotatory dispersion (ORD) and circular dichroism (CD) spectra of these compounds, and extended the measurements into the ultraviolet to include the region of absorption of the carboxyl group.[4-11] Although the carboxy sector rule[12] was shown to be suitable for the prediction of preferred alignments of many acids and esters of known conformations accompanied by restricted rotational possibilities,[13-16] other attempts to correlate ORD and CD data with conformational aspects of carboxylic acids have been confined mainly to studies of carboxyl groups in more rigid systems such as lactones.[12,17-19] For acylic carboxylic acids in solution, conformational assignments were considered to be difficult because of the rotation about the single bond between the carboxyl group and adjacent carbon atom.[20]

More recent studies have, however, uncovered some fine points in the CD spectra of carboxylic acids that are potentially useful for conformational analysis. We have shown that uronic acid derivatives with equatorial substituents at C-4 of the pyranose ring exhibit two overlapping CD bands which originate from the $n \rightarrow \pi^*$ transition of the carboxyl group.[21] We interpreted these results to indicate an equilibrium between two structural forms, but we were unable to distinguish between conformational and solvational effects. We also noted that overlapping bands are frequently encountered in the CD spectra of other carboxylic acids.[21] ORD and CD spectra of lactic acid and related compounds have been reported in numerous[4-10] studies, but Anand and Hargreaves[22] were the first to report the presence of two bands. The weak, longer wavelength band near 245 mμ was assigned to an $n \rightarrow \pi^*$ transition, and the more intense, shorter wavelength band was ascribed to the $\pi \rightarrow \pi^*$ transition. More recently, Barth, *et al.*,[23] have shown this same spectral aspect for some derivatives of lactic acid but attributed both bands to the $n \rightarrow \pi^*$ transition.

Because the electronic transitions are relatively fast compared with the rate of molecular motion, CD offers some inherent advantages over other commonly used methods such as nmr to resolve and study rapidly interconverting rotational isomers in solution. In the present report, the CD spectra of a wide variety of carboxylic acids of known absolute configuration were examined to determine conformational relationships. The effects of solvent, temperature, and pH were studied in order to elucidate underlying factors that define the two-band systems. Some of the structural features common to all compounds eliciting a double ellipticity band have been revealed and the results are explained on the basis of equilibria between rotational isomers about the sp^3–sp^2 carbon–carbon bond of these acids.

Results

The data presented in Table I summarize the position, magnitude, and sign of the ellipticity bands of selected

(1) Supported by Grants HE-11511 and GM-04428 from the National Institutes of Health and Grant GB 6053 from the National Science Foundation.

(2) Senior Investigator, New York Heart Association.

(3) T. M. Lowry, "Optical Rotatory Power," Longmans, Green and Co., London, 1935, Chapter 23.

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TABLE I

CIRCULAR DICHROISM OF SOME α-HYDROXY ACIDS AND RELATED COMPOUNDS IN AQUEOUS SOLUTION

Compd	Registry no.	Ellipticity maxima and minima: pH 2.5 λ_1	pH 2.5 $[\theta]_{\lambda_1}$	pH 2.5 λ_2	pH 2.5 $[\theta]_{\lambda_2}$	pH 7.0 λ	pH 7.0 $[\theta]_{\lambda}$
L-(−)-Malic acid	97-67-6	246	−7	211	3100	207	6300
L-(+)-Lactic acid	79-33-4	244	−18	210	2900	215	700
L-(+)-α-Hydroxyisocaproic acid	13748-90-8	241	−21	208	4900	204	2200
L-(−)-α-Hydroxy-β-methylvaleric acid	23264-19-9	239	−65	208	3500	*b*	*b*
L-(+)-*erythro*-2,3-Dihydroxybutyric acid	23334-72-7	241	−82	209	3700	202	1200
L-(+)-2,4-Dihydroxy-3,3-dimethylbutyric acid[a]	1112-32-9	240	−70	210	2700	*b*	*b*
L-(−)-2-Ethoxysuccinic acid[a]	23264-21-3	245	−50	212	2700	210	7700
Dimethyl L-(−)-malate[c]	617-55-0	242	−21	211	2600	...	...
Ethyl L-(+)-lactate[c]	7699-00-5	238	−48	208	4200	...	...
L-(−)-Chlorosuccinic acid	4198-33-8	222	−2000	200	1700	240	−130
						201	7900

[a] Measurements were made on the enantiomers. [b] Multiple overlapping bands were observed for these compounds at neutral pH. [c] Measurements were made at pH 2.5 and 7.0.

TABLE II

CIRCULAR DICHROISM OF SOME CARBOXYLIC ACIDS EXHIBITING A SINGLE ELLIPTICITY BAND ABOVE 200 mμ

Compd	Registry no.	pH 2.5 λ	pH 2.5 [θ]	pH 7.0 λ	pH 7.0 [θ]
L-(+)-2-Methylbutyric acid	1730-91-2	210	650	195	−1700[a]
D-(+)-Ethylsuccinic acid	4074-24-2	207	3100	208[b]	−2300
D-(+)-Butylsuccinic acid	4254-59-5	207	3200	209[b]	−2600
D-(+)-Isopropylsuccinic acid	1187-70-8	207	3600	209[b]	−2600
D-(+)-Cyclohexylsuccinic acid	3975-92-6	209	5300	206[b]	−2400
D-(+)-Monodeuteriosuccinic acid	10013-03-3	208	150	213[b]	98
D-(−)-Isopropylglutaric acid	3972-39-2	210	2800	...	...

[a] No ellipticity extrema were observed. [b] These bands were very broad and the locations of the extrema are approximate.

α-hydroxy acids and related compounds in aqueous solution. At pH 2.5 the optically active absorption band near 210 mμ is common to all of the α-hydroxy acids; this band previously has been attributed to the n → π* transition of the carboxyl group.[21,22] In addition, at longer wavelengths, most of the acids also exhibit another ellipticity band of opposite sign and low intensity. The magnitudes of both dichroic bands are independent of concentration (from 0.001 to 1.0 *M* of acid) and the CD spectra have similar band shapes and energies. For the α-hydroxy acids, the intensity of the 210-mμ band always exceeded that of the long wavelength band by a factor of 30–450. Large background rotations obscured the long-wavelength Cotton effects thus to be expected in the ORD curves of these compounds. Also bands corresponding to these are not easily resolved in their ultraviolet absorption spectra, so that only weak bands near 205 mμ ($\epsilon \cong 60$, per carboxyl group),[24] with no obvious vibrational fine structure, are observed in aqueous solution. Because of their opposite signs, however, the two bands are clearly defined in CD spectra.

The CD of carboxylic acids with α-alkyl substituents in place of the hydroxyl groups are shown in Table II. A single ellipticity band near 210 mμ characterizes the CD spectra of these compounds, and in these instances no longer wavelength band is discernible. The differences in the rotational strengths among these compounds, especially the alkyl succinic acids, are consistent with the observations using ORD.[5] It is also significant that the signs of the 210-mμ ellipticity bands of the alkyl succinic acids in the D configuration are the same as those of the corresponding hydroxy, ethoxy, and chlorosuccinic acids in the L configuration.

(24) W. D. Closson, P. J. Orenski, and B. M. Goldschmidt, *J. Org. Chem.*, **32**, 3160 (1967).

Ionization of the carboxyl group induces substantial modifications in the ellipticity associated with it. Thus the ionization of the α-hydroxy acids generally results in the disappearance of the longer wavelength band (Table I). In addition, the sign of the ellipticity of most of the α-alkyl acids is inverted by the ionization of the carboxyl group (Table II). In contrast with the results obtained for the protonated forms, substituted succinic acids in the ionized form all display ellipticities of the same order of magnitude. Ionization of these compounds may be conveniently monitored by CD, and typical titration curves are shown in Figure 1. The known pK values of ethylsuccinic acid (pK_1 = 4.0, pK_2 = 5.7) and 2-methylbutyric acid (pK_1 = 4.8) correspond to the observed inflections in the curves. An intramolecular hydrogen bond has been postulated previously for the monoanion of substituted succinic acids,[25,26] and in this context the major CD changes accompany the ionization of the second carboxyl group.

Kresheck[27] has recently ascribed the change in sign of the CD band accompanying the ionization of ascorbic acid to conformational changes. Such an explanation, however, cannot be applied for the CD changes induced by the ionization of the carboxyl group of the compounds in the present study. The ionized carboxyl group is inherently different from, and more symmetrical than, the protonated form. Changes in characteristics and sign of the ellipticity bands are not unexpected, since the entire asymmetric system is altered.

The effect of solvent on the CD of these compounds may be seen from the spectra shown in Figure 2. The same pattern was observed for most of the other α-hy-

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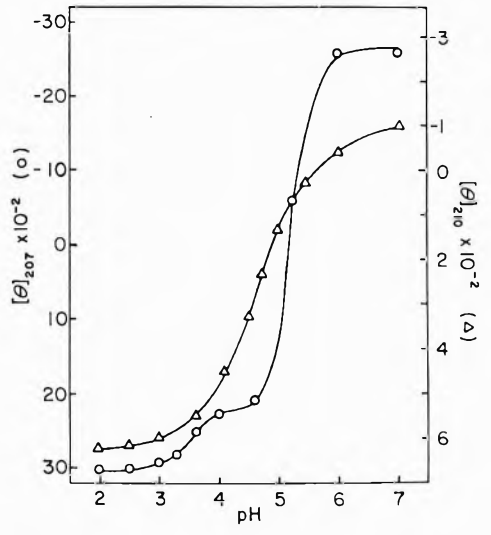

Figure 1.—Titration curves for D-ethylsuccinic acid (○) and L-2-methylbutyric acid (△). Measurements were made at the wavelength of maximum ellipticity of the acids at pH 2.0.

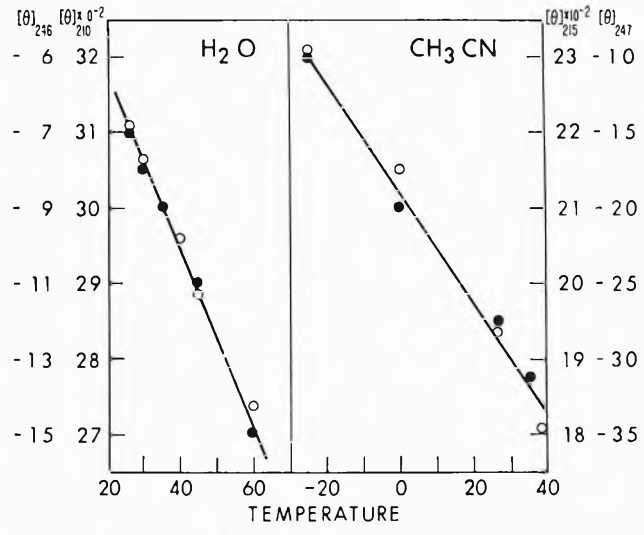

Figure 3.—Temperature-dependence studies; molar ellipticities of L-malic acid in water and acetonitrile. The open circles represent the longer wavelength band and the dark circles represent the short-wavelength band in both solvents.

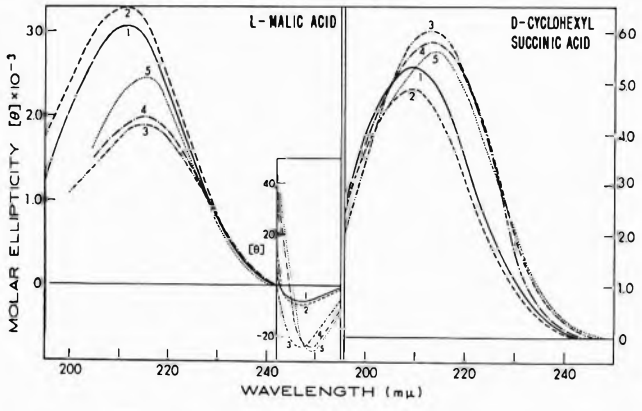

Figure 2.—Circular dichroism spectra of L-malic acid and D-cyclohexylsuccinic acid in various solvents. The solvents indicated are: 1, water, 2, trifluoroethanol; 3, acetonitrile; 4, heptane–dioxane (4:1); 5, dioxane.

droxy acids and esters and α-alkyl acids studied, and the representative compounds shown were selected to illustrate the types of effects observed. In general, an increase in the ratio of the long-wavelength ellipticity magnitude compared with that of the short-wavelength ellipticity is observed for the α-hydroxy acids in the nonaqueous solvents. The solvent effect is more pronounced for the α-ethoxy acid (not shown) and these effects are similar to, but not of comparable magnitude with, those observed previously for the uronic acids.[21] The red shift of the 210-mμ CD band in aprotic solvents is characteristic of an n → π* transition.[28,29] CD is not as reliable as ultraviolet absorption spectra to define these frequency shifts, however, since overlapping bands of opposite sign often distort the spectra. For these carboxylic acids it is likely that a π → π* transition overlaps the shorter wavelength end.[30] Indeed, the beginning of an intense negative band below 190 mμ has been observed in the CD spectrum of L-(+)-lactic acid in water, and some residual ellipticity above 210 mμ is obtained in concentrated H_2SO_4.

The temperature-dependence data for malic acid (Figure 3) illustrate typical effects observed with the hydroxy acids. For all of the α-hydroxy acids in Table I, an increase in temperature induces an increase in the intensity of the long-wavelength band near 240 mμ and a concomitant decrease in the band near 210 mμ, and a decrease in temperature induces the opposite effect. Similar results were obtained with lactic acid derivatives.[23] This behavior implies that the two bands are closely interrelated and are probably associated with a single electronic transition. By extrapolation of the data in Figure 3 to a zero value of the longer wavelength band, an estimated value of the intensity of the isolated short-wavelength band may be obtained. Based on the assumption that each band represents a single structural form, approximate equilibrium constants at the various temperatures were calculated and approximate ΔG°_{25} values were obtained for L-malic acid. Typical free-energy differences between the two forms (240 ⇌ 210 mμ) were $\Delta G^\circ_{25} = -1.1$ kcal/mol in water and $\Delta G^\circ_{25} = -0.8$ kcal/mol in acetonitrile. For the α-alkyl acids, the 210-mμ band generally diminishes in intensity at the higher temperatures. For example, $[\Theta]_{213}$ of D-cyclohexylsuccinic acid in acetonitrile is +7500° at −10° and +5600° at 50°.

The longer wavelength band was absent in the CD of some N-methyl-α-amino acids such as N-methyl-L-alanine ($[\Theta]_{201} = +3200°$), N-methyl-L-glutamic acid ($[\Theta]_{202} = +4500°$), and N-methyl-L-proline ($[\Theta]_{208} = +1800°$), and we were unable to detect the 248-mμ band that was previously reported for L-alanine at neutral pH.[31] Several complex α-hydroxy acids such as tartaric,[32] gluconic, and α-hydroxyglutaric acid

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(30) S. Nagakura, K. Kaya, and H. Tsubomura, *J. Mol. Spectrosc.*, **13**, 1 (1964).
(31) R. D. Anand and M. K. Hargreaves, *Chem. Ind.* (London), 880 (1968).
(32) The CD spectrum of the ionized form of tartaric acid was characterized by two bands of the same sign at 210 and 193 mμ.

were atypical and also showed only single bands. The structural features of these classes of compounds as well as a detailed account of the α-halo acids will be presented in future reports. It may be noted that 3-methyladipic acid, because its asymmetric center is removed from the direct proximity of the carboxyl chromophore, exhibits a weak ellipticity band ($[\theta]_{209}$ = +350). Also, in contrast to the great majority of α-hydroxy acids studied, β-hydroxybutyric acid exhibited a single CD band at 210 mμ.

Discussion

Most of the α-hydroxy mono- and dicarboxylic acids exhibited similar CD spectra with an optically active n → π* transition near 210 mμ and an additional band at longer wavelengths. It is particularly difficult to rationalize the presence of an n → π* transition for the carboxyl group at the long wavelengths of 239–246 mμ, but the overall appearance of the CD curves may be deceiving. The non-Gaussian nature and low intensity of the long-wavelength band suggest an appreciable overlap with the more intense 210-mμ band. Therefore the apparent location of this long-wavelength band most probably does not define the actual spectral region of the transition. It has been shown that the superimposition of overlapping bands of opposite sign and with maxima separated by 1–20 mμ yields a curve which appears to have two bands separated by 28–32 mμ.[33] Thus the observed frequency shifts of overlapping bands depend on their relative magnitudes and extent of overlap, but the actual frequency difference is generally much less than the observed value. For uronic acids we have shown that the energy differences between the two transitions are indeed much less than the measured values.[21] For the α-hydroxy acids, the observed spectral separations of *ca.* 35 mμ are also exaggerated, and both extrema are probably centered about the n → π* transition of the carboxyl group.

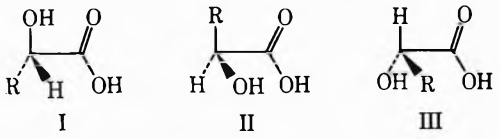
Certain possible explanations for the presence of the two overlapping CD bands may be rejected readily for the acids studied here. Monomer–dimer equilibria have often been described for carboxylic acids[34,35] and, because of the coupled transition moments, the optical activity of carboxyl groups in some cyclic systems is substantially different from that of the open-chain forms.[36,37] An interpretation based on the presence of associated forms may, however, be ruled out in the present study, since no concentration dependence was observed and the acids and esters both gave similar spectra. An intramolecular hydrogen bond between the α-hydroxyl and carbonyl group to give a five-membered ring is unfavored and furthermore need not be considered, since the α-alkoxy acids also show the two bands. In addition, it is difficult to rationalize the results in terms of hydrogen bonding to solvents or an equilibrium between solvated and hypothetical non-solvated forms.[38] If the long-wavelength band of the α-hydroxy acids is indeed a result of the presence of a nonsolvated species, the α-alkyl acids would also be expected to exhibit this long-wavelength band in hydrocarbon or nonpolar solvents. This effect, however, was not observed, and indeed the entire concept of a nonsolvated form has recently been considered to be unsatisfactory as an explanation of multiple CD bands.[39]

For carboxylic acids and esters, the interaction of the nonbonding electrons of the oxygen atom attached to the carbonyl group with the π orbitals of the carbonyl has been postulated to raise the energy of the antibonding π* orbital and cause the split of the bonding π orbital into two new orbitals.[40] An appreciable overlap of the lowest energy π → π* band with the n → π* band is reported in the present study. There are no indications, however, that the π → π* transition, or some other previously undefined transition moments, account for the long-wavelength band near 240 mμ. On the contrary, the observation that experimental conditions that induce an increase in the 240-mμ band always cause an attendant decrease in the other band suggests that both bands are associated with the same electronic transition. In all probability the latter is the n → π* transition.

The evidence presented here is entirely compatible with an established equilibrium between two structural or conformational forms of these α-hydroxy (alkoxy or halo) acids in solution. We consider an interpretation on the basis of conformation to be easily justifiable and the most reasonable. It is well known that the intensity and sign of an ellipticity band are directly contingent upon the alignment of substituents with respect to the transition dipole moment.[37,41] Since all of the acids studied have the identical carboxyl chromophore, the three-dimensional structure of the carboxyl group and its adjacent substituents must be considered in any interpretation of the CD spectra.[42] The atoms in the C_α–COOH group have been shown to be coplanar or very nearly coplanar on the basis of X-ray diffraction studies of carboxylic acids.[43] Also, staggered conformations are ordinarily favored on an energetic basis, and according to the "bent bond" or "banana type" concept of the double bond,[44] structures with α substituents eclipsing the double bond would be preferred (dihedral angles of less than 10° are generally found for these carboxylic acids[45,46]). For an α-hydroxy acid or related compound in the L configuration, a threefold barrier to rotation about the sp^3–sp^2 carbon–carbon single bond may therefore be assumed and, as a first

(33) K. M. Wellman, P. H. A. Laur, W. S. Briggs, A. Moscowitz, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 66 (1965).
(34) L. W. Reeves, *Can. J. Chem.*, **39**, 1711 (1961).
(35) J. C. Davis, Jr., and K. Pitzer, *J. Phys. Chem.*, **64**, 886 (1960).
(36) C. Toniolo, V. Perciaccante, J. Falcetta, R. Rupp, and M. Goodman, *J. Org. Chem.*, **35**, 6 (1970).
(37) D. W. Urry, *Ann. Rev. Phys. Chem.*, **19**, 477 (1968); J. A. Schellman and E. B. Nielsen, "Conformation of Biopolymers," Vol. 1, G. N. Ramachandran, Ed., Academic Press, New York, N. Y., 1967, p 109.
(38) A. Moscowitz, K. M. Wellman, and C. Djerassi, *Proc. Natl. Acad. Sci.*, U. S., **50**, 799 (1963).
(39) D. J. Severn and E. M. Kosower, *J. Amer. Chem. Soc.*, **91**, 1710 (1969).
(40) W. D. Closson and P. Haug, *ibid.*, **86**, 2384 (1964).
(41) H. Eyring, H. C. Liu, and D. Caldwell, *Chem. Rev.*, **68**, 525 (1968).
(42) The rotational isomers about the C_α–C_β bond probably do not contribute at all to the observed effects, since the energy barriers for their interconversion are larger than those for the sp^3–sp^2 bond, and even latic acid, with three equivalent isomers of this type, also gives the double band.
(43) J. H. Robertson, *Acta Crystallogr.*, **17**, 316 (1964).
(44) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," John Wiley & Sons, Inc., New York, N. Y., 1965, p 20.
(45) G. A. Bootsma and J. C. Schoone, *Acta Crystallogr.*, **22**, 522 (1967).
(46) J. A. Kanters, J. Kroon, A. F. Peerdman, and J. C. Schoone, *Tetrahedron*, **23**, 4027 (1967).

approximation, the preferred alignment of substituents about the carboxyl group may be represented as follows.



I II III

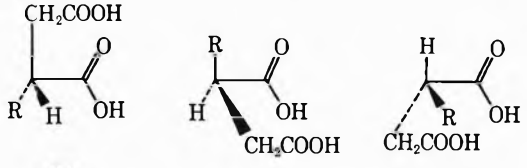
On the basis of nmr studies of α-halo aldehydes and ketones[47] and infrared spectra of α-halo esters,[48] structures with eclipsed halo substituents and carbonyls have been suggested as the preferred conformations. The present results with the α-hydroxy acids may be interpreted in terms of structure I as the favored rotational isomer, and also as the isomer responsible for the predominant CD band centered near 210 mμ. Structure III is the least favored, and it is therefore suggested that structure II generates the longer wavelength band, whereas the contribution of structure III is probably insignificant and cannot presently be assessed.

The above structural assignments of rotational isomers are consistent with the results of the temperature- and solvent-dependency studies. An increase in temperature should increase the population of the less favored isomer. This conclusion is compatible with the observed increased intensity of the longer wavelength CD band and decreased intensity of the shorter wavelength band as the temperature is increased (Figure 3). Lowering the temperature induces opposite effects. In addition, an increase in the ratio of the intensity of the shorter wavelength band, compared with the magnitude of ellipticity at the long-wavelength extremum, generally accompanies an increase in solvent polarity (Figure 2). These results, consistent with a preponderance of the more polar rotamer I in the more polar solvents, also shows that the shorter wavelength band is associated with rotamer I. Accordingly, in solvents of lower polarity, the population of rotamers II or III are increased.

Further verification of the foregoing structural interpretations may be deduced from our earlier studies of uronic acids.[21] For these compounds, adjacent substituents limit the rotational possibilities of the carboxyl group. If one assumes that structure I is the favored form for carboxylic acids of this type, the ring oxygen and carbonyl of the uronic acids would be in an eclipsed conformation. For galacturonic acid derivatives this is indeed the preponderant structure, and only a single ellipticity band was observed.[21] On the other hand, this carboxyl conformation for glucuronic and mannuronic acid derivatives gives rise to a nonbonded interaction with the adjacent equatorial hydroxyl group at C-4. It is reasonable that other conformations may prevail for the latter compounds, and indeed multiple CD bands have been observed.

The wavelength differences between the two ellipticity bands may be small, and since the electronic interactions have not been elucidated in the present study, reasons for these differences cannot be established. It has been shown, however, that the nonbonding distances between a carbonyl of a carboxylic acid and an eclipsed α-hydroxyl group is *ca.* 0.1–0.3 Å shorter than the corresponding distance between a carbonyl and alkyl substituent.[46] Conceivably, therefore, a slight overlap with a low-energy empty orbital of the hydroxyl, ethoxyl, or halo group on the α carbon stabilizes the antibonding orbital of the carbonyl, lowers the energy of the excited state, and gives the longer wavelength band. The energy levels of rotamers II and III would be degenerate if this were the case. In structure I this stabilization is also possible with the nonbonding electrons on the carbonyl and no spectral shift is expected. A similar interaction has been proposed for axial α-hydroxy, alkoxy, and halo ketones.[49,50] Although solvational effects cannot account for the gross character of the CD spectra, it is also possible that the mode of solvent binding to the chromophore may differ for these conformers and thereby account for the frequency shifts.

Rotational isomerism for carboxylic acids with α-alkyl substituents are more difficult to elucidate, as only a single CD band can be resolved for these compounds. This does not preclude the possibility that rotational isomers exist, since a wavelength shift for rotamers would not be expected if the proposed interactions with the excited states are required. Indeed, with the alkyl-substituted succininc acids an increase in intensity of the 210-mμ CD band is observed as the size of the α substituent is increased (Table II) or as the temperature is lowered. This probably indicates a greater preponderance of the favored rotational isomer as the size of the alkyl substituent is increased or the temperature lowered. Structures IV, V, and VI may



IV V VI

be considered to represent the three preferred rotamers of the D-alkylsuccinic acids; IV is the preferred isomer with VI as the least stable. As the bulkiness of the R group increases, structure V may become even less favored because of nonbonded interactions with the carbonyl group, and structure IV would thus be accommodated to an even greater extent. The increase in magnitude of ellipticity in the order R = ethyl or butyl > isopropyl > cyclohexyl is consistent with this interpretation. The energy difference between the two favored isomers of L-(+)-2-methylbutyric acid (VII and VIII) is probably not appreciable, and rapid

VII VIII

interconversion between the two forms (with a slight preference for structure VIII) may be anticipated. These two forms should contribute rotational strengths of opposite sign, and thus it is not surprising that the resultant low-intensity CD band is observed (Table II).

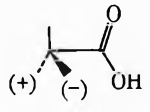
(47) G. J. Karabatsos and D. J. Fenoglio, *J. Amer. Chem. Soc.*, **91**, 1124 (1969).

(48) T. L. Brown, *Spectrochim. Acta*, **18**, 1615 (1962).

(49) R. C. Cookson and S. H. Dandegaonker, *J. Chem. Soc.*, 352 (1955).

(50) R. C. Cookson, *ibid.*, 282 (1954).

Several limitations and approximations in the approach suggested here are recognized. Thus any partial double bond character of both carbon–oxygen bonds of the carboxyl group are not taken into consideration in structures I–VIII. Also the possible deviations from the staggered conformations shown to give other rotational isomers are not considered. In addition, the optically active transitions of carboxyl groups are difficult to compare with those of the well-characterized keto groups because of the inherent electronic differences induced by the additional oxygen atom bonded directly to the carbonyl. Rigorous theoretical relationships are difficult to establish. It is significant, however, that some of the preferred conformations suggested here are consistent with the conformational assignments for analogous acids in the crystalline state.[45,46] In the assumed structures represented in I–VIII, the substituent eclipsing the double bond lies in a nodal plane of the nonbonding electrons on the carbonyl oxygen and therefore may not contribute appreciably to the observed optical activity associated with the $n \rightarrow \pi^*$ transition. On the basis of this assumption, a simple empirical rule may be proposed for the carboxylic acids (or esters) viewed as shown in the structure IX. Substituents projecting in the direction



IX

toward the viewer contribute negative ellipticity at 210 mμ and substituents projecting away contribute positive ellipticity. This hypothesis explains why the alkyl succinic acids in the D configuration and favoring conformer IV have the same 210-mμ ellipticity signs as the α-hydroxy-, alkoxy-, and halosuccinic acidsi n the L configuration, which exist mainly as rotamer I.

Experimental Section

Solvents.—The dioxane (Fisher Scientific Co.) and trifluoroethanol (Halocarbon, Inc.) were dried and distilled prior to use, and the acetonitrile and heptane (Eastman) were spectro grade and employed without further purification. The pH of each aqueous solution was adjusted by the addition of small amounts of HCl or NaOH. Identical CD spectra were obtained when low ionic strength buffers were used to adjust the pH.

Carboxylic Acids.—Samples of L-(−)-malic, L-(+)-lactic, L-(+)-α-hydroxyisocaproic, L-(+)-α-hydroxyglutaric, and L-(−)-α-hydroxy-β-methylvaleric acids were obtained from Sigma Chemical Co., 3-methyladipic acid from Aldrich, and the N-methyl amino acids from Cyclo Chemical Co. We are most grateful to Dr. A. Fredga and Dr. W. Klyne for supplying the samples of the D-(−)-ethyl-, butyl-, isopropyl-, cyclohexyl-, and ethoxysuccinic acids. We also thank Dr. A. Hayashi for the L-(+)-*erythro*-2,3 dihydroxybutyric acid, and Dr. S. Kumar for the L-(+)-β-hydroxybutyric acid.

L-(−)-Chlorosuccinic and D-(+)-monodeuteriosuccinic acids were prepared by us for earlier studies.[51,52] Pantoyl lactone (K & K Chemical Co.) was hydrolyzed to give the pantoic acid. Dimethyl L-(−)-malate (bp 240–245°, $n^{20}D$ 1.442, d^{20}_4 1.23, $[\alpha]D$ −16°) was prepared by esterification of the L-(−)-malic acid in methanol and H_2SO_4, and L-(+)-2-methylbutyric acid (bp 175°, $n^{20}D$ 1.410, d^{20}_4 0.94, $[\alpha]D$ +21°) was prepared by alkaline permanganate oxidation of L-(−)-isoamyl alcohol (Aldrich). The optical purity of each compound was checked by measurement of its $[\alpha]D$ value and comparison with values reported in the literature.

Methods.—CD measurements were made using a Cary Model 60 spectropolarimeter with a 6001 CD accessory. The instrument records the angle of ellipticity Θ in degrees, and the molecular ellipticity [Θ] was calculated using the relationship $[\Theta] = \Theta M/10lc$ (deg cm²/decimol), where M is the molecular weight, c is the concentration (g/ml), and l is the path length in centimeters. The slit width of the polarimeter was programmed to give half-band widths of less than 1.5 mμ through the entire spectral range, and all molar ellipticities were obtained using solutions with absorption values of less than 2.0. Strain-free cylindrical cells with quartz windows of 20–22 mm diameter and path lengths of 0.005, 0.02, 0.1, 1.0, and 5.0 cm were used; the shorther path length cells were employed mainly for the concentration-dependence studies and the studies in dioxane. A jacketed 1-cm cell with quartz windows of 14-mm diameter was employed for the temperature-dependence studies. All other measurements were made at 27°, the temperature of the cell compartment. Corrections for density or refractive index changes as a function of temperature were not made, since these factors were relatively small compared with changes in ellipticity.

The ellipticity values at the long-wavelength extrema were obtained from at least two independent measurements. A typical result may be represented as follows: for a 5% malic acid solution in water (Θ_{246} = −6.9 deg cm²/decimol) in a 1-cm cell, the observed ellipticity value, Θ, was 0.026°; the noise level of the instrument under these conditions was *ca.* 0.001° and the reproducibility was better than 0.002°.

Acknowledgment.—We are most grateful for the laboratory assistance of Louis Mandelbaum and Julianne Bohm. We also thank Dr. Murray Goodman for permitting us to read a manuscript prior to publication.

(51) S. Englard, J. S. Britten, and I. Listowsky, *J. Biol. Chem.*, **242**, 2255 (1967).

(52) S. Englard and I. Listowsky, *Biochem. Biophys. Res. Commun.*, **12**, 356 (1963).

Reactions of 1-Halo-2-methyl-3-alkoxy- and 3-alkylaminopropenes with Potassium *t*-Butoxide in Tetrahydrofuran[1]

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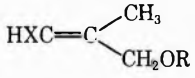
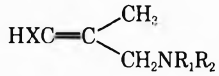
Received July 28, 1969

Several *cis*- and *trans*-1-halo-2-methyl-3-alkoxypropenes (**1a–1f**) and 1-halo-2-methyl-3-alkylaminopropenes (**2a–2c**) were prepared and treated with potassium *t*-butoxide (KO-*t*-Bu) in boiling tetrahydrofuran (THF). The principal products obtained from the methyl, ethyl, and isopropyl ethers (**1a–1e**) were the corresponding 2,5-dihydrofuran (**3**), 2-methyl-3-*t*-butoxy-3-alkoxypropene (**5**), and 2-*t*-butoxymethyl-3-alkoxypropene (**6**). The *t*-butyl ether **1f** gave 1-methylene-2-*t*-butoxycyclopropane (**7**) as the only cyclic product, together with the corresponding acetal **5d**, diether **6d**, and two isomeric vinyl ethers. Geometrical assignments were made to **1a–1f** and **2a–2c** on the basis of their nmr spectra; in all cases, the higher boiling isomer was assigned the *trans* configuration. The *cis* isomers of **1a–1f** consistently gave more cyclic product and acetal, but less diether, than the *trans* isomers. Second-order rate constants for formation of **3**, **5**, and **6** from *trans*-1-chloro-2-methyl-3-isopropoxypropene (**1a**) and *cis*- and *trans*-1-chloro-2-methyl-3-isopropoxypropene (**1d**) were determined. Each of the 3-alkylaminopropenes **2a–2c** gave the corresponding 3-pyrroline (**4**) and 2-*t*-butoxymethyl-3-alkylaminopropene (**19**). 1-Methylamino-2-butyne and 2-methyl-2-propenal methylimine were also identified as products from 1-bromo-2-methyl-3-methylaminopropene (**2a**). The *cis* isomers of **2a–2c** gave greater yields of **4** and lesser yields of **19** than the *trans* isomers.

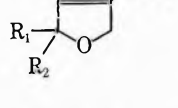
In 1963, Tanabe and Walsh[2] reported that the reaction of isocrotyl chloride with potassium *t*-butoxide (KO-*t*-Bu) in a 4:1 (by volume) mixture of tetrahydrofuran (THF) and cyclohexene gave a modest yield of 7-isopropylidenenorcarane, and they proposed that this product was formed by a mechanism involving 2,2-dimethylethylidene carbene. This suggested to us that similar treatment of compounds such as **1** might give alkylidene carbenes or carbenoids that would undergo intramolecular insertion into carbon–hydrogen bonds.[3]



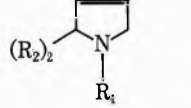
1a, X = Cl; R = CH_3
b, X = Br; R = CH_3
c, X = Cl; R = C_2H_5
d, X = Cl; R = i-C_3H_7
e, X = Br; R = i-C_3H_7
f, X = Cl; R = t-C_4H_9



2a, X = Br; R_1 = H; R_2 = CH_3
b, X = Cl; R_1 = H; R_2 = i-C_3H_7
c, X = Cl; R_1 = R_2 = CH_3



3a, R_1 = R_2 = H
b, R_1 = H; R_2 = CH_3
c, R_1 = R_2 = CH_3



4a, R_1 = R_2 = H
b, R_1 = H; R_2 = CH_3
c, R_1 = CH_3; R_2 = H

Preliminary experiments with the bromo amine **2a** revealed that reaction with KO-*t*-Bu in THF converted it into a complex mixture of amines from which 3-methyl-3-pyrroline (**4a**) could be isolated, and subsequent experiments with the chloro ether **1a** showed that it gave the corresponding heterocycle, 3-methyl-2,5-dihydrofuran (**3a**), together with several other products. Further, samples enriched in the lower boiling isomer of **1a** or **2a** gave significantly greater yields of the heterocyclic product.

In order to assess the value of 2,2-disubstituted 1-haloethylenes as precursors of cyclic systems, we examined the reactions of *cis* and *trans* isomers of **1a–1f** and **2a–2c** with KO-*t*-Bu in THF.

Isocrotyl bromide was converted by the action of N-bromosuccinimide into a 2.4:1 mixture of the higher and lower boiling isomers of 1,3-dibromo-2-methylpropene. Similarly, isocrotyl chloride gave a 2.1:1 mixture of the 1-chloro-2-methyl-3-bromopropenes, with the higher boiling isomer again predominating. The mixtures of dihalides were not separated but converted directly into mixtures of *cis* and *trans* ethers or alkylamines by treatment with alkoxide in alcohol or with excess amine. Except for **1f**, which was obtained in 53% yield, yields ranged from 77 to 90%, and the product from every reaction consisted of 70 ± 3% of the higher boiling isomer.

Stereochemical assignments to the dihalides, ethers, and alkylamines were made on the basis of their nmr spectra. From consideration of nmr data for propene and substituted propenes,[4] it seems reasonable to expect than an aminomethyl, halomethyl, or hydroxymethyl group will deshield, and that the methyl group will shield a *cis*-C_1 proton in compounds of the type HXC=$C(CH_3)CH_2Z$. Further, it can also be expected that the C_1 halogen will exert a greater deshielding effect on the methylene protons of the *cis* isomer. For every pair of *cis*- and *trans*-1-halo-2-methyl-3-alkoxypropenes (**1a–1f**), 1-halo-2-methyl-3-alkylaminopropenes, and 1,3-dihalo-2-methylpropenes, the signal of the C_1 proton of the lower boiling isomer is more shielded than that of the higher boiling isomer by 0.09–0.33 ppm, whereas the signal which is due to its C_3 proton is less shielded by 0.10–0.28 ppm. These data are completely consistent with assignment of the *trans* configuration to all of the higher boiling isomers. Interestingly, the *trans* isomers of 1,3-dibromopropene,[5,6] 1,3-dichloropropene,[7]

(1) Taken from the Ph.D. Thesis of R. A. Walsh, University of California, Davis, 1969. Supported by Grants GM 10606 and CA 10740 from the National Institutes of Health, Public Health Service.

(2) M. Tanabe and R. A. Walsh, *J. Amer. Chem. Soc.*, **85**, 3522 (1963).

(3) K. L. Erickson and J. Wolinski [*ibid.*, **87**, 1142 (1965)] have described such a reaction. They found that heating 1-bromo-2-ethyl-1-hexene with sublimed KO-*t*-Bu gave a *ca.* 30% yield of 1-ethyl-3-methylcyclopentene, as well as other products, including 3-octyne.

(4) M. Y. De Wolf and J. D. Baldeschwieler, *J. Mol. Spectrosc.*, **13**, 344 (1964), and references 1–13 cited therein.

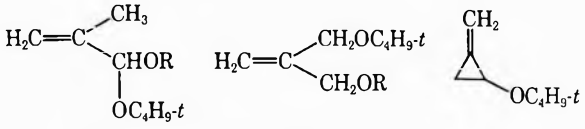
(5) L. F. Hatch and K. E. Harwell, *J. Amer. Chem. Soc.*, **75**, 6002 (1953).

(6) A. T. Bottini, B. J. King, and J. M. Lucas, *J. Org. Chem.*, **27**, 3688 (1962).

(7) L. F. Hatch and R. H. Perry, *J. Amer. Chem. Soc.*, **71**, 3262 (1949).

1-bromo-3-*n*-butylaminopropene,[6] 1-bromo-3-hydroxypropene,[5] and 1-chloro-3-hydroxypropene[7] are also the higher boiling isomers. It should also be pointed out that no correlation between the geometry of these compounds and their refractive index or the chemical shift of their C_2-methyl protons is apparent.

The major products isolated from reactions of the ethers **1a**–**1e** with a slight excess (<12%) of KO-*t*-Bu in THF were the corresponding 2,5-dihydrofuran (**3**), 3-*t*-butoxy-3-alkoxypropene (**5**), and 2-*t*-butoxymethyl-3-alkoxypropene (**6**). The only cyclic product obtained from similar treatment of 1-chloro-2-methyl-3-*t*-butoxypropene (**1f**) was 1-methylene-2-*t*-butoxycyclopropane (**7**); the corresponding acetal (**5d**) and diether (**6d**) were also obtained. Minor products were observed in all product mixtures, and it was estimated that these accounted for 5–10% of the starting materials. Without taking into account the tarry distillation residues, which were 10–15% of the weight of the starting ethers, material balances from these reactions ranged from 60 to 80%.



5 **6** **7**

a, R = CH_3; **b**, R = C_2H_5; **c**, R = *i*-C_3H_7; **d**, R = *t*-C_4H_9

Yields of **3** (or **7**), **5**, and **6** from samples enriched in the *cis* and *trans* isomers of **1a**–**1f** are summarized in Table I. All of the reactions studied were examined by glpc at various degrees of completion; no isomerization of the starting ethers under the reaction conditions was detected. Note that the *cis* isomers consistently gave more cyclic product and acetal, but less diether, than the *trans* isomers. It should also be noted that yields obtained using 30:70 mixtures of the *cis* and *trans* halo ethers were entirely consistent with those obtained from the enriched samples.

TABLE I

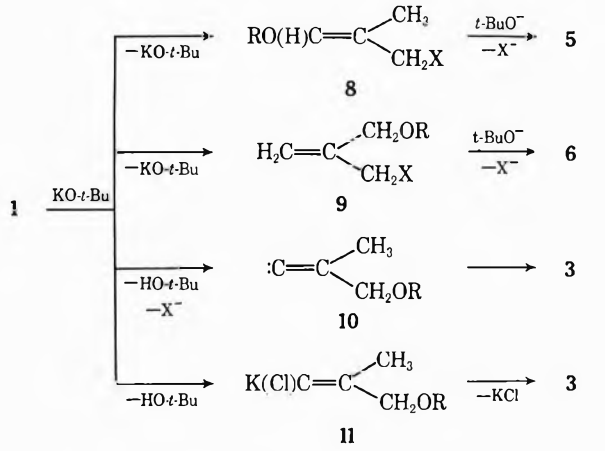
YIELDS FROM REACTIONS OF 1-HALO-2-METHYL-3-ALKOXYPROPENES (**1a**–**1f**) WITH KO-*t*-Bu IN THF

Reactant (purity, %[a])	Yield,[b] % 3	5	6
cis-**1a** (86)	16	15	19
trans-**1a** (96)	9	8	36
cis-**1b** (84)	30	8	23
trans-**1b** (95)	8	3	52
cis-**1c** (82)	23	26	14
trans-**1c** (94)	18	18	32
cis-**1d** (95)	33	32	18
trans-**1d** (99)	25	15	38
cis-**1e** (93)	36	7	17
trans-**1e** (97)	29	2	33
cis-**1f** (86)	10[c]	8	13
trans-**1f** (99)	5[c]	3	31

[a] The single contaminant was the isomeric halo ether. [b] Yields from the chloro ethers were corrected for recovered starting material, which amounted to 4–12%. [c] **7**.

Formation of the acetal **5** is most readily explained as occurring by prototropic rearrangement of the starting ether to the corresponding 1-alkoxy-2-methyl-3-halopropene (**8**), followed by SN2′ attack of *t*-butoxide. Similarly, rearrangement of the starting ether to the corresponding 2-alkoxymethyl-3-halopropene (**9**), followed by SN2 and/or SN2′ attack of *t*-butoxide, will lead to the diether **6**. The dependence of yields of **5** and **6** on the stereochemistry of the starting ether shows that the preferred, but not exclusive, direction of prototropic rearrangement is to the carbon of **1** that is *cis* to the halogen.[8] Formation of a 2,5-dihydrofuran (**3**) can be explained on the basis of the intermediacy of a free alkylidene carbene (**10**), which inserts into an α-C–H bond of the alkoxyl group, or an organometallic alkylidene carbenoid (**11**), from which potassium chloride is displaced by the same C–H bond.[11] These pathways are summarized in Scheme I.

SCHEME I



Alternative mechanisms for formation of **3** involving α-dehydrohalogenation of **8** and **9** are not consistent with the results. The intermediate from **8** (**12**) would give a 2,3-dihydrofuran, a vinyl ether that would be stable with respect to **3**.[12] The intermediate from **9** (**13**) would give a 3-methylenetetrahydrofuran; although it is conceivable that this product would rearrange to **3** under the reaction conditions, yield data for **3** and **6** show that the same intermediate, specifically **9**, is not involved in the formation of more than a fraction of these products. Mechanisms for formation of

12 **13**

3 involving abstraction of an α hydrogen of the alkoxyl group of **1**, *e.g.*, an addition–elimination reaction, also seem unlikely. This is because *cis*- and *trans*-1-ethoxy-4-*t*-butylcyclohexane undergo negligible exchange of

(8) Prototropic rearrangements of *allyl* to *propenyl* ethers occur with a high degree (*ca.* 99%) of stereoselectivity.[9] Similar rearrangements of amines[9c] and thioethers[10] occur with markedly less stereoselectivity. In all those rearrangements of allyl compounds, the *cis*-propenyl compound is the major product.

(9) (a) T. J. Prosser, *J. Amer. Chem. Soc.*, **83**, 1701 (1961); (b) C. C. Price and W. H. Snyder, *i bid.*, **83**, 1773 (1961); (c) *Tetrahedron Lett.*, 69 (1962); (d) C. D. Broaddus, *J. Amer. Chem. Soc.*, **87**, 3706 (1965).

(10) C. C. Price and W. H. Snyder, *J. Org. Chem.*, **27**, 4639 (1962).

(11) See G. Kobrich, *Angew. Chem. Intern. Ed. Engl.*, **4**, 49 (1967).

(12) Treatment of a 60:40 mixture of **2** and 2,3-dihydrofuran with 1.1 equiv of KO-*t*-Bu in dimethyl sulfoxide at 60° for 6 hr destroyed 60% of the 2,5 isomer and less than 5% of the 2,3 isomer.[13]

(13) F. P. Corson, Ph.D. Thesis, University of California, Davis, 1967.

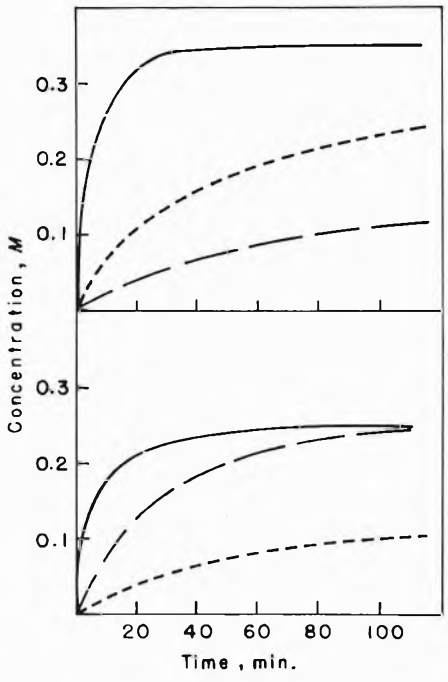


Figure 1.—Rates of formation of 2,2,4-trimethyl-2,5-dihydrofuran (———), 2-methyl-3-*t*-butoxy-3-isopropoxypropene (– – – –), and 2-*t*-butoxymethyl-3-isopropoxypropene (— — —) from reactions of *cis*- (upper) and *trans*-1-chloro-2-methyl-3-isopropoxypropene (lower) with potassium *t*-butoxide in tetrahydrofuran.

α hydrogens when treated with 1.5 equiv of KO-*t*-Bu in tritiated dimethyl sulfoxide at 100° for 6 hr.[13]

A carbene or carbenoid from **1f** (**10** or **11**, R = *t*-C_4H_9) is a likely intermediate in the formation of **7**. Cyclization involving a C_3–H bond would give 1-methyl-3-*t*-butoxycyclopropene, which would be expected to rearrange to the less strained **7** under the reaction conditions.[14] Our failure to find *t*-butoxymethylenecyclopropane, which would arise by cyclization involving a C–H bond of the methyl group at C_2 followed by *exo* migration of the double bond, indicates that either this product is unstable under the reaction conditions or that the carbene or carbenoid from **1f** shows a marked degree of selectivity toward the two types of C–H bonds.

In order to obtain a more detailed picture of these reactions, we determined the rates of reaction of *cis*- and *trans*-1-chloro-2-methyl-3-isopropoxypropene (**1d**) and *trans*-1-chloro-2-methyl-3-methoxypropene (**1a**) with equimolar amounts of KO-*t*-Bu in boiling THF. The rates of appearance of the three major products from the reactions of *cis*- and *trans*-**1d** are presented graphically in Figure 1. The striking feature of these reactions is the rapid decrease in the rate of formation of the cyclic product. By the time half of the starting ether was consumed, the rate of formation of the cyclic product is virtually nil. This can be explained in terms of the effect of *t*-butyl alcohol on the basicity of KO-*t*-Bu. For each mole of 2,5-dihydrofuran formed, a mole of *t*-butyl alcohol is formed. *t*-Butyl alcohol forms a sparingly soluble 1:1 complex with KO-*t*-Bu,[15] and the effective basicity of the *t*-butoxide ion, particularly its ability to abstract a vinyl hydrogen, is substantially reduced.[16] It is apparent that this decrease in basicity does not affect to the same extent the rates of formation of the two allyl chlorides **8** and **9**, which are the precursors of the acetal **5** and the diether **6**.

These results suggested that improved yields of 2,5-dihydrofuran could be obtained by using a KO-*t*-Bu:**1** mole ratio of greater than 1.1:1. When this mole ratio was increased to 2:1 with *trans*-1-chloro-2-methyl-3-methoxypropene (**1a**), the yield of **3a** was increased from 9 to 24%, and the combined yields of **5a** and **6a** fell from 44 to 15%.[17a] Further, when *cis*-enriched 1-chloro-2-methyl-3-ethoxypropene (**1c**) was treated with a slurry prepared from equivalent amounts of KO-*t*-Bu and *t*-butyl alcohol, only 3% was converted into the dihydrofuran **3b**; the corrected yields (83% conversion of **1c**) of the acetal **5b** and diether **6b** were 33 and 14%.[17b]

Because of the rapid falloff in rates of reaction, the apparent second-order rate constants that we determined for *trans*-**1a** and *cis*- and *trans*-**1d**, which are summarized in Table II, were calculated using data obtained during the first 30–35% of the reactions. In these calculations, the rate constant for disappearance of **1** was taken as equal to the sum of the rate constants for formation of **3**, **5**, and **6**.

TABLE II

APPARENT SECOND-ORDER RATE CONSTANTS FOR REACTIONS OF 1-CHLORO-2-METHYL-3-ALKOXYPROPENES WITH KO-*t*-Bu IN BOILING THF

Reactant	k_3[a]	k_5[a]	k_6[a]
trans-**1a**	4.0	0.37	1.8
cis-**1d**	6.8	2.0	0.53
trans-**1d**	3.7	0.57	1.7

[a] $\times 10^4\ M^{-1}\ \text{sec}^{-1}$.

These data clarify several features of the reactions. The rate constants for formation of **5** and **6** from a given chloro ether differ by a factor of 4 to 5, the acetal being formed more rapidly from the *cis* isomer and less rapidly from the *trans* isomer. From this, the degree of stereoselectivity in prototropic rearrangements of the chloro ethers to **8** and **9** can be estimated as 80 ± 5%; *i.e.*, of the starting ether that undergoes prototropic rearrangement, 80 ± 5% rearranges by migration of the double bond to the carbon *cis* to halogen. Although the rate constant for formation of **3c** from *cis*-**1d** is almost twice that of the *trans* isomer, the sum of the rate constants for formation of the acetal and diether is nearly the same for the two halo ethers. Thus the greater yields of cyclic products from the *cis* isomers are due to faster rates of conversion of *cis*-**1** into **3** (or **7**) rather than slower rates of conversion into **5** and **6**. The greater rate of cyclization of the *cis* isomer appears to result from the lesser hindrance to attack by *t*-butoxide ion in the rate-limiting abstraction of the vinyl hydrogen. Interestingly, change of the alkoxyl group from methoxyl to

(14) See N. C. Baird and M. J. S. Dewar, *J. Amer. Chem. Soc.*, **89**, 3966 (1967).

(15) A. J. Speziale, K. W. Ratts, and D. E. Bissing, *Org. Syn.*, **45**, 35 (1965).

(16) See V. A. Bessenov, P. P. Alikhanov, E. N. Gur'yanova, A. P. Simonov, I. O. Shapiro, E. A. Yakovleva, and A. I. Shatenshtein, *J. Gen. Chem. USSR*, **37**, 96 (1967).

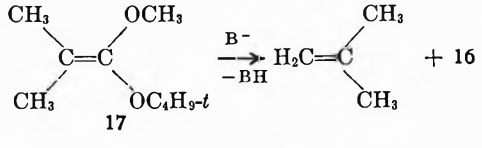
(17) (a) Part of the large decrease in yield of **5a** and **6a** is due to their instability, relative to **3a**, when treated with KO-*t*-Bu in THF. Treatment of a 1:0.27:1.25 mixture of **3c**, **5c**, and **6c** (total concentration, 0.57 *M*) with 0.79 *M* KO-*t*-Bu in boiling THF for 18 hr destroyed <5% of **3c**, 72% of **5c**, and 42% of **6c**. (b) Experiment carried out by Mr. K. A. Frost after submittal of this paper.

isopropoxyl has relatively little affect on the rates of all three processes. Finally, these data do not allow us to choose between the free carbene or organometallic carbenoid pathway for cyclization.

Although change of the alkoxyl group has no appreciable affect on the rates of reaction of the *trans* isomers of **1a** and **1d**, change of halogen has a large affect. The *cis* and *trans* isomers of 1-bromo-2-methyl-3-isopropoxypropene (**1e**) underwent reaction too rapidly to measure at the boiling temperature of THF. That terminal vinyl bromides react faster than chlorides is in agreement with the observation that α-halogen substituents facilitate carbanion formation in the order I $\cong$ Br > Cl > F.[18]

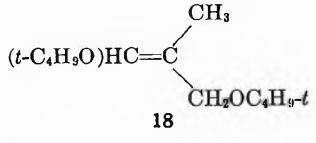
As mentioned earlier, it was estimated that minor products accounted for 5–10% of the starting materials. Except for minor products from **1a**, **1b**, and **1f**, which were examined in some detail, these estimates were based on the assumptions that each minor product had the same molecular weight and thermal conductivity as the major product that had most nearly the same retention time on the glpc column used for analysis.

Compounds **1a** and **1b** gave three minor products in combined yields of 4–10%, and they were identified as 2-methyl-3,3-dimethoxypropene (**14**), 2-methoxymethyl-3-methoxypropene (**15**), and methyl isobutyrate (**16**). Examination by glpc showed that **14**–**16** were not present in the starting materials. Formation of the acetal **14** and the diether **15** indicates that *t*-butoxide displaces methoxide from the starting halo ether and possibly one or more of the acyclic products, and that methoxide competes with *t*-butoxide in reactions of the allylic halides (**8** and **9**) formed by prototropic rearrangement of **1a** and **1b**. A plausible pathway by which the ester could be formed is prototropic rearrangement of **5a** to the mixed dimethylketene acetal **17**, followed by elimination of isobutylene.



17

In addition to **5d**, **6d**, and **7**, *cis*- and *trans*-1-chloro-2-methyl-3-*t*-butoxypropene (**1f**) gave nearly equal amounts of two other products in combined yields of 8–9%. The retention times and nmr spectra of these products indicated that they were the *cis* and *trans* isomers of 1,3-di-*t*-butoxy-2-methylpropene (**18**).

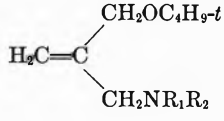


18

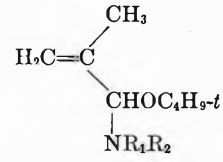
Each of the ethyl and isopropyl halo ethers (**1c**–**1e**) gave three unidentified products in combined yields of 4–9%. Of these, two appeared to be isomeric with the corresponding diether and acetal. The third minor product was probably isomeric with the corresponding 2,5-dihydrofuran; it was formed in greatest amount (3% yield) from **1c**.

(18) J. Hine, N. W. Burske, M. Hine, and P. B. Langford, *J. Amer. Chem. Soc.*, **79**, 1406 (1957).

Treatment of each of the 1-halo-2-methyl-3-alkylaminopropenes (**2a**–**2c**) with KO-*t*-Bu in the same manner as the 1-halo-2-methyl-3-alkoxypropenes (**1a**–**1f**) gave the corresponding 3-pyrroline (**4**) and 2-*t*-butoxymethyl-3-alkylaminopropene (**19**). Note that **19** would be formed from **2** by a mechanism analogous to that proposed for formation of the diethers (**6a**–**6d**) from **1a**–**1f**. As might be expected from the behavior of **1a**–**1f**, samples enriched in the *cis* isomers of **2a**–**2c** gave higher yields of **4** and lower yields of **19** than those obtained from samples enriched in the *trans* isomers. These yield data are summarized in Table III.



19



20

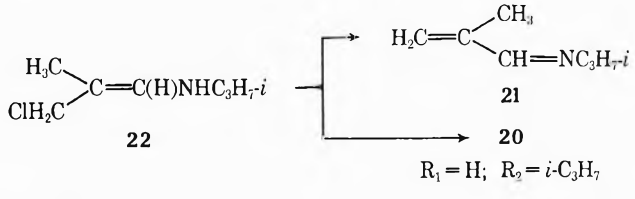
TABLE III

YIELDS FROM REACTIONS OF 1-HALO-2-METHYL-3-ALKYLAMINOPROPENES (**2a**–**2c**) WITH KO-*t*-Bu IN THF

Reactant (purity, %[a])	Yield,[b] % 4	19
cis-**2a** (99)	18	5
trans-**2a** (94)	4	22
cis-**2b** (86)	14	3
trans-**2b** (92)	17	18
cis-**2c** (71)	36	6
trans-**2c** (83)	30	13

[a] The single contaminant was the geometric isomer. [b] Corrected for 8–18% recovered starting material.

No 2-methyl-3-*t*-butoxy-3-alkylaminopropene (**20**), which would correspond to the acetals (**5a**–**5d**) obtained from the halo ethers, was identified as a product from **2a**–**2c**. However, 2-methyl-2-propenal isopropylimine (**21**) was isolated in yields of 25 and 14%, respectively, from samples enriched in *cis*- and *trans*-1-chloro-2-methyl-3-isopropylaminopropene (**2b**). Again by analogy with the halo ethers, it seems likely that **2b** rearranges to the vinylamine **22**, and that **22** undergoes dehydrochlorination to **21** more rapidly that it undergoes SN2′ attack by *t*-butoxide.



22 21 20

$R_1 = H$; $R_2 = i\text{-}C_3H_7$

Compounds **2a**–**2c** gave other products, but only two of these accounted for more than an estimated 2% of the starting amine.[19] At least 7% of both *cis*- and *trans*-**2b** were converted into an unidentified, thermally unstable product, which was probably isomeric with **4b** and **22**. *cis*-Enriched and *trans*-enriched 1-bromo-2-methyl-3-methylaminopropene (**2a**) gave 1-methyl-

(19) As with minor products from the halo ethers, estimates were based on the assumptions that each minor product had the same molecular weight and thermal conductivity as the major product that had most nearly the same retention time on the glpc column used for analysis. Each of the starting amines gave one to three additional products that were probably isomeric with **4**, and at least one that was probably isomeric with **19**.

TABLE IV

BOILING POINTS, REFRACTIVE INDICES, AND ELEMENTAL ANALYSES OF ENRICHED SAMPLES OF *cis*- AND *trans*-1-HALO-2-METHYL-3-ALKOXY- AND -3-ALKYLAMINOPROPENES

				Calcd, %		Found, %	
Compd	Purity, %	Bp, °C (mm)	$n^{25}D$	C	H	C	H
cis-1a	86	120–122	1.4390	49.75	7.55[a]	49.45	7.24
trans-1a	96	126–128	1.4412			49.55	7.53
cis-1b	84	134–136	1.4728	36.36	5.52[b]	36.17[c]	5.39[c]
trans-1b	95	146–148	1.4705				
cis-1c	82	140–142	1.4372	53.49	8.25[d]	53.44	8.26
trans-1c	94	145–147	1.4373			53.55	8.34
cis-1d	95	80–82 (90)	1.4355[e]	56.55	8.82[f]	56.73	8.69
trans-1d	99	85–86 (90)	1.4348[e]			56.70	8.69
cis-1e	93	90–92(65)	1.4586	43.52	6.79[g]	43.65[c]	6.78[c]
trans-1e	97	95–97 (65)	1.4587				
cis-1f	86	99–101 (88)	1.4370	59.07	9.29[h]	59.10[c]	9.25[c]
trans-1f	99	105–107 (88)	1.4390				
cis-2a	99	77–78.5 (41)	1.4931[i]	36.59	6.16	36.38[c]	5.92[c]
trans-2a	94	82.5–84 (41)	1.4957[i]				
cis-2b	86	96–98 (80)	1.4580[i]	42.56[j]	4.68[j]	42.53[k]	4.43[k]
trans-2b	92	99–101 (80)	1.4548[i]			42.59[l]	4.46[l]
cis-2c	71	139	1.4486[i]	53.89	9.06[m]	54.04	8.69
trans-2c	83	140	1.4486[i]			54.08	8.78

[a] Calcd: Cl, 29.44. Found: *cis*, 29.48; *trans*, 29.63. [b] Calcd: Br, 48.42. Found:[c] Br, 48.65. [c] Analysis of *ca.* 30% *cis*–70% *trans* mixture. [d] Calcd: Cl, 26.37. Found: *cis*, 26.09; *trans*, 26.34. [e] At 25°. [f] Calcd: Cl, 23.68. Found: *cis*, 23.61; *trans*, 23.73. [g] Calcd: Br, 41.40. Found:[c] 41.68. [h] Calcd: Cl, 21.80. Found:[c] Cl, 21.85. [i] At 22°. [j] Calculated for *p*-bromobenzenesulfonamide. [k] Analysis of *p*-bromobenzenesulfonamide, mp 97.5–98.5°. Calcd: N, 3.82. Found: N, 3.56. [l] Analysis of *p*-bromobenzenesulfonamide, mp 72.5–73.5°. Calcd: N, 3.82. Found: N, 3.55. [m] Calcd: Cl, 26.57. Found: *cis*, 26.62; *trans*, 26.65.

amino-2-butyne (**23**) in yields of 12 and 2%, respectively. Conversion of a 2,2-disubstituted 1-haloethylene into an acetylene by treatment with a strong base is not a novel reaction,[3] and it is noteworthy that such a rearrangement plays no more than a minor role in reactions of most of the 2,2-disubstituted 1-haloethylenes described here.

$$H_3CC{\equiv}CCH_2NHCH_3$$
23

Experimental Section

Temperatures are uncorrected. Ir spectra were obtained with either a Beckman IR-8 or Perkin-Elmer 237B spectrophotometer; spectra of samples available in only microliter quantities were obtained using micro NaCl plates with the Beckman IR-8 fittted with a beam condenser. Nmr spectra were obtained of CCl_4 solutions with a Varian Associates A-60A spectrometer; resonance frequencies in nmr spectra were determined relative to 1–2% internal tetramethylsilane. Glpc chromatograms were obtained with an Aerograph Model A-700 of A-90-P3 or a Varian Model 90-P. Stationary phases and dimensions of columns used were: 20% SE 30, 12 ft × 0.25 in.; 30% SE 30, 10 ft × 0.25 in.; 20% XF 1150, 16 ft × 0.25 in.; 20% FFAP, 15 ft × 0.25 in. The packing for the last column was DMCS-treated Chromosorb P; the packing for the other columns was Chromosorb W. Microanalyses were performed at The Microanalytical Laboratory, University of California, Berkeley; Galbraith Laboratories, Inc., Knoxville, Tenn., and Chemalytics, Inc., Tempe, Ariz. Potassium *t*-butoxide (KO-*t*-Bu) was obtained from MSA Research Corp. Tetrahydrofuran (THF) was filtered through Woelm basic alumina, activity grade one, immediately prior to use. All of the vinyl halides used showed definite signs of decomposition, accompanied by evolution of hydrogen halide, within 24 hr of their purification. The rate of decomposition was reduced substantially by storage under nitrogen. Before any vinyl halide that gave evidence of decomposition was treated with KO-*t*-Bu, it was filtered through basic alumina and its purity was checked by examination of its nmr spectrum.

The 1,3-Dihalo-2-methylpropenes.—A procedure patterned after that described for the preparation of 4-bromo-2-heptene[20] was used to convert 193 g of isocrotyl bromide into 200 g (75%) of a 1:2.4 mixture of *cis*- and *trans*-1,3-dibromo-2-methylpropene: bp 85–90° (44 mm), $n^{23}D$ 1.5478; nmr for lower boiling (*cis*) isomer, δ 6.11 (m, 1, =CH), 4.09 (d, 2, J = 1.4 Hz, CH_2), and 1.93 (d, 3, J = 1.4 Hz, CH_3); for higher boiling (*trans*) isomer, 6.43 (m, 1, =CH), 3.99 (d, 2, J = 1.4 Hz, CH_2), and 1.93 (d, 3, J = 1.4 Hz, CH_3).

Anal. Calcd for $C_4H_6Br_2$: C, 22.45; H, 2.81. Found: C, 22.23; H, 2.73.

A similar procedure was used to convert 151 g of freshly distilled isocrotyl chloride, bp 67–68°, into 228 g (81%) of a 1:2.1 mixture of *cis*- and *trans*-1-chloro-2-methyl-3-bromopropene: bp 90–100° (90–100 mm); $n^{23}D$ 1.5142; nmr for lower boiling (*cis*) isomer, δ 5.96 (m, 1, =CH), 4.08 (d, 2, J = 1.4 Hz, CH_2), and 1.92 (d, 3, J = 1.4 Hz, CH_3); for higher boiling (*trans*) isomer, 6.29 (m, 1, =CH), 3.97 (d, 2, J = 1.4 Hz, CH_2), and 1.92 (d, 3, J = 1.4 Hz, CH_3).

Anal. Calcd for C_4H_6BrCl: C, 28.34; H, 3.54. Found: C, 28.35; H, 3.50.

Preparation of the 1-Halo-2-methyl-3-alkoxypropenes (1a–1f).—Except that KO-*t*-Bu, not sodium *t*-butoxide, was used to prepare **1f**, the following procedure, used for the preparation and isolation of *cis*- and *trans*-1-chloro-2-methyl-3-ethoxypropene (**1c**), is typical.

To a stirred solution prepared from 18.4 g of sodium and 700 ml of absolute ethanol under nitrogen was added dropwise, in 10 min, 120 g of 1-chloro-2-methyl-3-bromopropene. When the addition was complete, the mixture was heated cautiously to reflux, held there for 3 hr, cooled, and added to 800 ml of water. The aqueous solution was extracted with CCl_4 (four 120-ml portions), and the extracts were combined, washed with water (three 150-ml portions), and dried (K_2CO_3). Distillation gave an 84.2-g fraction, bp 75–82° (88 mm), that was a 1:2.2 mixture of *cis*- and *trans*-**1c**. This fraction was redistilled through a 60 × 0.8 cm spinning-band column, and three fractions, bp 140–144°, 144–145°, and 145–147°, were collected. The lowest boiling fraction was redistilled through the same column to give a 17.0-g fraction, bp 140–142°, which was an 82:18 mixture of *cis*- and *trans*-**1c**: The highest boiling fraction consisted of 94% *trans*- and 6% *cis*-**1c**: nmr for lower boiling (*cis*) isomer, δ 5.95 (m, 1, =CH), 4.09 (d, 2, J = 1.4 Hz, CH_2), 3.28 (s, 3, OCH_3), and 1.77 (d, 3, J = 1.4 Hz, CCH_3); for higher boiling (*trans*) isomer, 6.10 (m, 1, =CH), 3.81 (d, 2, J = 1.4 Hz, CH_2), 3.26 (s, 3, OCH_3), and 1.77 (d, 2, J = 1.4 Hz, CCH_3).

The boiling points, refractive indices, and elemental analyses of fractions enriched in the *cis* and *trans* isomers of **1a–1f** are included in Table IV.

(20) F. L. Greenwood, M. D. Kellert, and J. Sedlak, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 108.

Preparation of the 1-Halo-2-methyl-3-alkylaminopropenes (2a–2c).—The following procedure, used for preparation and isolation of *cis*- and *trans*-1-chloro-2-methyl-3-dimethylaminopropene (2c), is typical.

A 160-g sample of the 1:2.1 mixture of *cis*- and *trans*-1-chloro-2-methyl-3-bromopropene was added dropwise in 45 min to *ca.* 600 ml of stirred, refluxing dimethylamine. When the addition was complete, the mixture was allowed to reflux for 4 hr, and then most of the excess dimethylamine was removed by distillation through a 30 × 1.5 cm column packed with glass helices. The residue was cooled with an ice bath, and 60 g (1.5 mol) of NaOH was added in portions. Water (100 ml) was added carefully until all the solid material in the mixture dissolved, the aqueous layer was separated and extracted with ether (two 75-ml portions), and the extracts were combined with the organic layer. This was washed with water (40 ml) and saturated NaCl solution (two 75-ml portions), dried (KOH), and distilled to give a 108-g fraction, bp 138–141°. Several distillations through a 60-cm annular spinning-band column gave a 38.6-g fraction which was a 1:5 mixture of *cis*- and *trans*-2c. Only 8.9 g of predominantly (71%) *cis*-2c was obtained: nmr for lower boiling (*cis*) isomer, δ 6.00 (m, 1, =CH), 3.06 (d, 2, J = 1.4 Hz, CH_2), 2.19 (s, 6, NCH_3), and 1.80 (d, 3, J = 1.4 Hz, CCH_3); for higher boiling (*trans*) isomer, 6.10 (m, 1, =CH), 2.82 (d, 2, J = 1.4 Hz, CH_2), 2.15 (s, 6, NCH_3), and 1.80 (d, 3, J = 1.4 Hz, CCH_3).

The boiling points, refractive indices, and elemental analyses of fractions enriched in the *cis* and *trans* isomers of 2a–2c are included in Table IV.

Reactions of the 1-Halo-2-methyl-3-alkoxy- and -3-alkylaminopropenes with KO-*t*-Bu in THF.—The following procedure is typical. To a stirred mixture of 30.2 g (0.27 mol) of KO-*t*-Bu and 150 ml of THF under nitrogen was added 30.0 g (0.25 mol) of a 1:2.0 mixture of *cis*- and *trans*-1-chloro-2-methyl-3-methoxypropene (1a). The reaction mixture, which turned brown immediately, was heated at reflux for 16 hr, cooled, and added to 150 ml of cold 2 M K_2CO_3 solution. The organic phase was separated and the aqueous phase was extracted with 50 ml of ether. The organic solutions were combined, washed with saturated K_2CO_3 solution, dried (KOH), and distilled.

Reactions with 1-bromo-2-methyl-3-methylaminopropene (2a) were the most exothermic, and these reaction mixtures were filtered through Filter Aid before work-up.

Identification of Products.—Products obtained from 30:70 mixtures of *cis* and *trans* isomers were separated by a combination of fractional distillation and glpc, and these products were used for purposes of identification as well as estimating the relative thermal conductivities of the major products. Products from enriched samples of the *cis* and *trans* isomers were collected with a minimum of fractionation and analyzed by means of glpc and nmr spectroscopy.

Summarized below are spectral bands common to the various classes of compounds obtained from 1a–1f and 2a–2c, as well as pertinent data for individual compounds. The stationary phase of the glpc column used for purifying the compound is given in parentheses. Unless a compound was isolated in a relatively pure state (>97%) by distillation, its boiling point is not given.

3-Methyl-2,5-dihydrofurans (3a–3c) gave the following data: nmr δ 5.37–5.45 (m, 1, =CH), 4.42–4.45 (m, 2 or 4, CH_2O), and 1.69–1.74 (m, 3, $=CCH_3$); ir 1665–1670 cm^{-1} (C=C).

3-Methyl-2,5-dihydrofuran (3a) (SE 30) gave the following data: $n^{22}D$ 1.4369; lit.[21] bp 83–85°.

Anal. Calcd for C_5H_8O: C, 71.43; H, 9.52. Found: C, 71.16; H, 9.38.

2,4-Dimethyl-2,5-dihydrofuran (3b) (SE 30) gave the following data: nmr δ 4.65–5.12 (m, 1, C_2H) and 1.17 (d, 3, J = 6 Hz, C_2CH_3); $n^{23}D$ 1.4294.

Anal. Calcd for $C_6H_{10}O$: C, 73.39; H, 10.30. Found: C, 73.10; H, 10.38.

2,2,4-Trimethyl-2,5-dihydrofuran (3c) (XF 1150 and SE 30) gave the following data: nmr δ 1.22 (s, 6, C_2CH_3); $n^{24}D$ 1.4226.

Anal. Calcd for $C_7H_{12}O$: C, 74.93; H, 10.79. Found: C, 74.79; H, 10.55.

2-Methyl-3-*t*-butoxy-3-alkoxypropenes (5a–5d) gave the following data: nmr δ 4.71–5.15 (s or 3 multiplets, 3, H_2C=CCH), 1.67–1.72 (m, 3, C_2CH_3), and 1.20–1.26 (s, 9 or 18, *t*-C_4H_9); ir 910 and 1655–1660 cm^{-1} (C=C).

2-Methyl-3-*t*-butoxy-3-methoxypropene (5a) (SE 30 and FFAP) gave the following data: nmr δ 3.05 (s, 3, OCH_3); $n^{23}D$ 1.4106.

Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.45. Found: C, 68.59; H, 11.47.

2-Methyl-3-*t*-butoxy-3-ethoxypropene (5b) (SE 30) gave the following data: nmr δ 3.39 (q, 2, J = 7.5 Hz, OCH_2CH_3) and 1.14 (t, 3, J = 7.5 Hz, OCH_2CH_3); $n^{23}D$ 1.4125.

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.69; H, 11.73. Found: C, 69.53; H, 12.03.

2-Methyl-3-*t*-butoxy-3-isopropoxypropene (5c) (SE 30 and XF 1150) gave the following data: nmr δ 3.71 [septet, 1, J = 6 Hz, $OCH(CH_3)_2$] and 1.10 [d, 6, J = 6 Hz, $OCH(CH_3)_2$].

Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.97; H, 11.83. Found: C, 70.77; H, 11.15.

2-*t*-Butoxymethyl-3-alkoxypropenes (6a–6d) gave the following data: nmr δ 5.01–5.17 (1 or 2 multiplets, 2, $=CH_2$), 3.83–3.99 (1 or 2 multiplets, 4, OCH_2), and 1.17–1.20 (s, 9 or 18, *t*-C_4H_9); ir 895–905 and 1660–1670 cm^{-1} (C=C).

2-*t*-Butoxymethyl-3-methoxypropene (6a) gave the following data: nmr δ 3.23 (s, 3, OCH_3); bp 101–102° (91 mm); $n^{22}D$ 1.4210.

Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.45. Found: C, 68.43; H, 11.55.

2-*t*-Butoxymethyl-3-ethoxypropene (6b) gave the following data: nmr δ 3.49 (q, 2, J = 7 Hz, OCH_2CH_3) and 1.18 (t, 3, J = 7 Hz, OCH_2CH_3); bp 112° (90 mm); $n^{23}D$ 1.4220.

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.69; H, 11.73. Found: C, 69.89; H, 11.79.

2-*t*-Buoxymethyl-3-isopropoxypropene (6c) gave the following data: nmr δ 3.56 [septet, 1, J = 6 Hz, $HC(CH_3)_2$] and 1.10 [d, 6, $C(CH_3)_2$]; bp 114–116° (63 mm); $n^{22}D$ 1.4210.

Anal. Calcd for $C_{11}H_{22}O$: C, 70.97; H, 11.83. Found: C, 70.69; H, 11.68.

2-*t*-Butoxymethyl-3-*t*-butoxypropene (6d) (SE 30 and XF 1150) was not obtained pure, and was analyzed as the major component of a mixture with *cis*- and *trans*-18.

Anal. Calcd for $C_{12}H_{24}O_2$: C, 70.52; H, 11.85. Found: C, 70.73; H, 12.05.

1-Methylene-2-*t*-butoxycyclopropane (7) (SE 30) gave the following data: nmr δ 5.67 (m, 1, =CH), 5.51 (m, 1, =CH), 3.69 (m, 1, OCH), 1.33 (m, 2, CH_2), and 1.23 (s, 9, *t*-C_4H_9); ir 1790 cm^{-1} (C=C); $n^{23}D$ 1.4314.

Anal. Calcd for $C_8H_{14}O$: C, 76.13; H, 11.18. Found: C, 75.77; H, 11.46.

2-Methyl-3,3-dimethoxypropene (14) (SE 30 and FFAP) gave the following data: nmr δ 4.48–5.05 (3 multiplets, 3, H_2C=CCH), 3.19 (s, 6, OCH_3), and 1.63 (m, 3, CCH_3); ir 900 and 1655 cm^{-1} (C=C).

2-Methoxymethyl-3-methoxypropene (15) (SE 30 and FFAP) gave the following data: nmr δ 5.08 (m, 2, $=CH_2$), 3.82 (m, 4, CH_2), and 1.73 (2, 6, OCH_3).

1,3-Di-*t*-butoxy-2-methylpropene (19) gave the following data: nmr for first isomer, δ 5.94 (m, 1, =CH), 3.89 (broadened 2, s, OCH_2), 1.56 (d, 3, J = 1.2 Hz, $=CCH_3$), and 1.22 (s, 18, *t*-C_4H_9); nmr for second isomer, 6.21 (m, 1, =CH), 3.68 (broadened s, 2, OCH_2), 1.56 (d, 3, J = 1.2 Hz, $=CCH_3$), and 1.21 (s, 18, *t*-C_4H_9); ir for both isomers, 1685 cm^{-1} (C=C). A mixture of both isomers and 6d was analyzed (see under 6d).

3-Pyrrolines (4a–4c) (SE 30) gave the following data: nmr δ 5.32–5.36 (m, 1, =CH) and 1.72–1.73 (m, 3, $=CCH_3$); ir 1660–1665 cm^{-1} (C=C).

3-Methyl-3-pyrroline (4a) gave the following data: nmr δ 3.65 (m, 4, NCH_2) and 1.4 (variable, s, 1, NH).

Anal. Calcd for C_5H_9N: C, 72.29; H, 10.85; N, 16.87. Found: C, 72.01; H, 10.83; N, 16.62.

2,2,4-Trimethyl-3-pyrroline (4b) gave the following data: nmr δ 3.61 (m, 2, NCH_2), 1.4 (variable, s, 1, NH), and 1.14 (s, 6, C_2CH_3); $n^{23}D$ 1.4441. Several attempts failed to give a satisfactory analysis, so a sample was converted into the *p*-bromobenzenesulfonamide, mp 96.5–97.0° (80% EtOH).

Anal. Calcd for $C_{13}H_{16}BrNO_2S$: C, 47.26; H, 4.88; N, 4.24. Found: C, 47.44; H, 4.83; N, 4.07.

1,3-Dimethyl-3-pyrroline (4c) gave the following data: nmr δ 3.33 (m, 4, NCH_2) and 2.39 (s, 3, NCH_3); $n^{23}D$ 1.4404.

Anal. Calcd for $C_6H_{11}N$: C, 74.15; H, 11.43; N, 14.42. Found: C, 73.77; H, 11.33; N, 14.47.

2-*t*-Butoxymethyl-3-alkylaminopropenes (19a–19c) (SE 30) gave the following data: nmr δ 3.85–3.96 (broadened 2, s, OCH_2) and 1.20–1.23 (s, 9, *t*-C_4H_9); ir 905–910 and 1650–1655 cm^{-1} (C=C).

(21) E. E. Schweizer and J. H. Liehr, *J. Org. Chem.*, 33, 583 (1968).

2-*t*-Butoxymethyl-3-methylaminopropene (19a) gave the following data: nmr δ 5.11 (broadened 2, 1, =CH), 5.00 (m, 1, =CH), 3.20 (broadened s, 2, NCH_2), and 2.40 (s, 3, NCH_3).

Anal. Calcd for $C_9H_{19}NO$: C, 68.72; H, 12.20; N, 8.91. Found: C, 68.55; H, 11.96; N, 9.17.

2-*t*-Butoxymethyl-3-isopropylaminopropene (19b) gave the following data: nmr δ 5.12 (m, 2, $=CH_2$), 3.27 (broadened s, 2, NCH_2), 2.83 [septet, 1, J = 6.5 Hz, $HC(CH_3)_2$], 1.02 [d, 6, J = 6.5 Hz, $C(CH_3)_2$], and 0.9 (variable, s, 1, NH), $n^{23}D$ 1.4343. This compound was not obtained analytically pure, and these values may not be characteristic.

2-*t*-Butoxymethyl-3-dimethylaminopropene (19c) gave the following data: nmr δ 5.18 (broadened s, 1, =CH), 5.00 (m, 1, =CH), 2.84 (broadened s, 2, NCH_2), and 2.15 (s, 6, NCH_3); $n^{23}D$ 1.4275.

Anal. Calcd for $C_{10}H_{21}NO$: C, 70.09; H, 12.38; N, 8.18. Found: C, 70.21; H, 12.17; N, 8.25.

2-Methyl-2-propenal isopropylimine (21) (SE 30) gave the following data: nmr δ 7.98 (s, 1, N=CH), 5.55 (m, 1, HC=), 3.39 [septet, 1, J = 6.5 Hz, $CH(CH_3)_2$], 1.92 (m, 3, $=CCH_3$), 1.17 [d, 6, J = 6.5 Hz, $CH(CH_3)_2$]; ir 1620 and 1640 cm^{-1} (C=N and C=C); $n^{23}D$ 1.4270.

Anal. Calcd for $C_7H_{13}N$: C, 75.61; H, 11.79; N, 12.60. Found: C, 75.86; H, 11.75; N, 12.41.

1-Methylamino-2-butyne (23) (SE 30) gave the following data: nmr δ 3.32 (q, 2, J = 2.4 Hz, NCH_2), 2.45 (s, 3, NCH_3), and 1.76 (t, 3, J = 2.4 Hz, CCH_3).

Rates of Reaction of *trans*-1-Chloro-2-methyl-3-methoxypropene (1a) and *cis*- and *trans*-1-Chloro-2-methyl-3-isopropoxypropene (1d) with KO-*t*-Bu in THF.—A 0.87 M solution of KO-*t*-Bu in THF under nitrogen, contained in a 100-ml round-bottom flask fitted with a side arm, was stirred with a magnetic stirrer and heated to boiling. Chloroether sufficient to give a 0.87 M solution was added by means of a syringe through the side arm, which was covered by a rubber septum, and the timer was started when one-half had been added (addition time of *ca.* 6 sec). At measured time intervals (five times in the first 13 min), 0.5-ml samples were withdrawn with the syringe. Each was immediately added to 0.2 ml of water and shaken thoroughly, and the aqueous layer was separated with a pipet. The organic layer was dried (K_2CO_3) and analyzed by glpc (30% SE 30). At 1.5–2 hr after each reaction was initiated, the combined yields of **3**, **5**, and **6**, as estimated by glpc and corrected for unreacted starting material, exceeded 94%. With data obtained in the first 30–35% of the reaction, the apparent second-order rate constant for the disappearance of starting material was determined by plotting the reciprocal of the concentration of starting material *vs.* time. Rate constants for formation of **3** (k_3), **5** (k_5), and **6** (k_6) were estimated by assuming that these products were formed by second-order processes and that the sum of the rate constants for their formation was equal to the rate constant for disappearance of the starting material. The rate constants are summarized in Table II.

Relative Stability of 2,2,4-Trimethyl-2,5-dihydrofuran (3c), 2-Methyl-3-*t*-butoxy-3-isopropoxypropene (5c), and 2-*t*-Butoxymethyl-3-isopropoxypropene (6c) in Boiling THF Containing KO-*t*-Bu.—To 17 ml of THF under nitrogen was added 1.5 g of a 28:15:57 wt % mixture of **3c**, **5c**, and **6c**. *o*-Xylene (0.2 g) was added as an internal reference, and then 1.5 g (13 mmol) of KO-*t*-Bu was added. The solution was heated to reflux, and after measured time intervals, 0.5-ml samples were withdrawn with a syringe from a side arm of the flask that was covered with a rubber septum. Each sample was immediately added to 0.5 ml of water, and the aqueous phase was separated with a pipet. The organic phase was dried (K_2CO_3) and analyzed by glpc (30% SE 30). After 18 hr, the area ratio of the bands which were due to **3c** and *o*-xylene was the same within the precision of the measurements (*ca.* 5%), but the area ratios of the bands which were due to **5c** and o-xylene and **6c** and *o*-xylene had decreased to 28 and 58% of their original value. After 42 hr, the band which was due to **6c** was replaced by two bands with nearly equal areas at slightly longer retention times. The band which was due to **5c** was replaced by another with a slightly longer retention time. The nmr spectrum of the solution possessed a band at δ 5.80, characteristic of C_1 protons of 1-alkoxyalkenes.

Registry No.—Potassium *t*-butoxide, 865-47-4; tetrahydrofuran, 109-99-9; *cis*-**1a**, 23240-29-1; *trans*-**1a**, 23240-30-4; *cis*-**1b**, 23240-31-5; *trans*-**1b**, 23240-32-6; *cis*-**1c**, 23240-33-7; *trans*-**1c**, 23240-34-8; *cis*-**1d**, 23240-35-9; *trans*-**1d**, 23240-36-0; *cis*-**1e**, 23240-37-1; *trans*-**1e**, 23240-38-2; *cis*-**1f**, 23240-39-3; *trans*-**1f**, 23240-40-6; **cis-2a**, 23240-41-7; *trans*-**2a**, 23240-42-8; *cis*-**2b**, 23240-43-9; *trans*-**2b**, 23240-44-0; *cis*-**2c**, 23240-45-1; *trans*-**2c**, 23240-46-2; **3a**, 1708-31-2; **3b**, 23240-48-4; **3c**, 23230-79-7; **4a**, 23230-80-0; **4b**, 23230-81-1; **4c**, 23230-82-2; **5a**, 23230-83-3; **5b**, 23230-84-4; **5c**, 23230-85-5; **6a**, 23230-86-6; **6b**, 23230-87-7; **6c**, 23230-88-8; **6d**, 23230-89-9; **7**, 23230-90-2; **14**, 23230-91-3; **15**, 23230-92-4; **18**, 23230-93-5; **19a**, 23230-94-6; **19b**, 23230-95-7; **19c**, 23230-96-8; **21**, 23230-97-9; **23**, 23230-98-0; **4b** (*p*-bromobenzenesulfonamide), 23230-99-1.

Acknowledgment.—We are grateful to Dr. G. Müller and Dr. B. J. King for their assistance in the early stages of this research.

Synthetic Intermediates Potentially Useful for the Synthesis of Tetrodotoxin and Derivatives. II.[1] Reaction of Diazomethane with Some Shikimic Acid Derivatives

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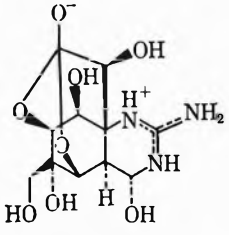
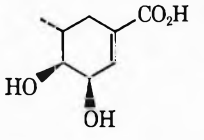
Received September 22, 1969

The reaction of diazomethane with three readily available derivatives, **3**–**5**, of natural shikimic acid has led to a series of new pyrazolines, the stereochemical assignments of which are discussed herein.

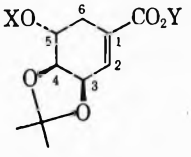
Our continuing interest in the synthesis of the Japanese puffer fish (*Fugu*)[2] and California newt (*Taricha Torosa*)[3] neuropoison tetrodotoxin (**1**) and closely related derivatives has led us to examine the reaction of diazomethane with alcohol **3**,[4] acetate **4**, and mesylate **5**, three readily available derivatives of natural shikimic acid (**2**). The pyrazolines which resulted, together with some of their chemistry, are described herein.



1



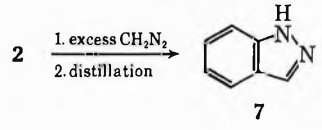
2



3, X = Y = H
4, X = Ac; Y = H
5, X = Ms; Y = H
6, X = Ac; Y = CH_3

The pyrazolines were prepared with the idea that it should be possible to reduce them to the corresponding substituted 1,3-diaminopropane,[5] condensation of which with either cyanogen bromide[6] or nitroguanidine[7] should lead to a cyclic guanidine, a structural moiety present in tetrodotoxin. Subsequent elaboration of the carbocyclic ring would then lead to a toxin derivative.

The action of diazomethane on shikimic acid itself has been reported by Grewe[8] to afford an oil, presumably a mixture of stereoisomeric pyrazolines, which was not characterized but instead was distilled, affording indazole **7**. Grewe[8] also reported that addition of diazomethane to ester **6** gave an oil which could be



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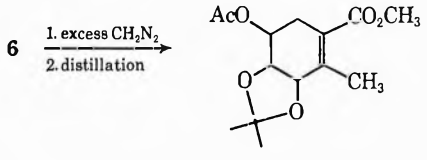
pyrolyzed to a mixture from which ester **8** could be isolated.



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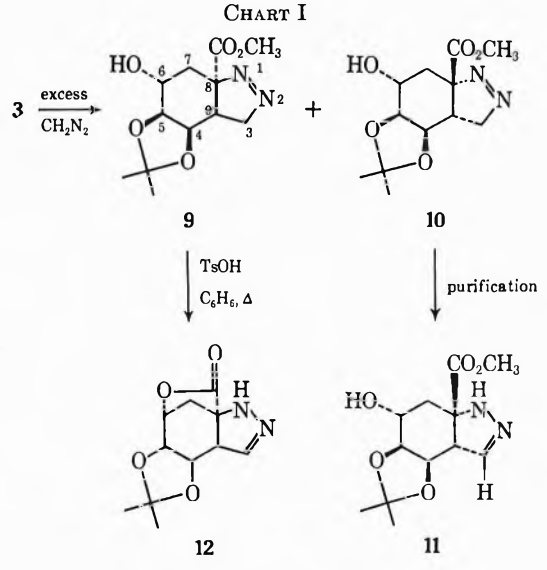
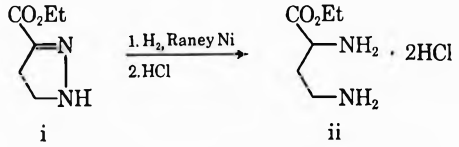
When hydroxy acid **3** (Chart I) was allowed to react with excess diazomethane in methanol–ether, a colorless oil was produced which, after chromatography over silica gel, afforded pyrazoline **9**, mp 108–109°, in 23% yield and pyrazoline **11**, mp 82–84°, in 75% yield.

CHART I



Presumably the Δ^1 isomer **10** was produced initially and then this substance suffered rearrangement during the purification process to the more stable[9] Δ^2 isomer **11** (see below). That pyrazoline **11** was indeed a Δ^2



i ii

(1) Part I: J. F. W. Keana, F. P. Mason, and J. S. Bland, *J. Org. Chem.*, **34**, 3705 (1969).

(2) K. Tsuda, *Naturwissenschaften*, **53**, 171 (1966); C. Y. Kao, *Pharmacol. Rev.*, **18**, 997 (1966); R. B. Woodward and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, **86**, 5030 (1964); K. Tsuda, S. Ikuma, M. Kawamura, R. Tachikawa, K. Sakai, C. Tamura, and O. Amakasu, *Chem. Pharm. Bull.* (Tokyo), **12**, 1357 (1964); T. Goto, Y. Kishi, S. Takahashi, and Y. Hirata, *Tetrahedron*, **21**, 2059 (1965); C. Tamura, O. Amakasu, Y. Sassada, and K. Tsuda, *Acta Crystallogr.*, **21**, 219, 226 (1966).

(3) H. S. Mosher, F. A. Fuhrman, H. D. Buchwald, and H. G. Fischer, *Science*, **144**, 1100 (1964).

(4) H. O. L. Fischer and G. Dangschat, *Helv. Chim. Acta*, **18**, 1206 (1935).

(5) For example, pyrazoline i has been reduced in high yield with Raney nickel and hydrogen in ethanol to the diamine ii, isolated as the dihydrochloride after treatment of the reduction product with hot hydrochloric acid: H. E. Carter, F. R. Van Abeele, and J. W. Rothrock, *J. Biol. Chem.*, **178**, 325 (1949). For the reduction of hydrazones to amines with platinum and hydrogen, see, *inter alia*, F. W. Lichtenthaler, H. Leinert, and T. Suami, *Chem. Ber.*, **100**, 2383 (1967).

(6) P. Pierron, *Ann. Chim.* (Paris), **11**(9), 361 (1919).

(7) A. F. McKay, *Chem. Rev.*, **51**, 301 (1952).

(8) R. Grewe and A. Bokranz, *Chem. Ber.*, **88**, 49 (1955).

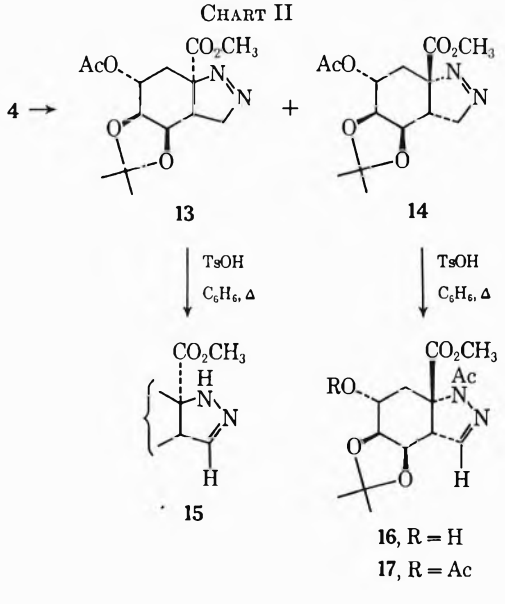
(9) See, *inter alia*, R. J. Crawford, A. Mishra, and R. J. Dummel, *J. Amer. Chem. Soc.*, **88**, 3959 (1966).

pyrazoline was clearly shown by its nmr spectrum,[10] which displayed a one-proton doublet (J = 1.5 Hz) at δ 6.9 owing to the proton at C-3 together with a broad NH absorption at δ 6.0–6.5. Pyrazoline **9** showed no absorption in this region. The two singlets which were due to the nonequivalent acetonide methyl groups of **9** were separated from one another by 4 Hz, whereas in **11** the separation was 9 Hz. This latter observation proved to be general for several stereoisomeric pyrazoline pairs resulting from the addition of diazomethane to various shikimic acid derivatives (see below and unpublished results).

Rinehart[11] has shown that diazomethane adds in a stereospecific *cis* manner to methyl angelate and methyl tiglate, leading to the corresponding Δ^1 pyrazolines. It is reasonable to assume that diazomethane will likewise add in a sterospecific *cis* manner to the rather analogous shikimic acid derivatives. Two Δ^1 pyrazolines, therefore, should be produced from **3**, and to the extent that the approach of diazomethane to **3** is sensitive to steric bulk, one would expect pyrazoline **10**, resulting from approach of diazomethane from the side opposite the bulky acetonide residue, to predominate. The stereochemistry of **9** was secured by reaction of this substance with a trace of *p*-toluenesulfonic acid in refluxing benzene, whereupon lactone **12**, mp 200–201°, was produced in moderate yield. Lactonization was accompanied by isomerization to a Δ^2 pyrazoline, as seen from the nmr spectrum of **12**, which displayed a one-proton doublet (J = 1.5 Hz) at δ 6.80 corresponding to the proton at C-3. The ir spectrum of **12** displayed a strong absorption at 1770 cm^{-1}, expected for a γ lactone. In order for lactone formation to occur with **9**, the C-6 α-hydroxy group and the C-8 carbomethoxy group must be *cis* to one another. Treatment of ester **11** under identical lactone-forming conditions led only to recovered starting material.

In another series of experiments, the acetylated derivative **4** (Chart II) was converted by excess diazomethane into an oily mixture of pyrazolines **13** and **14**.

CHART II

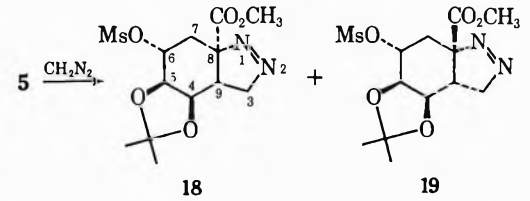


Chromatography over silica gel afforded **13** as a crystalline solid, mp 84–85°, in 27% yield and **14** as a homogeneous oil in 65% yield. It was expected that the preponderant isomer should have structure **14** (steric reasons, see above). Consistent with this formulation, the difference (see above) between the two singlets which were due to the methyl groups of the acetonide ring in **14** was 9 Hz, whereas this difference was 5 Hz in the case of **13**. Chemical proof of the stereochemical assignment was provided by the observation that **14** underwent a smooth *p*-toluenesulfonic acid catalyzed isomerization in refluxing benzene to Δ^2-pyrazoline **16**, mp 197–198°, in 78% yield, a process accompanied by migration of the acetyl group from oxygen to nitrogen.

This rather unusual *acid-catalyzed*[12] OAc → NAc migration was revealed by the nmr spectrum of pyrazoline **16**, which displayed the acetyl group as a sharp three-proton singlet at δ 2.25 rather than at δ 1.9–2.0, where it appeared with substances **13**–**15**, and by the ir spectrum of **16**, which showed a new strong band at 1620 cm^{-1} ascribed to the –HC=N– linkage. This band was not observed in the ir spectra of pyrazolines **11**, **12**, and **15**. Apparently the presence of the acetyl group on N-1 of pyrazoline **16** greatly enhanced the –HC=N– double bond absorption.

Pyrazoline **16**, upon treatment with acetic anhydride in pyridine, smoothly afforded diacetate **17**, mp 113–114°, the nmr spectrum of which displayed two three-proton acetyl singlets at δ 1.98 (OAc) and 2.23 (NAc). A strong band at 1620 cm^{-1} (–HC=N–) was present in the ir spectrum of this last substance. Treatment of pyrazoline **13** with *p*-toluenesulfonic acid in refluxing benzene led only to Δ^2-pyrazoline **15** (by nmr). From the above transformations, it follows that in pyrazoline **14** the C-6 acetoxy group and the pyrazoline ring are *cis* to one another.

Since it was important for later planned synthetic transformations to have a good leaving group attached to the 6 position, the mesylate acid **5** was prepared and subsequently treated with diazomethane. Again, two pyrazolines were isolated by silica gel chromatography of the reaction mixture. The preponderant isomer, an oil obtained in 36% yield, was assigned the stereochemistry embodied in structure **19**. The nmr spectrum of this substance showed a chemical-shift difference of 9 Hz between the two acetonide methyl singlets. The minor crystalline pyrazoline, mp 115–116°, was obtained in 21% yield and was assigned structure **18**. This last substance showed a corresponding chemical-shift difference of 4 Hz, in accord with differences shown by the pyrazoline pairs discussed above in which the stereochemistry was proven by chemical means.



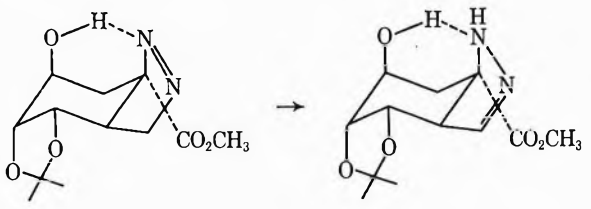
It is interesting that only in the case of the hydroxy-

(10) Complete spectral data for pertinent compounds are found in the Experimental Section.

(11) T. V. Van Auken and K. L. Rinehart, Jr., *J. Amer. Chem. Soc.*, **84**, 3736 (1962).

(12) OAc → NAc migrations are normally base catalyzed, whereas NAc → OAc migrations are normally acid catalyzed. See, *inter alia*, T. Posternak, "The Cyclitols," Holden-Day, Inc., San Francisco, Calif., 1965, p 31.

Δ^1-pyrazoline **10** was the Δ^1 isomer too easily isomerized to permit ready isolation. Quite possibly the hydroxy group assisted the isomerization in an intramolecular manner.



Experimental Section

Infrared spectra were recorded with a Beckman IR-5 spectrophotometer. Ultraviolet spectra were recorded with a Cary Model 15 spectrophotometer. Nmr spectra were determined on a Varian Associates Model A-60 high-resolution spectrometer. Chemical shifts are recorded in parts per million (δ) downfield from internal TMS, employing deuteriochloroform as solvent unless otherwise stated. Elemental analyses were performed by either Alfred Bernhard Laboratories, Mullheim, Germany, or Chemalytics, Inc., Tempe, Ariz. Mass spectra (70 eV) were determined on a CEC-110 spectrometer equipped with a direct inlet attachment. Melting points were determined in a stirred oil bath and are uncorrected. All chemicals were reagent grade. Solvents were routinely distilled prior to use.

Shikimic Acid 3,4-Acetonide (3).—The procedure of Fischer[4] was followed exactly. From 2.00 g of shikimic acid (Aldrich Chemical Co., mp 185–186°) there was obtained 2.17 g (87%) of **3**, mp 184.5–185.5° (lit.[4] mp 184°).

Diazomethane.—Diazomethane was prepared from Diazald[13] (Aldrich Chemical Co.). The resulting ether solution of diazomethane was distilled and the diazomethane content was estimated by portionwise addition of benzoic acid to an aliquot until the yellow color of the solution was discharged.

4β,5β,6α-Trihydroxy-8α-carbomethoxy-4,5,6,7,8,9α-hexahydro-3(H)-indazole 4,5-Acetonide (9) and 4β,5β,6α-Trihydroxy-8β-carbomethoxy-4,5,6,7,8,9β-hexahydro-1(H)-indazole 4,5-Acetonide (11).—A solution of 1.06 g (4.95 mmol) of acetonide **3** in 3 ml of methanol was added to a stirred solution of 1.5 g (36 mmol) of diazomethane in 60 ml of ether at 0°. After addition was complete, the resulting solution, protected from light by aluminum foil, was stirred at 0° for 1 hr and then at 25° for 12 hr. Removal of the solvent at reduced pressure afforded 1.64 g of a colorless oil which was chromatographed over 30 g of silica gel. Elution with 1% methanol in chloroform afforded first, crystalline minor pyrazoline **9**. Recrystallization of combined fractions from ether gave 320 mg (23%) of **9** as white needles: mp 108–109°; nmr δ 1.24 (s, 3, acetonide methyl), 1.30 (s, 3, acetonide methyl), 2.13 (q, 1, H-9), 2.6–3.2 (m, 2, H-7), 3.70 (s, 3, methyl ester protons), and 3.8–5.3 (m, 5, H-3–6); ir ($CHCl_3$) 3500 (w) and 1740 cm^{-1} (s); uv max (EtOH) 322 mμ (ϵ 182);[9] mass spectrum *m/e* 255 (loss of a methyl from the acetonide moiety[14]), 228 (loss of diazomethane or ketene), 167, 153, 135, 123, and 107.

Anal. Calcd for $C_{12}H_{18}N_2O_5$: C, 53.33; H, 6.71; N, 10.36. Found: C, 53.92; H, 6.98; N, 10.27.

Continued elution with the same solvent system afforded oily pyrazoline **11**, which slowly crystallized in the cold room, probably picking up water (see analysis). Recrystallization from ether–hexane afforded 950 mg (75%) of **11** as white needles: mp 82–84°; nmr δ 1.38 (s, 3, acetonide methyl), 1.52 (s, 3, acetonide methyl), 1.7–2.5 (m, 2, H-7), 3.45–3.70 (m, 1, H-9), 3.80 (s, 3, methyl ester protons), 3.8–4.4 (m, 3, H-4–6), *ca.* 5.0–6.0 (broad, 1, H-1), and 6.90 (d, 1, J = 1.5 Hz, H-3); ir ($CHCl_3$) 3400 (m) and 1740 cm^{-1} (s).

Anal. Calcd for $C_{12}H_{18}N_2O_5 \cdot H_2O$: C, 49.99; H, 6.99; N, 9.72. Found: C, 50.25; H, 6.93; N, 9.76.

4β,5β,6α-Trihydroxy-8α-carboxy-4,5,6,7,8,9α-hexahydro-1(H)-indazole 4,5-Acetonide 8α→6α-Lactone (12).—A solution of 100 mg of pyrazoline **9** and 2 mg of *p*-toluenesulfonic acid monohydrate in 3 ml of dry benzene was heated at reflux under nitrogen for 12 hr. Removal of the benzene under reduced pressure afforded 84 mg of a reddish, crystalline solid. Recrystallization from ether–chloroform gave 35 mg (34%) of **12** as white needles: mp 200–201°; nmr δ 1.37 (s, 3, acetonide methyl), 1.50 (s, 3, acetonide methyl), 1.8–3.0 (m, 2, H-7), 3.4–5.0 (m, 4, H-4–6, -9), 5.6–6.0 (broad, 1, NH), and 6.80 (d, 1, J = 1.5 Hz, H-3); ir ($CHCl_3$) 3300 (w) and 1770 cm^{-1} (s).

Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.46; H, 5.92; N, 11.76. Found: C, 55.32; H, 5.83; N, 11.88.

5-Acetylshikimic Acid 3,4-Acetonide (4).—To a solution of 2.66 g (12.4 mmol) of acetonide **3** in 10 ml of pyridine at 25° was added 1.3 ml (18 mmol) of acetic anhydride. The solution was allowed to stand under nitrogen for 24 hr at 25° and then the volatile solvents were removed under high vacuum at 25°, affording a slightly orange, viscous oil. The oil was dissolved in 50 ml of chloroform, washed with several portions of ice-cold 2% hydrochloric acid, dried ($MgSO_4$), and evaporated, affording 3.2 g (100%) of a viscous, colorless oil which slowly crystallized upon standing in the cold room. Because of its low melting point, recrystallization was not attempted. Molecular distillation at *ca.* 10^{-5} mm in a 100° oil bath afforded the analytical specimen as a colorless, hard oil: nmr δ 1.42 (s, 6, acetonide methyl) 2.10 (s, 3, acetyl protons), 2.1–2.8 (m, 2, H-6), 4.1–5.3 (m, 3, H-3–5), 6.9–7.2 (m, 1, H-2), and 8.7 (s, 1, acid proton); ir ($CHCl_3$) 2400–3000 (broad), 1750 (m), 1730 (s), 1670 (s), and 1650 cm^{-1} (w).

Anal. Calcd for $C_{12}H_{16}O_6 \cdot {}^1/_2H_2O$: C, 54.34; H, 6.41. Found: C, 54.51; H, 6.21.

4β,5β-Dihydroxy-6α-acetoxy-8α-carbomethoxy-4,5,6,7,8,9α-hexahydro-3(H)-indazole 4,5-Acetonide (13) and 4β,5β-Dihydroxy-6α-acetoxy-8β-carbomethoxy-4,5,6,7,8,9β-hexahydro-3-(H)-indazole 4,5-Acetonide (14).—To a solution of 1.5 g (36 mmol) of diazomethane in 60 ml of ether was added with stirring at 0° a solution of 2.1 g (8.2 mmol) of acetate **4** (sticky glass) in 20 ml of ether. The solution was allowed to stir protected from light for 12 hr at 25° and then the ether was evaporated, affording 2.3 g of a colorless oil. Chromatography over 45 g of silica gel and elution with 0.5% methanol in chloroform afforded first 700 mg (27%) of crude, crystalline **13**, mp 84–85°, suitable for further reactions. Recrystallization of a 500-mg portion from ether–hexane produced 200 mg of the analytical specimen as white prisms: mp 85–86°; nmr δ 1.26 (s, 3, acetonide methyl), 1.35 (s, 3, acetonide methyl), 1.8–2.8 (m, 1, H-9), 1.93 (s, 3, acetyl protons), 2.5–3.0 (m, 2, H-7), 3.0–5.3 (m, 5, H-3–6), and 3.72 (s, 3, methyl ester protons); ir (CCl_4) 3000 (m) and 1745 cm^{-1} (s).

Anal. Calcd for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.45; N, 8.96. Found: C, 53.84; H, 6.19; N, 9.17.

Continued elution with the same solvent system afforded 1.6 g (65%) of **14** as a homogeneous (tlc), colorless oil. Molecular distillation at *ca.* 10^{-5} mm in a 110° oil bath afforded the analytical specimen as a colorless, hard oil: nmr (CCl_4) δ 1.28 (s, 3, acetonide methyl), 1.40 (s, 3, acetonide methyl), 1.7–2.2 (m, 1, H-9), 1.90 (s, 3, acetyl protons), 2.3–3.0 (m, 2, H-7), 3.5–5.3 (m, 5, H-3–6), and 3.80 (s, 3, methyl ester protons); ir (CCl_4) 3000 (m) and 1745 cm^{-1} (s); mass spectrum *m/e* 312 (parent ion), 298, 297 (loss of methyl), 270 (loss of diazomethane or ketene), and 269.

Anal. Calcd for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.45; N, 8.96. Found: C, 53.25; H, 6.19; N, 8.97.

1-Acetyl-4β,5β,6α-trihydroxy-8β-carbomethoxy-4,5,6,7,8,9β-hexahydro-1(H)-indazole 4,5-Acetonide (16).—A solution of 700 mg of **14** (hard oil), 2 mg of *p*-toluenesulfonic acid monohydrate, and 10 ml of benzene was heated at reflux under nitrogen for 60 min. Evaporation of the benzene produced a reddish glass which was chromatographed over 10 g of silica gel. Elution with 2% methanol in chloroform gave 550 mg (78%) of crystalline **16**, mp 197–198°. Two further recrystallizations from chloroform–hexane afforded the analytical specimen as white needles: mp 197–198°; nmr δ 1.32 (s, 3, acetonide methyl), 1.47 (s, 3, acetonide methyl), 2.25 (s, 3, N acetate), 2.5–3.2 (m, 2, H-7), 3.4–4.6 (m, 4, H-4–6, -9), and 6.86 (d, 1, J = 1.5 Hz, H-3); ir ($CHCl_3$) 3400 (m), 3000 (m), 1750 (s), 1670 (s), and 1620 cm^{-1} (s); mass spectrum *m/e* 312 (parent ion), 297 (loss of methyl), 256, 255, and 254.

Anal. Calcd for $C_{14}H_{20}N_2O_6$: C, 53.84; H, 6.45; N, 8.96. Found: C, 54.04; H, 6.48; N, 9.00.

1-Acetyl-4β,5β-dihydroxy-6α-acetoxy-8β-carbomethoxy-4,5,6,7,8,9β-hexahydro-1(H)-indazole 4,5-Acetonide (17).—To a

(13) T. J. DeBoer and H. J. Backer, *Rec. Trav. Chim. Pays-Bas*, **73**, 229 (1954).

(14) Acetonides frequently do not show a parent ion. See J. A. McCloskey and M. J. McClelland, *J. Amer. Chem. Soc.*, **87**, 5090 (1965).

solution of 200 mg (0.670 mmol) of **16** in 1.5 ml of pyridine at 0° was added under nitrogen 135 mg (1.33 mmol) of acetic anhydride. The solution was stirred for 12 hr at 25°, after which time the pyridine and excess acetic anhydride were removed by high vacuum distillation at 25°, affording 251 mg of a yellow, viscous oil. The oil was dissolved in 10 ml of chloroform and washed with ice-cold 2% hydrochloric acid. The chloroform layer was dried ($MgSO_4$) and then evaporated, affording 230 mg of pale yellow crystals. Recrystallization from ether–hexane gave 150 mg (65%) of **17** as white needles: mp 113–114°; nmr δ 1.32 (s, 3, acetonide methyl), 1.48 (s, 3, acetonide methyl), 1.98 (s, 3, O-acetate), 2.23 (s, 3, N-acetate), 2.3–2.8 (m, 2, H-7), 3.80 (s, 3, methyl ester protons), 3.8–5.2 (m, 4, H-4–6, -9), and 6.78 (broadened singlet, 1, H-3); ir ($CHCl_3$) 3000 (m), 1740 (s), 1670 (s), and 1620 cm^{-1} (s); mass spectrum *m/e* 354 (parent ion), 339 (loss of methyl), and 237.

Anal. Calcd for $C_{16}H_{22}N_2O_7$: C, 54.23; H, 6.26; N, 7.91. Found: C, 53.87; H, 6.07; N, 7.95.

4β,5β-Dihydroxy-6α-acetoxy-8β-carbomethoxy-4,5,6,7,8,9β-hexahydro-3(H)-indazole 4,5-Acetonide (15).—A solution of 1.7 g of the original mixture of Δ^1-pyrazolines **13** and **14** formed by the addition of diazomethane to acetate **4** (see above) and 15 mg of *p*-toluenesulfonic acid monohydrate in 15 ml of benzene was heated at reflux for 60 min under nitrogen and then the solvent was evaporated, leaving a reddish oil. Chromatography over 30 g of silica gel and elution with 0.5% methanol in chloroform afforded *ca.* 600 mg (24%, based on starting **4**) of **15** as a colorless, homogeneous (tlc) oil suitable for further reactions. The oil decomposed on attempted molecular distillation at *ca.* 10^{-5} mm in a 110° oil bath, forming a yellow oil, the elemental analysis of which showed <1% nitrogen (calcd: 8.98). An acceptable mass spectrum could not be obtained. Nevertheless, the nmr and ir spectra were completely consistent with those expected for **15**: nmr δ 1.32 (s, 3, acetonide methyl), 1.50 (s, 3, acetonide methyl), 2.00 (s, 3, acetate), 1.9–2.4 (m, 2, H-7), 3.7–5.1 (m, 4, H-4–6, -9), 3.75 (s, 3, methyl ester protons), 5.0–5.8 (broad, 1, NH), and 6.80 (d, 1, J = 1.5 Hz, H-3); ir ($CHCl_3$) 3400 (m), 3000 (m), and 1747 cm^{-1} (s). Another experiment utilizing crystalline **13** as starting material for the isomerization also afforded an oil identical with **15** above by nmr.

Continued elution with 2% methanol in chloroform afforded 564 mg (23%, based on starting **4**) of crystalline **16** (see above), suitable for further reactions.

5-Mesylshikimic Acid 3,4-Acetonide (5).—To a solution of 500 mg (2.34 mmol) of acetonide **3**, 500 mg (4.95 mmol) of triethylamine, and 20 ml of benzene was added dropwise with stirring at 5° under nitrogen 570 mg (5.0 mmol) of methanesulfonyl chloride. After addition was complete the triethylamine hydrochloride was removed by filtration and the solvent was removed at 25° under vacuum, affording a viscous, reddish oil. This was dissolved in 30 ml of chloroform and washed with ice-cold 3% hydrochloric acid. The chloroform layer was dried ($MgSO_4$) and evaporated, producing 626 mg of a yellow oil. This oil contained some of the corresponding acid chloride and was therefore treated with a solution of 3 ml of acetone and 3 ml of 2% aqueous sodium bicarbonate at 25° for 12 hr. The solution was then acidified with 2% hydrochloric acid at 0° and then extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated, producing 488 mg (72%) of **5** as a colorless foam. Molecular distillation at 120° and *ca.* 10^{-5} mm afforded the analytical specimen as a colorless, hard oil: nmr δ 1.43 (s, 3, acetonide methyl), 1.47 (s, 3, acetonide methyl), 2.5–3.0 (m, 2, H-6), 3.17 (s, 3, mesylate), 4.1–5.1 (m, 3, H-3–5), and 6.9–7.2 (m, 1, H-2); ir ($CHCl_3$) 3600–2400 (broad), 3000 (m), 1780 (s), and 1725 cm^{-1} (s).

Anal. Calcd for $C_{11}H_{16}O_7S$: C, 45.20; H, 5.49. Found: C, 44.69; H, 5.37. Analytically pure **5** acquired a deep red-brown coloration while standing for several days.

4β,5β-Dihydroxy-6α-mesyloxy-8α-carbomethoxy-4,5,6,7,8,9α-hexahydro-3(H)-indazole 4,5-Acetonide (18) and 4β,5β-Dihydroxy-6α-mesyloxy-8β-carbomethoxy-4,5,6,7,8,9β-hexahydro-3(H)-indazole 4,5-Acetonide (19).—To a solution of *ca.* 50 mg (1.2 mmol) of diazomethane in ether was added at 0° with stirring a solution of 100 mg (0.34 mmol) of crude mesylate **5** (yellow oil) in 1 ml of methanol. The solution was stirred for 12 hr at 25° and then the solvent was evaporated, affording 130 mg of a reddish oil. Chromatography over 10 g of silica gel and elution with chloroform afforded first 25 mg (21%) of crystalline **18**. Recrystallization of the combined fractions from ether–hexane afforded 20 mg of **18** as white needles: mp 115–116°; nmr δ 1.28 (s, 3, acetonide methyl), 1.35 (s, 3, acetonide methyl), 1.5–3.5 (m, 3, H-7, -9), 3.05 (s, 3, mesylate), 3.75 (s, 3, methyl ester protons), and 4.0–5.3 (m, 5, H-3–6); ir ($CHCl_3$) 3000 (m) and 1745 cm^{-1} (s).

Anal. Calcd for $C_{13}H_{20}N_2O_7S$: C, 44.83; H, 5.75; N, 8.05. Found: C, 44.87; H, 5.78; N, 8.03.

Continued elution with chloroform afforded 45 mg (36%) of **19** as a homogeneous (tlc) oil which resisted attempts at crystallization. Molecular distillation at *ca.* 10^{-5} mm in a 110° oil bath produced the analytical specimen of **19** as a colorless, hard oil: nmr δ 1.30 (s, 3, acetonide methyl), 1.48 (s, 3, acetonide methyl), 1.5–3.5 (m, 3, H-7, -9), 3.05 (s, 3, mesylate), 3.83 (s, 3, methyl ester protons), and 4.0–5.4 (m, 5, H-3–6); ir ($CHCl_3$) 3000 (m) and 1745 cm^{-1} (s).

Anal. Calcd for $C_{13}H_{20}N_2O_7S$: C, 44.83; H, 5.75; N, 8.05. Found: C, 44.50; H, 5.63; N, 8.12.

Registry No.—**1**, 4368-28-9; **4**, 23330-72-5; **5**, 23367-55-7; **9**, 23367-56-8; **11**, 23330-73-6; **12**, 23367-57-9; **13**, 23328-30-5; **14**, 23328-31-6; **15**, 23367-58-0; **16**, 23367-59-1; **17**, 23328-32-7; **18**, 23328-33-8; **19**, 23328-34-9; diazomethane, 334-88-3.

Acknowledgment.—The authors thank the National Science Foundation (GP 10736) and the National Institutes of Health (5-R01-NB07586-02) for generous financial support of this work, and Hoffman-LaRoche for a generous gift of shikimic acid.

A New Synthesis of Rosoxides. *cis*- and *trans*-2-(2-Methyl-1-propen-1-yl)-4-methyltetrahydropyran

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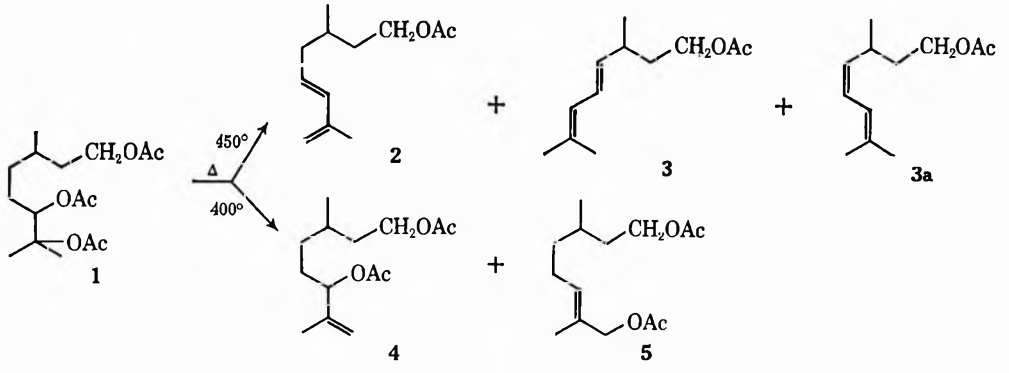
Received June 16, 1969

Pyrolysis of 2,6-dimethyl-2,3,8-triacetoxyoctane (**1**) at *ca.* 450° affords mainly *trans*-2,6-dimethyl-1,3-octadien-8-yl acetate (**2**), minor amounts of *trans* and *cis* isomers **3** and **3a**, respectively, an intermediate 2,6-dimethyl-3,8-diacetoxy-1-octene (**4**), and its allylomer **5**. In the presence of acids and acid salts, the pyrolysis favors the formation of **3** and **3a** over **2**. Rosoxide, *cis*- and *trans*-2-(2-methyl-1-propen-1-yl)-4-methyltetrahydropyran (**6** and **6a**), is obtained, in almost quantitative yield, through the facile acid cyclization of *trans*-2,6-dimethyl-1,3-octadien-8-ol (**8**) derived from **2**. On the other hand, the acid cyclization of *trans*- and *cis*-isomeric alcohols **9** and **9a**, derived from **3** and **3a**, is more difficult and affords, in addition to rosoxides **6** and **6a**, substantial amounts of their terminal methylene isomers **7** and **7a** as well as hydroxyrosoxides **10** and **10a**.

Rosoxide, *cis*- and *trans*-2-(2-methyl-1-propen-1-yl)-4-methyltetrahydropyran (**6** and **6a**), a minor but important olfactive ingredient of rose otto and geranium oil,[2] has been synthesized by various methods[3] difficult to scale up.

We would like to report a practical and economic synthesis of a key intermediate in the synthesis of rosoxides **6** and **6a**, namely, *trans*-2,6-dimethyl-1,3-octadien-8-yl acetate (**2**), which was reported earlier in impure state through a difficult synthetic route.[2]

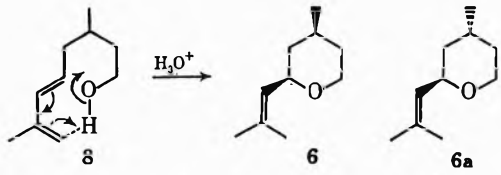
When 2,6-dimethyl-2,3,8-triacetoxyoctane (**1**) is pyrolyzed at *ca.* 450–475°, a mixture is obtained consisting of *ca.* 70–75% *trans*-2,6-dimethyl-1,3-octadien-8-yl acetate (**2**), 8–10% *trans*- and *cis*-2,6-dimethyl-2,4-octadien-8-yl acetate (**3** and **3a**), and 15–20% a mixture of 2,6-dimethyl-3,8-diacetoxy-1-octane (**4**) and its allylomer 2,6-dimethyl-1,8-diacetoxy-2-octene (**5**). Both **4** and **5** are eventually converted into **2** upon recycling. The overall yield of **2** from either **1** or **4** is *ca.* 75%.



It is noteworthy that the pyrolysis of **1** and **4** affords mainly *trans*-2,6-dimethyl-1,3-octadien-8-yl acetate (**2**) as the main component (the presence of the *cis* isomer **2a** could not be ascertained by vpc on a CW 20M column) and only minor amounts of *trans*- and *cis*-2,6-dimethyl-2,4-octadien-8-yl acetate (**3** and **3a**). However, in the presence of $KHSO_4$ or *p*-toluenesulfonic acid, **3** and **3a** are the major products of the pyrolysis. Oxalic acid, on the other hand, affords mainly **2**. The intermediate, 2,6-dimethyl-3,8-diacetoxy-1-octene (**4**), which becomes the major reaction product of the pyrolysis of **1** at *ca.* 400°, pyrolyzes further at higher temperatures (450–475°) to yield a pyrolysate identical with that of **1**.

Table I gives the data of the pyrolysis of both **1** (with or without catalysts) and **4**.

In the presence of strong mineral acids at room tem, perature, *trans*-2,6-dimethyl-1,3-octadien-8-ol (**8**), obtained from the corresponding acetate **2**, readily cyclizes in almost quantitative yield, into a 9:1 mixture of isomeric rosoxides **6** and **6a**.



However, the cyclization of *trans*-2,6-dimethyl-2,4-octadien-8-ol (**9**), derived from **3**, requires more drastic conditions and affords substantial amounts of the terminal methylene rosoxide isomers, *cis*- and *trans*-2-(2-methyl-2-propen-1-yl)-4-methyltetrahydropyran (**7** and **7a**, respectively),[4] together with some *cis*- and *trans*-2-(2-methyl-2-hydroxyprop-1-yl)-4-methyltetra-

(1) Presented at the 153rd National Meeting of the American Chemical Society, Miami, Fla., April 1967, Division of Cellulose, Wood, and Fiber Chemistry, Lecture 28.

(2) (a) C. F. Seidel, *et al.*, *Helv. Chim. Acta*, **42**, 1830 (1959); (b) U. S. Patent 3,161, 657 (1964); (c) Y. R. Naves, *et al.*, *Bull Soc. Chim. Fr.*, 645 (1961).

(3) U. S. Patent 3,161,657 (1964); G. Ohloff, *et al.*, *Angew. Chem.*, 578 (1961); German Patent 1,137,730 (1962); British Patent 1,010,056 (1956); French Patent 1,319,202 (1963); *Helv. Chim. Acta*, **48**, 182 (1965); A. Malera and Y. R. Naves, *Comp. Rend.*, **252**, 1937 (1961); Y. R. Naves and P. Ochsner, *Helv. Chim. Acta*, **45**, 397 (1962); U. S. Patent 3,166,575 (1965); French Patent 1,312,034 (1962); U. S. Patent 3,163,658 (1964); U. S. Patent 3,166,576 (1965); M. Julia and B. Jacquet, *Bull. Soc. Chim. Fr.*, 1983 (1963); French Patent 1,539,094 (1967). The list of patents is only partial and keeps on growing.

(4) See Naves and Ochsner.[3]

TABLE I

Starting material	Catalyst	Temp of pyrolysis, °C	Time, min	Rate of pyrolysis, ml/min	Yield[a] of 3a + 2 + 3, %	Isomeric distribution[b] 3a	2	3	Recovered intermediate, % 4	5
1	1% $KHSO_4$	260–280	10	Batchwise	50	16	27	57	35	4
1	1% *p*-toluenesulfonic acid	170–200	30	Batchwise	50	18	11	64	7	10
1	1% oxalic acid	280–330	70	Batchwise	50	5	75	20	14	25
1	None[c]	475	...	10	75	5	88	7	17	18
4	None[c]	475	...	15	77	6	86	8	4	12

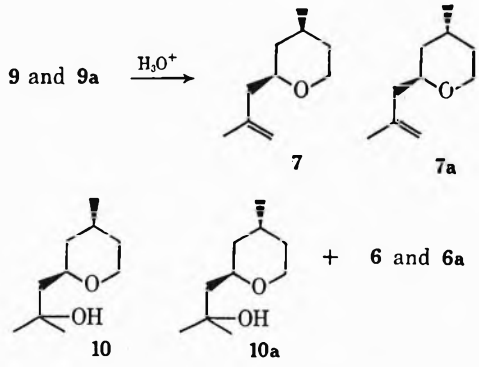
[a] Yield based on amount of consumed starting material (1 or 4) minus recovered intermediates 4 and 5. [b] Determined by vpc on a CW 20M 0.25-in. column at 200°. [c] Pyrolysis in a stainless steel, 15 ft × 0.25 in. tube coiled in 80 spirals, 22-mm o.d., capacity 52 ml, packed into a 4-ft upright furnace.

TABLE II

ACID CYCLIZATION OF 8, 9, AND 9a TO ROSOXIDE AND DERIVATIVES

Starting material (1 part)	Catalyst (2 parts)	Solvent	Temp, °C	Time, min	Reaction product, % 7, 7a	6, 6a	10, 10a	Unreacted material, % 8	9	9a
8	2.5% H_2SO_4	H_2O	100	90	4	87	9	>10		
8	10% H_2SO_4	H_2O	100	120	14	73	13	>10		
8	20% H_2SO_4	H_2O	25	600	...	99	1	>10		
8	30% H_2SO_4	H_2O	25	60	...	100	...	>5		
8	50% H_2SO_4	H_2O	25	150	4	70	26	>10		
8	50% H_2SO_4	H_2O	25	250	5	11	84	>10		
8	62% H_2SO_4	H_2O	25	1	1	2	97	>50		
8	42% H_3PO_4	H_2O	25	360	...	99	1	...		
9	30% H_2SO_4	H_2O	25	1680	4	96	...	...	76	
9	35% H_2SO_4	H_2O	25	240	30	59	11	10	12	
9	35% H_2SO_4	H_2O	25	480	2	8	90	...	...	
9	45% H_2SO_4	H_2O	25	120	22	78	...	...	54	
9	45% H_2SO_4	H_2O	25	960	25	75	...	...	40	
9	45% H_2SO_4	H_2O	100	10	4	15	81	...	...	
9	62% H_2SO_4	H_2O	25	5	...	...	100	...	>5	
9	1.5% *p*-Tos	Benzene	82	840	27	...	73	...	15	
9a	30% H_2SO_4	H_2O	25	1320	2	98	...	...	54	

hydropyran (**10** and **10a**) and only minor amounts of rosoxides **6** and **6a**.



Both the hydration with strong mineral acids of **7** and **7a** to **10** and **10a** and, in particular, their hydrogenation, with Pd–C, to dihydrorosoxides [*cis*- and *trans*-2-(2-methyl-prop-1-yl)-4-methyltetrahydropyran] proceed at a faster rate than with their isomeric rosoxides **6** and **6a**.

Table II shows the progress of acid cyclization of **8**, **9**, and **9a** under various conditions to yield isomeric rosoxides **6** and **6a** and **7** and **7a**, and hydroxyrosoxides **10** and **10a**. In most of the cases the *cis*- and *trans*-isomeric ratio was about 9:1 (vpc on CW 20M column).

Experimental Section

2,6-Dimethyl-3,8-diacetoxy-1-octene (4) and 2,6-Dimethyl-2,3,8-triacetoxyoctane (1).—Citronellyl acetate (60 g) in 40% formic acid (21 g) was hydroxylated by adding at 75–80°, within 0.5 hr, 30% H_2O_2 (37 g); the reaction was complete after 3–4 hr (vpc, SE-30, 225°). The reaction mixture was mixed with water (50 ml) and extracted with benzene (30 ml), and, after evaporation of the solvent, the residue (63 g) of 95% pure 2,6-dimethyl-2,3-dihydroxyoctan-8-yl acetate was acetylated with acetic anhydride (110 g) under reflux for 3–4 hr (140–142°).

Upon fractionation through a 1-ft Goodloe column, the following cuts were obtained: (1) (70 g), bp 80° (2 mm); (2) 2,6-dimethyl-3,8-diacetoxy-1-octene (**4**, 6 g, 96% pure), bp 110–115° (2 mm), $n^{20}D$ 1.4460, sapon equiv 413 (theory 432); (3) 2,6-dimethyl-2,3,8-triacetoxyoctane (**1**, 70 g, 95% pure), bp 140–145° (2 mm), $n^{20}D$ 1.4440, sapon equiv 509 (theory 530).

Pyrolysis of 1.—Triacetate **1** (275 g) was pyrolyzed at 10 ml/min at 475° in the apparatus described in Table I. After washing with water, neutralization, and distillation as described in the previous example, the following cuts (Table III) were obtained (vpc, 20M, 0.25-in. column, 200°).

TABLE III

Cut	Bp, °C (mm)	Yield, g	$n^{20}D$	Components, % X[a]	3a	2	3	4	5
1	80 (2)	2	1.4690	80	20[b]				
2	100 (2)	90	1.4665	5	88	7			
3	120 (2)	92	1.4520				10[b]	35	45

[a] Mostly hydrocarbons. [b] Includes **2**, **3**, and **3a**.

Pyrolysis of 4.—Diacetate **4** (100 g) was pyrolyzed at a rate of 15 ml/min at 475° in the apparatus described in Table I. The pyrolysate was treated as in **1**, giving the cuts below (Table IV).

***trans*-2,6-Dimethyl-1,3-octadien-8-yl Acetate (2) and *trans*-2,6-Dimethyl-1,3-octadien-8-ol (8).**[3]—Cut 2 (100 g) obtained in the two previous examples from the pyrolysis of **1** and **4** afforded, upon distillation through a 2-ft Goodloe column, 80 g of a main cut of *trans*-2,6-dimethyl-1,3-octadien-8-yl acetate (**2**): 98% pure (vpc, SE-30, 220°); bp 80–83° (3 mm); $n^{20}D$ 1.4680; sapon equiv 284 (theory 285.7); uv λ_{max} 230 mμ (ε 33,800) and

Table IV

Cut	Bp, °C (mm)	Yield, g	$n^{20}D$	Components, % X[a]	3a	2	3	4	5
1	80 (2)	30	1.4570	80		20[b]			
2	100 (2)	500	1.4650		6	86	8		
3	120 (2)	205	1.4525			15[b]		30	55

[a] Mostly hydrocarbons. [b] Includes **2**, **3**, and **3a**.

237 (23,100) [lit.[2a] λ_{max} 231.5 mμ (10,700) and 235 (8500)]; ir 6.2 and 11.35 (terminal $=CH_2$) and 10.34 μ (*trans* band).

The nmr spectrum follows: H at C_3, d, δ 6.25, $J_{3,4}$ = 15 Hz (*trans*); H at C_4, d of t, δ 5.65; 2 H of $CH_2=$, s, δ 4.9; 2 H of OCH_2, t, δ 4.16, J = 7 Hz; 3 H of OAc, s, δ 2.02; 3 H of $CH_3C=$, s, δ 1.84; 3 H of $CH_3CH<$, d, δ 0.9, J = 5 Hz.

The compound had a pleasant, fruity, pearlike odor. Upon hydrogenation of a sample in the presence of 5% Pd–C catalyst, it was converted into 2,6-dimethyl-8-octanyl acetate and was identified with an authentic sample by ir. Saponification of **2** with a 10% KOH alcoholic solution afforded *trans*-2,6-dimethyl-1,3-octadien-8-ol (**8**) in 95% yield. Distillation gave a main cut: bp 100° (4 mm); $n^{20}D$ 1.4860; purity 98% (vpc, SE-30, 0.25 in. × 6-ft column at 200°), uv λ_{max} 230 mμ (ε 25,810), 237, (9700); ir 6.2 and 11.4 ($=CH_2$) and 10.4 μ (*trans* band).

The nmr spectrum follows: H at C_3, d, δ 6.25, $J_{3,4}$ = 15 Hz (*trans*); H at C_4 m, δ 5.68; 2 H of $CH_2=$, s, δ 4.86; 2 H of OCH_2, t, δ 3.7, J = 6 Hz; 3 H of $CH_3C=$, s, δ 1.83; 3 H of $CH_3CH<$, d, δ 0.91, J = 5 Hz.

The ε values reported by Seidel, *et al.*[2a] were substantially lower, indicating a product of lesser purity.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.63; H, 11.59.

2,6-Dimethyl-1,8-diacetoxy-2-octene (5) and 2,6-Dimethyl-1,8-dihydroxy-2-octene.—Cut 3 (100 g) from the previous distillations of the pyrolyzates of **1** and **4** was redistilled through a 1-ft Goodloe column and gave, after removal of **4**, bp 110–115° (2 mm), $n^{20}D$ 1.4462, a main cut (50 g), bp 125–130° (2 mm), $n^{20}D$ 1.4530, of a 12:88 *cis* and *trans* isomer mixture (vpc, SE-30, 200°) of 2,6-dimethyl-1,8-diacetoxy-2-octene (**5**), sapon equiv 430 (theory 440 for $C_{14}H_{24}O_4$, mol wt 256). The mass spectrum showed a weak peak at *m/e* 256 and a strong one at *m/e* 214 representing a loss of ketene to yield 2,6-dimethyl-1-hydroxy-8-acetoxyoctane.

The nmr spectrum follows: H at C_3, t, δ 5.27, J = 7 Hz; 2 H of CH_2O, s (minor, 15%); δ 4.51, s (major, 85%); δ 4.38 (*cis* and *trans* isomers of OAc at C_1); 6 H of 2OAc, 2 s, δ 1.99 and 2.02; 3 H of $CH_3C=$, s, δ 1.63; 3 H of CH_3CH, d, δ 0.93, J = 4 Hz.

Upon saponification with 50% methanolic KOH, the compound yielded the corresponding glycol, bp 110–115° (2–3 mm), $n^{20}D$ 1.4780, as a mixture of *cis* and *trans* isomers of 2,6-dimethyl-1,8-dihydroxy-2-octene ($C_{10}H_{20}O_2$), mol wt 172.

The nmr spectrum follows: H at C_3, t, δ 5.32, J = 7 Hz (major isomer, 85%); t, δ 5.17, J = 7 Hz (minor isomer, 15%) (*cis* and *trans* isomer of OH at C_1); 2 H of CH_2OH, s, δ 3.88, with minor impurity, d, δ 4.02, J = 5 Hz; 2 H of CH_2OH, t, δ 3.56, J = 6 Hz; 2 H of OH, s, δ 3.07; 2 H of CH_2CH_2OH, m, δ 2.01; 3 H of $CH_3C=$, s, δ 1.51; 3 H of $CH_3CH<$, d, δ 0.87, J = 6 Hz.

Pyrolysis with $KHSO_4$. Preparation of 3, 3a, 9, and 9a.—Triacetate **1** (46 g) and $KHSO_4$ (0.5 g) were heated in a modified Claisen–Vigreux flask at 250–270° and kept at this temperature for 5–8 min while 7 g of acetic acid distilled at 100–130°. The pot temperature was then raised to 310° and the distillate was collected at 250–260°. The crude distillate (35 g) was washed with water (2 volumes) and neutralized with 10% soda ash. It afforded upon redistillation the following cuts (Table V) (vpc, CW 20M, 200°).

Table V

Cut	Bp, °C (mm)	Yield, g	$n^{20}D$	Components, % 3a	2	3	4	5
1	100 (2)	16.5	1.4600	18	11	64		
2	140 (2)	12.0	1.4500				90	10
3	160 (2)	2.0	1.4600				50	50

Both *cis*-2,6-dimethyl-2,4-octadien-8-yl acetate (**3a**) and *trans*-2,6-dimethyl-2,4-octadien-8-yl acetate (**3**) were obtained by redistillation of cut 1 through a 2-ft Goodloe column. The pure products had the constants given below.

trans-**2,6-Dimethyl-2,4-octadien-8-yl acetate** (**3**) gave the following data: bp 94° (3 mm); $n^{20}D$ 1.4755; sapon equiv 282 (theory 285.7); ir 10.45 μ (*trans* band); uv λ_{max} 237 mμ (ε 29,400) and 230 (27,050). Hydrogenation over Pd–C afforded 2,6-dimethyloctan-8-yl acetate.

The nmr spectrum follows: 3 H for H at C_3, H at C_4, and H at C_5, m, H at C_4, δ 6.27; H at C_3, δ 5.75; H at C_5, δ 5.4, J_3 = 1.2 Hz, [$(CH_3)_2C<$], $J_{4,5}$ = 15 Hz (*trans*), $J_{3,4}$ = 10 Hz, $J_{5,6}$ = 8 Hz; 2 H of OCH_2, t, δ 4.1, J = 6 Hz; 3 H of OAc, s, δ 2.21; 6 H of $(CH_3)_2CH$, d, δ 1.75, J = 7 Hz; 3 H of CH_3CH, d, J = 7 Hz.

trans-**2,6-Dimethyl-2,4-octadien-8-ol** (**9**) was obtained by saponification of **3**: bp 100° (3 mm); $n^{20}D$ 1.4960; lemon, rosy odor; ir 10.45 μ (*trans* band); uv λ_{max} 237 mμ (ε 29,000) and 230 (27,335).

The nmr spectrum follows: 3 H for H at C_3, H at C_4, and H at C_5, m, H at C_4, δ 6.26, H at C_3, δ 5.75, H at C_5, δ 5.42, $J_{4,5}$ = 15 Hz (*trans*), $J_{5,6}$ = 8 Hz, $J_{3,4}$ = 10 Hz; 2 H for CH_2O, t, δ 3.62, J = 6 Hz, H at C_6, δ 2.34, m, covered by OH proton; 6 H of $(CH_3)_2C<$, s, δ 1.75; 3 H of CH_3CH, d, δ 1.02, J = 7 Hz.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.89; H, 11.85.

cis-**2,6-Dimethyl-2,4-octadien-8-yl acetate** (**3a**) gave the following data: bp 84° (3 mm); $n^{20}D$ 1.4755 (90% pure); ir 13.25 μ (*cis* band); uv λ_{max} 237 mμ (ε 27,400). Hydrogenation over Pd–C yielded 2,6-dimethyloctan-8-yl acetate, identified with an authentic sample by infrared analysis.

The nmr spectrum follows: 2 H for H at C_3 and H at C_4, d, δ 6.15, $J_{3,4} \cong 8$ Hz; H at C_4, t, δ 5.12, $J \cong 9$ Hz, $J_{3,5} + J_{4,5} \cong 8$ Hz, $J_{4,5}$ = 5.5–11.5 Hz (*cis*), H at C_3 and H at C_4 are almost magnetically equivalent; 2 H of CH_2O, t, δ 4.05, J = 6 Hz; 3 H of OAc, s, δ 2.04; 6 H of $(CH_3)_2C<$, 2 s, δ 1.75 and 1.81; 3 H of CH_3CH, d, δ 1, J = 7 Hz.

cis-**2,6-Dimethyl-2,4-octadien-8-ol** (**9a**) was obtained from saponification of **3a**: bp 90–95° (3 mm); $n^{20}D$ 1.4940; green, rosy odor; ir 13.95 μ (*cis* band); uv λ_{max} 237 mu (ε 26,650).

The nmr spectrum follows: 2 H for H at C_3 and H at C_4, d, δ 5.95, $J \cong 8$ Hz; H at C_5, m, δ 5, 2 H for CH_2O, t, δ 3.5, J = 6 Hz; 1 H for OH, s, δ 3.25; 6 H for $(CH_3)_2C<$, 2, s, δ 1.73 and 1.77; 3 H for CH_3CH, d, δ 1, J = 7 Hz.

Hydrogenation over Pd–C afforded 2,6-dimethyloctan-8-ol, with which it was identified by ir with an authentic sample.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.75; H, 11.65.

Pyrolysis with Oxalic Acid.—Triacetate **1** (35 g) and oxalic acid (0.35 g) were heated in a modified Claisen–Vigreux flask at 280–300° for 30 min while acetic acid was collected (*ca.* 12 g). The residue was then distilled under vacuum, yielding the following cuts (Table VI) (vpc, 20M, 200°).

Table VI

Cut	Bp,° C (mm)	Yield, g	$n^{20}D$	Components, % 3a	2	3	4	5
1	110(3)	10	1.4570	5	75	20		
2	130(3)	13.5	1.4520				40	60

Pyrolysis with *p*-Toluenesulfonic Acid.—Triacetate **1** (50 g) and *p*-toluenesulfonic acid (0.5 g) were heated in a modified Claisen–Vigreux flask at 165–190° (20 mm). The distillate, which collected at 100–150° within 0.5 hr, was washed with 2 volumes of water and neutralized with 10% soda ash. It amounted to 29 g, $n^{20}D$ 1.4670, which, upon distillation, yielded the following cuts (Table VII), (vpc, 20M, 200°).

Table VII

Cut	Bp, °C (mm)	Yield, g	$n^{20}D$	Components, % X[a]	3a	2	3	4	5
1	86 (2)	1	1.4857	80		20[b]			
2	100 (2)	1.8	1.4720		18	11	64		
3	110 (2)	2	1.4620			20[b]		35	45
4	135 (2)	6	1.4480					40	60

[a] Mostly hydrocarbons. [b] Includes **2**, **3**, and **3a**.

Cyclization of 8.—*trans*-2,6-Dimethyl-1,3-octadien-8-ol (**8**, 100 g) and 30% H_2SO_4 (100 ml) were agitated under a N_2 atmosphere for 1.5 hr at room temperature (20–30°) until a sample of the reaction mixture showed the disappearance of the starting ma-

terial (vpc, SE-30, 200°). Upon distillation, a main cut, 94 g, bp 77° (15 mm), $n^{20}D$ 1.4545, of a 91:9 isomeric mixture of **6** and **6a** (vpc, 20M, 90°) was obtained.

Cyclization of 9.—*trans*-2,6-Dimethyl-2,4-octadien-8-ol (**9**, 16 g), benzene (32 ml), and *p*-toluenesulfonic acid (0.5 g) were refluxed for 14 hr; upon neutralization and evaporation of the solvent, 13 g were obtained, $n^{20}D$ 1.4620, showing the following composition: 23% **7** and **7a**; 53% **6**; 9% **6a**; and 15% unreacted **9**.

Cyclization of 9a.—*cis*-2,6-Dimethyl-2,4-octadien-8-ol (**9a**, 15 g) and 30% H_2SO_4 (15 ml) were vigorously agitated at room temperature (20–30°) for 22 hr. The reaction mixture, after neutralization, afforded 14 g, which showed the following composition (vpc, 20M, 90°): 1% **7** and **7a**; 39% **6**; 6% **6a**; and 54% unreacted **9a**.

***cis* and *trans*-2-(2-Methyl-2-hydroxyprop-1-yl)-4-methyltetrahydropyran (10 and 10a).**—*trans*-2,6-Dimethyl-2,4-octadien-8-ol (**9**, 100 g) was fed within 5 min, under cooling at 0–10°, into 62.5% H_2SO_4 (100 ml); the temperature was left to reach 20–25° within 5 min. The reaction product was then poured onto 30% NaOH (200 ml) under cooling (30–40°), and the top layer separated; it afforded, upon distillation, 75 g of a main cut, bp 75–80° (2 mm), $n^{20}D$ 1.4480, of a 95:5 *cis*–*trans* mixture of hydroxyrosoxide (**10** and **10a**) (vpc, SE-30, 190°).

Conversion of 10 into a Mixture of Rosoxides 6 and 6a.—Hydroxyrosoxide **10** (100 g), benzene (400 ml), and concentrated H_2SO_4 (4 g) were heated under reflux for 1 hr (80–82°) while water was azeotroped off in a Dean–Stark trap. The mixture, after neutralization and distillation, afforded 70 g, $n^{20}D$ 1.4550, consisting of 30% **7**, 2% **7a**, 64% **6**, and 4% **6a** (vpc, CW 20M, 90°); *cf.* ref 4.

***cis*-Rosoxide** [*cis*-2-(2-methyl-1-propen-1-yl)-4-methyltetrahydropyran, **6**], separated by distillation through a Nester–Faust Teflon spinning-band column, gave the following data: bp 86° (20 mm); $n^{20}D$ 1.4535.

The nmr spectrum follows: H at C_1, d, fine splitting, δ 5.09, J = 8.5 Hz; H at C_2 and H at C_6, m, δ 3.9; H at C_6, six-peak m, composed of 3 d, with axial fixed conformation, δ 3.38, J_{gem} = 12 Hz, J' = 12 Hz, J'' = 2.5 Hz; 6 H of $(CH_3)_2C=$, 2 d, δ 1.68, and 1.65, J = 1 Hz; 3 H of CH_3CH, d, δ 0.90, J = 5 Hz.

***trans*-Rosoxide** [*trans*-2-(2-methyl-1-propen-1-yl)-4-methyltetrahydropyran, **6a**, separated by distillation through a Nester–Faust Teflon spinning-band column, gave the following data: bp 88–89° (20 mm); $n^{20}D$ 1.4580.

The nmr spectrum follows: H at C_1, d, fine splitting, δ 5.22, J = 8 Hz; H at C_2, six-peak m, composed of 3 d, δ 4.29, J = 8 Hz, J' = 8 Hz, J'' = 4 Hz, 2 H at C_6, m, nearly equivalent protons owing to flipping of conformation of *trans* configuration, δ 3.5–3.8; 6 H of $(CH_3)_2C=$, d, δ 1.66 and 1.69, J = 1 Hz; 3 H of CH_3CH, d, δ 1.04, J = 6 Hz.

Registry No.—**1**, 23062-48-8; **2**, 23102-71-8; **3**, 23042-11-7; **3a**, 23061-96-3; **4**, 23062-49-9; *trans*-**5**, 23061-97-4; **6**, 876-17-5; **6a**, 876-18-6; **8**, 23062-00-2; **9**, 23062-01-3; **9a**, 23062-02-4; **10**, 23062-03-5; **10a**, 23062-04-6; *cis*-2,6-dimethyl-1,8-dihydroxy-2-octene, 23062-05-7; *trans*-2,6-dimethyl-1,8-dihydroxy-2-octene, 23062-07-9; *cis*-**5**, 23062-08-0.

Cherylline, a 4-Phenyl-1,2,3,4-tetrahydroisoquinoline Alkaloid

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Received September 2, 1969

A 4-phenyl-1,2,3,4-tetrahydroisoquinoline alkaloid, cherylline, has been isolated from *Crinum powellii*. The alkaloid has been assigned the structure **12** from spectral, degradative, and synthetic evidence. A facile synthesis of (±)-O,O-dimethyl-N-demethylcherylline (**5**) provided an intermediate capable of resolution. N-Methylation of the *S* enantiomer (**10a**) provided a product, the hydrochloride of which was identical with O,O-dimethylcherylline hydrochloride.

Isolation and separation procedures reported during the past 20 years have provided relatively few phenolic *Amaryllidaceae* alkaloids.[2] We wish to report the isolation and structure of cherylline, a new representative of this rare type of phenolic alkaloid. Cherylline,[3] which is optically active, has been isolated in *ca.* 0.004% yield from the alkali-soluble crude alkaloids of several species of *Crinum*. The nmr spectrum of cherylline in DMSO-d_6 exhibits an A_2B_2 pattern (δ 6.91 and 6.64) characteristic of a 1,4-disubstituted aromatic ring, two one-proton singlets (δ 6.49 and 6.23) indicative of two *para*-oriented protons on a second aromatic ring, and two three-proton singlets at δ 3.51 (OCH_3) and 2.24 (NCH_3) in addition to a few less well-defined signals. The ultraviolet spectrum of the compound has maxima at 285 and 280 mμ which undergo a bathochromic shift to 299 mμ upon the addition of base. The mass spectrum and elemental analysis of the alkaloid indicate a molecular weight of 285 and the empirical formula $C_{17}H_{19}NO_3$. These results are consistent with a compound containing two aromatic rings (both phenolic), N-methyl and methoxyl groups, and a C_3H_5 fragment. Structure **1** is in agreement with the spectroscopic data. Proof that the alkaloid does contain this skeleton was obtained by converting cherylline into O,O-dimethylcherylline (**1**, CH_3O instead of OH) with diazomethane. This fully methylated derivative exhibited R_f values on silica gel with several different solvent systems that were identical with those found for synthetic (±)-6,7-dimethoxy-4-(4′-methoxyphenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (**6**). The ir spectra (KBr) of the hydrochlorides of both compounds were superimposable, thus confirming their chemical identity.[4]

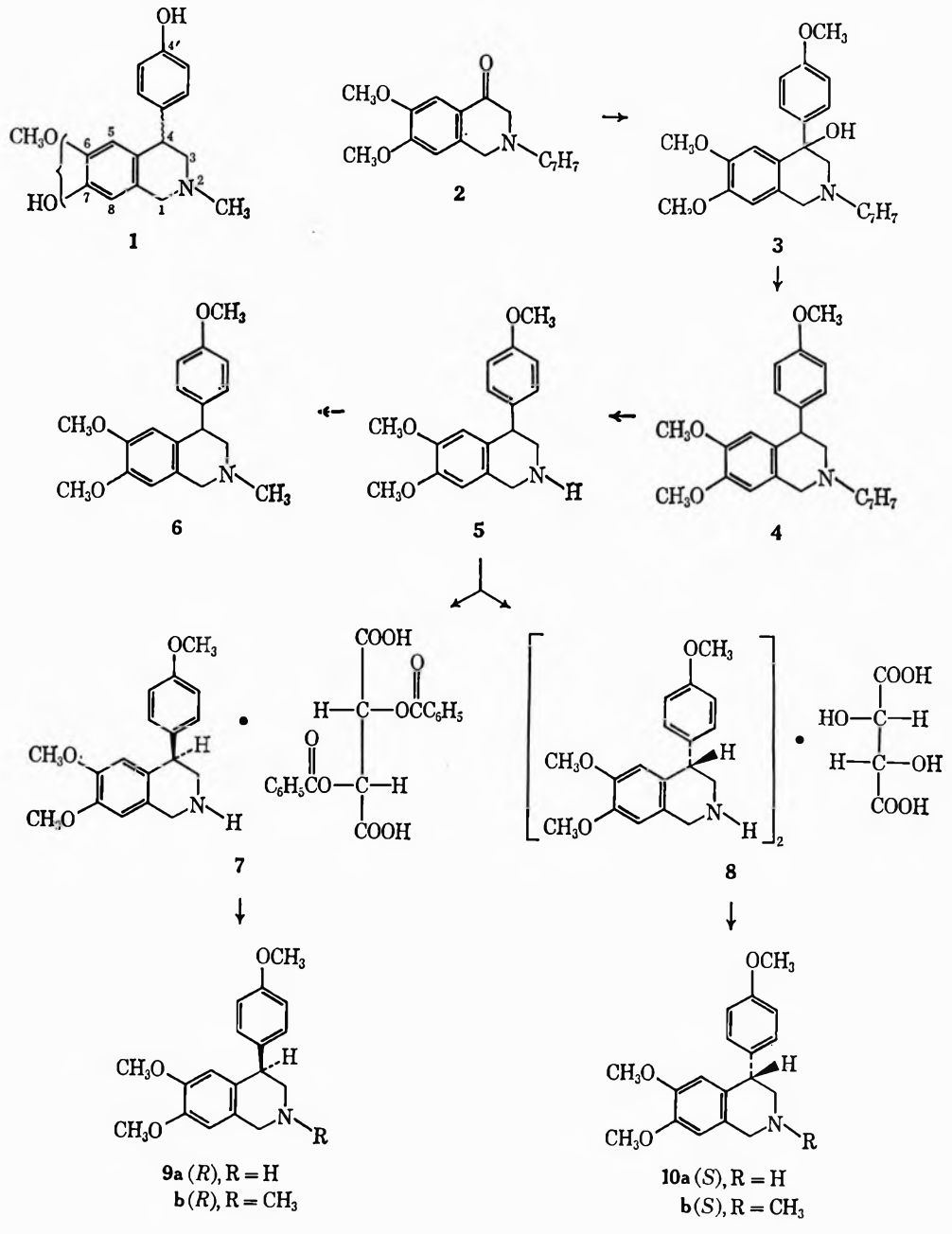
(1) We are grateful to the U. S. Public Health Service for partial support of this work (Grant He 7503).

(2) For a recent review, see W. C. Wildman in "The Alkaloids," Vol. XI, R. H. F. Manske, Ed., Academic Press Inc., New York, N. Y., 1968, Chapter 10.

(3) A comparison of cherylline and the phenolic alkaloid (crinin) isolated by H.-G. Boit, *Chem. Ber.*, **87**, 1704 (1954), has been performed by W. Döpke, Humboldt University, Berlin, who found the alkaloids to be identical. It is proposed that "crinin" should be referred to as cherylline to avoid confusion in the literature with crinine, a nonphenolic alkaloid.

(4) It was necessary to run the ir spectra in KBr pellets because of solubility problems. While the ir spectrum of an enantiomer frequently differs from that of the racemate when measured in the solid state, in this case the spectra are fortuitously superimposable and can be used as proof of chemical identity.

SCHEME I



The positions of the hydroxyl and methoxyl groups in ring A of cherylline were assigned by nmr spectroscopy. The spectrum in DMSO-d_6 shows two singlets at δ 6.23 and 6.49. Because of the shielding effect of the phenyl group at C-4, the signal at δ 6.23 is attributed to the proton at C-5 and the latter to the proton at C-8. On addition of a drop of NaOD in D_2O, both singlets are shifted upfield to δ 6.06, representing a shift of 10 and 26 Hz, respectively. Since on forming the phenolate the large upfield shift is observed for the proton at C-8, the hydroxyl group must be located at C-7.

The configuration of the alkaloid at the only asymmetric center (C-4) was determined by examination of the ORD and CD spectra of cherylline and of the two enantiomers of the O,O-dimethyl derivative, which were prepared in the following manner. Condensation of *p*-methoxyphenylmagnesium bromide with 2-benzyl-2,3-dihydro-6,7-dimethoxy-4(1H)-isoquinolone (**2**)[5] afforded the carbinol **3**, which was transformed by acid treatment and subsequent sodium borohydride reduction to the 4-phenyl-substituted tetrahydroisoquinoline **4**. Catalytic debenzylation of **4** gave the secondary amine **5**.[6] Reductive N-methylation of **5** provided (±)-O,O-dimethylcherylline hydrochloride (**6**·HCl), while resolution of **5** with dibenzoyl-*d*-tartaric acid and *l*-tartaric acid gave the diastereoisomers **7** and **8** which, on reductive N-methylation of the corresponding secondary amines **9a** and **10a**, were transformed to the respective enantiomers **9b** and **10b** (Scheme I).

The ORD curve of **9b** shows a positive Cotton effect at 294 mμ and the CD curve shows a maximum at 288 mμ. The ORD and CD spectra of **10b** are exact mirror

(5) G. Grethe, H. L. Lee, M. Uskoković, and A. Brossi, *J. Org. Chem.*, **33**, 491, 494 (1968).

(6) (a) This compound and the corresponding N-methyl derivative (**6**) were initially prepared by an alternate procedure by A. Rheiner, Jr., of F. Hoffmann-La Roche & Co., A. G., Basle, Switzerland; (b) A. Rheiner, Jr. *Helv. Chim. Acta*, in press.

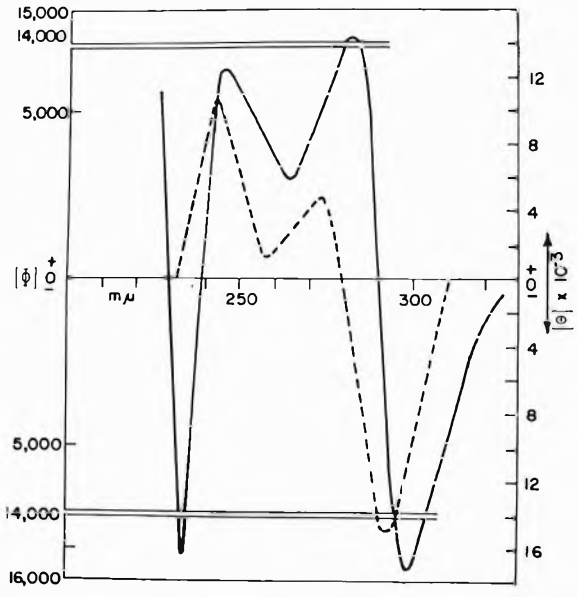
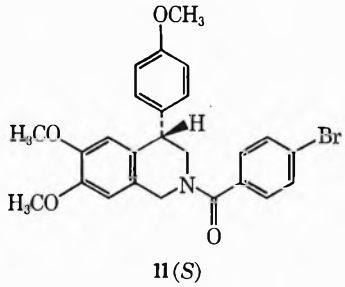
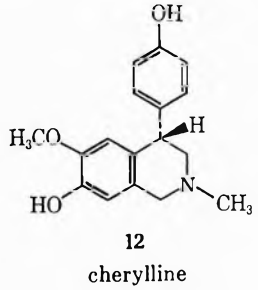


Figure 1.—ORD (—) and CD (---) curves of cherylline (**12**) (*c* 0.02, CH_3OH).

images of those of **9b**. By analogy to structural assignments of ORD spectra in the 4-aryltetralin (lignan) series,[7] the *R* configuration was assigned to **9a** and **9b** and the *S* configuration to the enantiomers **10a** and **10b**.[8] Comparison of the ORD and CD spectra of cherylline (Figure 1) with those of the synthetic compounds indicated that the alkaloid possesses the *S* configuration. The absolute configurations assigned above have been verified by an X-ray crystallographic study[8] of **11**. From this information cherylline can be assigned structure **12**.



11 (*S*)



12
cherylline

Experimental Section[9]

Isolation of Cherylline.—Ground, fresh bulbs of *Crinum powellii* var. *alba* (16.45 kg) were extracted several times with ethanol at 30°. The extract was filtered and evaporated under reduced pressure at 30° until turbidity appeared. The concentrate was diluted with water, acidified to pH 2 with tartaric acid, and extracted three times with benzene and three times with chloroform. Separate concentration of these extracts afforded 51.5 and 25.3 g of benzene- and chloroform-soluble materials, respectively. The aqueous solution was adjusted to pH 8 with ammonium hydroxide and extracted five times with chloroform. Evaporation of the chloroform extract under reduced pressure gave 33.2 g of alkaloidal material. Lycorine[2] (3.0 g, identified by melting point and ir spectra) precipitated during concentration of the chloroform. The aqueous raffinate was adjusted to pH 10 and extracted three times with chloroform. Concentration of the chloroform gave an additional 4.4 g of mainly alkaloidal material. One gram of the chloroform-soluble pH 8 extract was chromatographed by thick layer chromatography on 20 × 20 cm plates of silica gel PF (254 + 366) (0.5 mm). Development with chloroform–methanol–diethylamine (90:5:5) provided four bands, of which the second least mobile had major quantities of alkaloid.[10] This material was eluted from the silica gel with methanol and rechromatographed on the same support using ethyl acetate–methanol (70:30) as eluent. Nine distinct substances were observed. The two materials most mobile in the solvent system were in minor amounts; the last four (least mobile) components proved to be the expected major alkaloids, crinine and powelline. The intermediate fractions were crystallized initially from chloroform and then recrystallized from acetone to give 20 mg of cherylline: mp 217–218°; $[\alpha]^{26}D$ −69° (*c* 0.20, CH_3OH); uv max 225 mμ (ε 15,000) (sh), 280 (3960), 285 (4050), and 294 (2480) (sh). Basification of this ethanolic solution caused the maximum to shift to 299 mμ. Cherylline forms a hydrochloride, mp 238–239°, after recrystallization from acetone.

Treatment of cherylline in 95% ethanol with excess diazomethane at 0° for 1 week provided an O-methyl derivative which gave the same R_f values as **6** with three solvent systems, namely EtOAc–MeOH (70:30), EtOAc–MeOH (50:50), and $CHCl_3$–MeOH–$(C_2H_5)_2NH$ (92:3:5). Treatment of the O-methyl derivative with ethanolic HCl, concentration, and crystallization from acetone–methanol gave a hydrochloride, mp 229–230°, identical in chromatographic behavior and in ir (KBr) spectrum with synthetic **6**·HCl. A mixture of the two hydrochlorides showed no melting point depression.

Racemic 2-Benzyl-6,7-dimethoxy-4-(4-methoxyphenyl)-1,2,3,4-tetrahydro-4-isoquinolinol Hydrochloride (3·HCl).—To a stirred mixture of 2.4 g (0.1 mol) of dry magnesium turnings and a trace of iodine in 14 ml of dry tetrahydrofuran was added a solution of 21 g (0.112 mol) of *p*-bromoanisole in 14 ml of dry tetrahydrofuran over 10 min. The mixture was stirred and refluxed for 1 hr; then a solution of 25 g (0.084 mol) of 2-benzyl-2,3-dihydro-6,7-dimethoxy-4(1H)-isoquinolone (**2**), obtained by neutralization of the corresponding hydrochloride[5] in 200 ml of dry tetrahydrofuran was added over 10 min. The reaction mixture was stirred and refluxed for 4 hr, cooled, poured into 100 ml of an ice-cold, saturated solution of ammonium chloride, and extracted with three 100-ml portions of ether. The ether extracts were evaporated and the residue was dissolved in 200 ml of ethanol and rendered acidic with 6 *N* hydrochloric acid. The resulting white crystals were filtered, washed with ether, and dried to give 26 g (70%) of **3**·HCl, mp 178–181°. An analytical specimen was prepared from ethanol: mp 180–181°; uv max 225 mμ (ε 22,400) (sh), 275 (4720) (sh), 280 (4960), and 298 (3400) (sh); nmr δ 3.52 (s, 3, OCH_3-4′), 3.77 (s, 6, OCH_3-6, -7), 6.35 (s, 1, CH-5), 6.86 (s, 1, CH-8), 6.91 and 7.29 (AA′,BB′ pattern, 4, *J* = 10 Hz, CH-2′, CH-3′, CH-5′, CH-6′), and 11.35 (b, 1, +NH).

Anal. Calcd for $C_{25}H_{27}NO_4$·HCl (mol wt, 441.96): C, 67.94; H, 6.39. Found: C, 67.99; H, 6.13.

Racemic 2-Benzyl-6,7-dimethoxy-4-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline Hydrochloride (4·HCl).—A solution of 20 g (0.045 mol) of **3** in 170 ml of 35% ethanolic hydrogen chloride was refluxed for 2 hr and evaporated under reduced pressure. The residue was dissolved in 300 ml of methanol, and 15 g (0.4

(7) P. Crabbé in "Advances in Stereochemistry," Vol. I, N. J. Allinger and E. L. Eliel, Ed., p 144, 1967, and references therein.

(8) V. Toome, J. F. Blount, G. Grethe, and M. Uskoković, Chemical Research Department, Hoffmann-La Roche Inc., Nutley, N. J. Details will be published elsewhere.

(9) Melting points of synthetic materials were taken in open capillary tubes with a Thomas–Hoover melting point apparatus; those of cherylline and derivatives were observed on a Kofler microscope hot stage. All melting points are corrected. Infrared spectra were determined either with a Beckman Infrared Model IR-9 or Model IR-12 spectrophotometer. The uv spectra were recorded on a Cary recording spectrophotometer, Model 14M, in ethanol unless noted to the contrary. Rotatory dispersion curves were measured at 23° with a Durrum–Jasco spectrophotometer, Model 5, using 1-cm, 0.1-cm, or 0.1-mm cells. Specific rotations are given for the highest and lowest wavelength measured, for intersections, and for peaks and troughs. Circular dichroism curves were measured on the same instrument and they are recorded in molecular ellipticity units [Θ]. Optical rotations were measured on a Perkin–Elmer polarimeter, Model 141. Nuclear magnetic resonance spectra were obtained on a Varian Associates Model A-60 or HA-100 spectrophotometer using DMSO-d_6 as solvent unless otherwise indicated. Chemical shifts are reported in δ units using tetramethylsilane as internal reference. The following abbreviations are used in connection with the nmr data: s, singlet; cp, complex pattern; m, multiplet. The mass spectra were taken with a CEC 21-110 mass spectrometer at 70 eV using a direct insertion probe.

Extracts of products in organic solvents were washed with water and dried over anhydrous sodium sulfate.

(10) Meaningful R_f values could not be obtained because of variations in band width and migration.

mol) of sodium borohydride was added to the stirred solution over 30 min. The reaction mixture was stirred for 2 hr and evaporated. The residue was suspended in water and extracted with methylene chloride. The organic extract was evaporated and the residue was dissolved in ethanol and rendered acidic with ethanolic hydrogen chloride. Addition of ether afforded 13 g (68%) of **4**·HCl, mp 194–195°. An analytical sample was prepared from ethanol: mp 196–197°; uv max 225 mμ (ε 19,700) (sh), 278 (4620), 283 (4780), and 292 (3050) (sh); nmr δ 3.51 (s, 3, OCH_3-4′), 3.76 and 3.79 (s, 3 H each, OCH_3-6, -7), 6.23 (s, 1, CH-5), 6.83 (s, 1, CH-8), 6.96 and 7.17 (AA′BB′ pattern, 4, J = 9 Hz, CH-2′, CH-3′, CH-5′, CH-6′), and 12.1 (b, 1, $^+$NH).

Anal. Calcd for $C_{25}H_{27}NO_3$·HCl (mol wt, 425.96): C, 70.49; H, 6.63; N, 3.29. Found: C, 70.52; H, 6.80; N, 3.15.

Racemic 6,7-Dimethoxy-4-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (5) and Hydrochloride (5·HCl).—A mixture of 12.8 g (0.03 mol) of **4** and 3 g of 10% Pd–C in 20 ml of glacial acetic acid was hydrogenated at 50° under atmospheric pressure for 4 hr and cooled, and the catalyst was filtered. The filtrate was evaporated under reduced pressure and the residue was crystallized from methanol–ether to give 9 g (89%) of **5**, mp 230–231°. An analytical specimen was prepared from methanol–ether: mp 234–235°; uv max 227 mμ (ε 19,400), 278 (4660), 284 (4780), and 292 (3200)(sh); nmr δ 3.52 (s, 3, OCH_3-4′), 3.78 (s, 6, OCH_3-6, -7), 6.27 (s, 1, CH-5), 6.90 (s, 1, CH-8), 6.94 and 7.17 (AA′BB′ pattern, 4, J = 9 Hz, CH-2′, CH-3′, CH-5′, CH-6′), and 10.0 (b, 2, $^+NH_2$).

Anal. Calcd for $C_{18}H_{21}NO_3$·HCl (mol wt, 335.84): Cl, 10.56. Found: Cl, 10.60.

An aliquot of **5**·HCl was dissolved in water, rendered alkaline with ammonium hydroxide, and extracted with methylene chloride. The organic extract was evaporated and the residue was recrystallized twice from ether to afford **5**, mp 91–92°.

Anal. Calcd for $C_{18}H_{21}NO_3$ (mol wt, 299.37): C, 72.22; H, 7.07; N, 4.68. Found: C, 72.01; H, 6.80; N, 4.30.

Racemic 6,7-Dimethoxy-4-(4-methoxyphenyl)-2-methyl-1,2,-3,4-tetrahydroisoquinoline Hydrochloride (6·HCl).—A mixture of 9.85 g (0.033 mol) of **5** in 20 ml (0.52 mol) of 98–100% formic acid and 10 ml (0.13 mol) of 37% formaldehyde was heated at 100° for 3 hr and refluxed for 8 hr, and the volatiles were evaporated under reduced pressure. The residue was dissolved in water, rendered alkaline with 5% sodium hydroxide, and extracted with methylene chloride. The organic extract was evaporated, and the residue was dissolved in ethanol, acidified with ethanolic hydrogen chloride, and evaporated. The resulting solid was recrystallized twice from methanol–ether to give 6.3 g (55%) of **6**·HCl: mp 228–229°; uv max 226 mμ (ε 19,000), 276 (4460), 282 (4600), and 290 (2950)(sh); nmr δ 2.89 (s, 3, NCH_3), 3.53 (s, 3, OCH_3-4′), 3.80 (s, 6, OCH_3-6, -7), 6.27 (s, 1, CH-5), 6.85 (s, 1, CH-8), and 6.95 and 7.17 (AA′BB′ pattern, 4, J = 9 Hz, CH-2′, CH-3′, CH-5′, CH-6′).

Anal. Calcd for $C_{19}H_{23}NO_3$·HCl (mol wt, 349.87): C, 65.23; H, 6.92; Cl, 10.13. Found: C, 65.57; H, 7.12; Cl, 10.22.

(+)-6,7-Dimethoxy-4(*R*)-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (9a).—To a solution of 5.245 g (15.6 mmol) of **5**·HCl in methanol was added 845 mg (15.6 mmol) of sodium methoxide. The solvent was removed under reduced pressure and the residue was extracted three times with dichloromethane. The combined extracts were filtered and evaporated to dryness under reduced pressure. The resulting free base was dissolved in 15 ml of ethanol and combined with a solution of 5.6 g (15.6 mmol) of dibenzoyl-*d*-tartaric acid in 15 ml of ethanol. The crystalline material (6.2 g) which precipitated from this solution on standing at room temperature was recrystallized twice from methanol to give 3.4 g (66%) of the dibenzoyl-*d*-tartrate (**7**): mp 186–188°; $[\alpha]^{25}D$ −45.8° (*c* 1.03, MeOH). An analytical sample, after recrystallization from methanol and drying at 75° for 24 hr, showed the following physical properties: mp 191–193°; $[\alpha]^{25}D$ −45.8° (*c* 1.0, MeOH); ORD (*c* 0.164, MeOH) $[\alpha]_{317}$ −360° (tr), $[\alpha]_{304}$ 0°, $[\alpha]_{293}$ +1090° (pk), $[\alpha]_{288}$ 0°, $[\alpha]_{276}$ −6200° (tr), $[\alpha]_{265}$ −4560° (pk), $[\alpha]_{243}$ −20,000° (tr), $[\alpha]_{236}$ 0°, $[\alpha]_{227}$ +28,600° (pk), and $[\alpha]_{210}$ +6700°; CD $[\Theta]_{300}$ 0, $[\Theta]_{287}$ +36,960, $[\Theta]_{278}$ 0, $[\Theta]_{271}$ −17,160, $[\Theta]_{262}$ −18,480, $[\Theta]_{238}$ −27,060, $[\Theta]_{228}$ 0, $[\Theta]_{223}$ +95,040.

Anal. Calcd for $C_{18}H_{21}NO_3 \cdot C_{18}H_{14}O_8$ (mol wt, 657.65): C, 65.75; H, 5.36; N, 2.13. Found: C, 65.51; H, 5.44; N, 2.14.

To an aqueous solution of 3.2 g of **7** was added excess 6 *N* sodium hydroxide and the free base was extracted with chloroform. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated to dryness. The crystalline residue, after recrystallization from ether, afforded in several crops a total of 1.074 g (41%) of the free base (**9a**): mp 110–112°; $[\alpha]^{25}D$ +36° (*c* 1.05, MeOH). An analytical sample from a previous experiment, after recrystallization from ether and drying at 55° for 70 hr under reduced pressure, showed the following physical properties: mp 108–110°; $[\alpha]^{25}D$ +38.4° (*c* 1.22, MeOH); ORD (*c* 0.292, MeOH) $[\alpha]_{293}$ +3420° (pk), $[\alpha]_{287}$ 0°, $[\alpha]_{277}$ −6150° (tr), $[\alpha]_{261}$ −1760° (pk), $[\alpha]_{243}$ −5820° (tr), $[\alpha]_{236}$ 0°, $[\alpha]_{227}$ +13,000° (pk), $[\alpha]_{218}$ 0°, $[\alpha]_{214}$ −1470° (tr), $[\alpha]_{211}$ 0°, and $[\alpha]_{210}$ +2060°; CD $[\Theta]_{310}$ 0, $[\Theta]_{288}$ +21,683, $[\Theta]_{278}$ 0, $[\Theta]_{272}$ −6776, $[\Theta]_{267}$ −2032, $[\Theta]_{239}$ −38,532, $[\Theta]_{232}$ 0, $[\Theta]_{224}$ +29,744, and $[\Theta]_{212}$ +12,168; ir ($CHCl_3$) *ca.* 3300 (broad, NH), 1615, 1585, 1515 and 1468 (phenyl), and 1255 cm^{-1} (OCH_3); uv max (MeOH) 236–237 mμ (ε 20,600), 279–280 (5070), and 284–285 (5060); nmr ($CDCl_3$) δ 2.70 (broad, s, 1, -NH), 2.9–3.5 (cp, 2, CH_2-3), 3.68, 3.78, 3.86 (s, 3 each, OCH_3), 4.04 (s, 2, CH_2-1), *ca.* 3.9 partially hidden underneath other signals (m, 1, CH-4), 6.38 (s, 1, CH-5), 6.56 (s, 1, CH-8), and 6.83 and 7.02 (AA′BB′ pattern, 4, J = 9 Hz, CH-2′, CH-3′, CH-5′, CH-6′); mass spectrum (70 eV) *m/e* (rel intensity) 299 (30), 270 (35), 239 (100), 209 (25), 195 (25), 183 (45), 165 (45), 152 (45), 141 (35), 121 (30), 115 (45), 91 (30), and 77 (45).

Anal. Calcd for $C_{18}H_{21}NO_3$ (mol wt, 299.36): C, 72.21; H, 7.07; N, 4.68. Found: C, 72.09; H, 7.05; N, 4.45.

(−)-6,7-Dimethoxy-4(*S*)-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (10a).—The mother liquors from the crystallization of **7** were combined and evaporated to dryness. The residue was taken up in water, excess sodium hydroxide was added to the aqueous solution, and the free base was extracted with chloroform. The combined organic layer was washed with water, dried, and evaporated to dryness. The residue (2.375 g) was dissolved in 15 ml of ethanol. Addition of 1.15 g of *l*-tartaric acid in 15 ml of ethanol afforded a crystalline salt. After two recrystallizations from methanol the tartrate (**8**) weighed 2.1 g, $[\alpha]^{25.4}D$ −59° (*c* 1.27, H_2O), mp 183–184° dec. To an aqueous solution of **8** was added excess 6 *N* sodium hydroxide, and the liberated free base was extracted with three portions of chloroform. The combined organic layer was washed with water, dried, and evaporated to dryness to give, after recrystallization from ether, 0.9 g (34%) of **10a**, mp 110–112°. An analytical sample, after recrystallization from ether, showed the following physical properties: mp 111–113°; $[\alpha]^{25}D$ −38.2° (*c* 1.12, MeOH); ORD (*c* 0.292, MeOH) $[\alpha]_{293}$ −3700° (tr), $[\alpha]_{287}$ 0°, $[\alpha]_{277}$ +6040° (pk), $[\alpha]_{261}$ +1540° (tr), $[\alpha]_{242}$ +5620° (pk), $[\alpha]_{238}$ 0°, $[\alpha]_{228}$ −17,000° (tr), and $[\alpha]_{217}$ −3020° (pk); CD $[\Theta]_{310}$ 0, $[\Theta]_{289}$ −22,022, $[\Theta]_{278}$ 0, $[\Theta]_{272}$ +6098, $[\Theta]_{257}$ +1694, $[\Theta]_{238}$ +45,292, $[\Theta]_{222}$ 0, $[\Theta]_{224}$ −34,476, and $[\Theta]_{214}$ −6760.

Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.21; H, 7.07; N, 4.68. Found: C, 72.20; H, 7.20; N, 4.70.

(+)-6,7-Dimethoxy-2-methyl-4(*R*)-(4-methoxyphenyl)-1,2,3,-4-tetrahydroisoquinoline (9b).—A solution of 950 mg of **9a** and 2.82 ml of 37% formaldehyde in 30 ml of methanol was allowed to stand at room temperature for 4 hr. The mixture was then hydrogenated at 1 atm over Raney nickel at room temperature overnight. The catalyst was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in ether, insoluble material was removed by filtration, and petroleum ether (bp 30–60°) was added to the filtrate to afford 651 mg (65%) of crystalline N-methylated product (**9b**), mp 83–85°. Recrystallization from ether–petroleum ether gave 627 mg of analytically pure **9b**: mp 87–89° (after drying under reduced pressure for 4 days at 40°); $[\alpha]^{24.9}D$ +21.58° (*c* 1.01, MeOH); ORD (*c* 0.313, MeOH) $[\alpha]_{294}$ +3960° (pk), $[\alpha]_{287}$ 0°, $[\alpha]_{278}$ −6250° (tr), $[\alpha]_{263}$ −2040° (pk), $[\alpha]_{243}$ −6060° (tr), $[\alpha]_{237}$ 0°, $[\alpha]_{229}$ +13,550° (pk), $[\alpha]_{221}$ 0°, $[\alpha]_{214}$ −4150° (tr), and $[\alpha]_{211}$ −3090°; CD $[\Theta]_{304}$ 0, $[\Theta]_{288}$ +23,670, $[\Theta]_{278}$ 0, $[\Theta]_{272}$ −5940, $[\Theta]_{257}$ −1980, $[\Theta]_{244}$ −15,180, $[\Theta]_{235}$ 0, $[\Theta]_{227}$ +71,280, $[\Theta]_{214}$ +7920, $[\Theta]_{205}$ +95,040, $[\Theta]_{200}$ 0, and $[\Theta]_{196}$ −60,720; ir ($CHCl_3$) 2790, 2770 (Bohlmann bands), 1610, 1585, 1515 and 1465 (phenyl), and 1265 and 1255 cm^{-1} (OCH_3); uv max (MeOH) 225 mμ (ε 20,600), 277 (5000), 283 (5020), and 290 (3400)(sh); nmr ($CDCl_3$) δ 2.42 (s, 3, NCH_3), 2.4–3.2 (cp, 2, CH_2-1), 3.66, 3.80, 3.88 (s, 3 H each, OCH_3), 3.5–4.4, partially hidden beneath OCH_3 signals (cp, 3, CH_2-3 and CH-4), 6.38 (s, 1, CH-5), 6.59 (s, 1, CH-8), and 6.85 and 7.12 (AA′BB′ pattern, 4, J = 9 Hz, CH-2′, CH-3′, CH-5′, CH-6′); mass spectrum (70 eV) *m/e* (rel intensity) 313 (25), 270 (47), 239 (100), 224 (7), 208 (8), 195 (7), 181 (6), 165 (10), 151 (8), and 135 (17).

Anal. Calcd for $C_{19}H_{23}NO_3$ (313.38): C, 72.82; H, 7.40; N, 4.47. Found: C, 73.04; H, 7.60; N, 4.44.

(−)-6,7-Dimethoxy-2-methyl-4(*S*)-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (10b).—Reductive N-methylation of 850 mg of 10a as described in the previous experiment afforded 636 mg (71%) of 10b, mp 83–85°, after crystallization from ether–petroleum ether. Recrystallization from the same solvent mixture gave 400 mg of analytically pure 10b, mp 87–88°, after drying under reduced pressure at 40° for 4 days: $[\alpha]^{24.9}D$ −21.65° (*c* 0.965, MeOH); ORD (*c* 0.3134, MeOH), $[\alpha]_{294}$ −3960° (tr), $[\alpha]_{288}$ 0°, $[\alpha]_{279}$ +6760° (pk), $[\alpha]_{264}$ +2170° (tr), $[\alpha]_{244}$ +5750° (pk), $[\alpha]_{239}$ 0°, $[\alpha]_{232}$ −15,900° (tr), $[\alpha]_{222}$ 0°, $[\alpha]_{217}$ +4470° (pk), and $[\alpha]_{215}$ +2870°; CD $[\Theta]_{304}$ 0, $[\Theta]_{288}$ −24,090, $[\Theta]_{278}$ 0, $[\Theta]_{272}$ +5610, $[\Theta]_{257}$ +1980, $[\Theta]_{243}$ +14,850, $[\Theta]_{234}$ 0, $[\Theta]_{226}$ −68,640, $[\Theta]_{214}$ −5280, $[\Theta]_{205}$ −102,960, $[\Theta]_{200}$ 0, and $[\Theta]_{197}$ +58,080.

Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.77; H, 7.51; N, 4.49.

(+)-2-(4-Bromobenzoyl)-6,7-dimethoxy-4(*S*)-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (11).—To a stirred solution of 299 mg (1 mmol) of 10a in 20 ml of benzene was added a solution of 300 mg (2.2 mmol) of potassium carbonate in 5 ml of water followed by the portionwise addition of 500 mg (2.3 mmol) of 4-bromobenzoyl chloride. After the addition was complete, stirring was continued for 2 hr. The benzene layer was separated and washed successively with 6 *N* sodium hydroxide, three portions of 2 *N* hydrochloric acid, and water. After drying (Na_2SO_4) and evaporation, the crystalline residue was washed with ether to give 323 mg (67%) of 11, mp 158–160°. A sample was recrystallized from ether to afford analytically pure 11 as long needles: mp 159–161°; $[\alpha]^{24}D$ +120.3° (*c* 1.28, $CHCl_3$); ir ($CHCl_3$) 1630 (amide C=O), 1615 (sh), 1590, 1510, and 1460 (phenyl), and 1260 cm^{-1} (OCH_3); uv max (CH_3OH) 226 mμ (ε 35,500), 278 (6270), 283–284 (6060), and 291–292 (3800)(sh); nmr ($CDCl_3$) δ 3.72, 3.82, and 3.90 (s, 3 H each, OCH_3) 4.67 and 5.10 (cp, 2 H each, CH_2NCH_2), and 6.3–7.2 (cp, 10, aromatic H); ORD (*c* 0.482, methanol) $[\alpha]_{301}$ +1310° (pk), $[\alpha]_{291}$ +1240° (tr), $[\alpha]_{274}$ +26,000° (pk), $[\alpha]_{243}$ 0°, $[\alpha]_{225}$ −21,300° (tr), $[\alpha]_{213}$ −13,000° (sh), and $[\alpha]_{203}$ 0°; CD $[\Theta]_{300}$ 0, $[\Theta]_{288}$ −13,200, $[\Theta]_{271}$ 0, $[\Theta]_{238}$ +125,400, $[\Theta]_{228}$ 0, $[\Theta]_{208}$ −75,900, and $[\Theta]_{200}$ 0; mass spectrum (70 eV) *m/e* (rel intensity) 483 (30), 481 (30), 403 (5), 373 (5), 282 (20), 270 (45), 239 (100), 183 (30), and 121 (30).

Anal. Calcd for $C_{25}H_{24}BrNO_4$ (mol wt, 482.40): C, 62.25; H, 502; N, 2.90. Found: C, 62.25; H, 4.75; N, 3.20.

Registry No.—**3**·HCl, 23349-28-2; **4**·HCl, 23349-29-3; **5**, 23349-30-6; **5**·HCl, 23349-31-7; **6**·HCl, 23349-32-8; **7**, 23330-74-7; **9a**, 23330-75-8; **9b**, 23330-76-9; **10a**, 23330-77-0; **10b**, 23367-60-4; **11**, 23330-78-1; **12**, 23367-61-5; **12**·HCl, 23330-44-1.

Acknowledgment.—We are indebted to the Physical Chemistry Department, Hoffmann-La Roche Inc., Nutley, N. J., under the supervision of Dr. P. Bommer, for the analytical and spectral data. We are particularly grateful to Dr. V. Toome for the ORD and CD determinations.

Constituents of *Eurycoma longifolia* Jack

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Received December 23, 1963

Investigation of the constituents of *Eurycoma longifolia* Jack, obtained from several regions of Viet Nam, has resulted in the isolation of two steroids, namely β-sitosterol and campesterol, 2,6-dimethoxybenzoquinone, and a bitter principle called eurycomalactone (1a). Eurycomalactone is closely related to the other bitter principles previously encountered in the family *Simaroubaceae*. Eurycomalactone is the first compound of this series with a keto group at C-6 and a γ-lactone group between positions 14 and 7. The configuration is discussed. Dihydroeurycomalactone (2a) is also isolated from the bark of *Eurycoma longifolia* originated from Dinh-Quan.

Numerous plants of the *Simaroubaceae* are known in herbal medicine for their therapeutic activities, and several of them have been shown to be effective antiamebic agents.[2] Various studies on the bitter principles occurring in several genera of the family *Simaroubaceae* have shown that they belong to a group of structurally related compounds with close chemical and botanical relationships to each other.[3]

This work describes the investigation of the chemical constituents of *Eurycoma longifolia* Jack, a bush which is common in Viet Nam, especially around Bien-Hoa, Trang-Bom, and Dinh-Quan. Its local name is "cây bá binh" (tree which cures hundred of diseases), and its bark is used in the Vietnamese pharmacopaeia.

Chromatography of the bark afforded, besides β-sitosterol and campesterol, characterized as their acetates (see Experimental Section), eurycomalactone (**1a**) and 2,6-dimethoxybenzoquinone, which is a common chemical constituent of the Simaroubaceae family.[4]

Eurycomalactone (**1a**)[5] was also isolated from extracts of the leaves of *Eurycoma longifolia* (albeit in a much lower yield, *ca.* 10%) and analyzed for $C_{19}H_{24}O_6$. This was confirmed by its mass spectrum. Its infrared (ir) spectrum showed bands for hydroxyls, a saturated and an α,β-unsaturated ketone, and a γ-lactone grouping. The ultraviolet (uv) spectrum confirms the presence of a conjugated keto chromophore, which seemed to be homoconjugated with a saturated carbonyl. The nuclear magnetic resonance (nmr) spectrum showed resonances for four methyl groups, one secondary methyl, one vinylic methyl, and two tertiary methyls (see Experimental Section). A signal integrating for one vinylic proton appeared at 6.1 ppm, and a resonance for one proton situated on a carbon-bearing oxygen atom is observed at 4.8 ppm. Finally, eurycomalactone (**1a**) gives a mono- and a bis-2,4-dinitro-

(1) Taken in part from the D.Sc. Thesis of N.-N.-S. For a preliminary communication, see Le-Van-Thoi, Nguyen-Ngoc-Suong, and P. Crabbé, *Chem. Commun.*, 821 (1969).

(2) T. A. Geissman, *Ann. Rev. Pharmacol.*, **4**, 305 (1964).

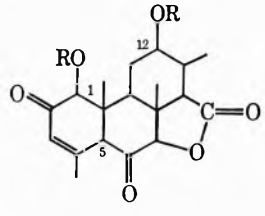
(3) For a review of the literature on simaroubaceous plants, see J. Polonsky, *Planta Med. Suppl.*, 107 (1966).

(4) See, among others, (a) J. Polonsky and E. Lederer, *Bull. Soc. Chim Fr.*, 1157 (1959); (b) W. Karrer, *Helv. Chim. Acta*, **13**, 1424 (1930); (c) D. J. Cosgrove, D. G. H. Daniels, E. N. Greer, J. B. Hutchinson, T. Moran, and J. K. Whitehead, *Nature*, **169**, 966 (1952); (d) D. J. Cosgrove, D. G. Daniels, K. J. Whitehead, and J. D. S. Goulden, *J. Chem. Soc.*, 4821 (1952).

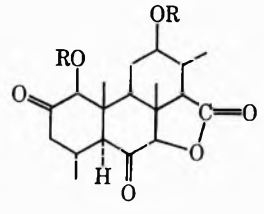
(5) Preliminary communications on the isolation of this substance have already appeared: (a) Le-Van-Thoi and Nguyen-Ngoc-Suong, *Ann. Fac. Sci. Saigon*, 89 (1962); (b) Le-Van-Thoi and Nguyen-Ngoc-Suong, International Symposium on the Chemistry of Natural Products, Kyoto, April 1964, Abstracts of Papers, p 51.

phenylhydrazone, thus confirming the presence of two keto groupings in the molecule.

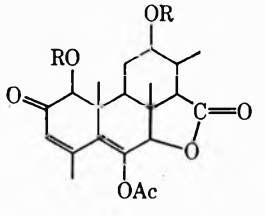
Catalytic hydrogenation of **1a** affords dihydroeurycomalactone (**2a**). Compound **2a** was also isolated from the bark of *Eurycoma longifolia* originated from Dinh-Quan. The dihydro derivative **2a** shows a weak uv band at 280 mμ and one strong saturated carbonyl band in the ir. A new signal (appearing as a doublet centered at 0.95 ppm) confirms the secondary nature of the methyl situated at C-4.



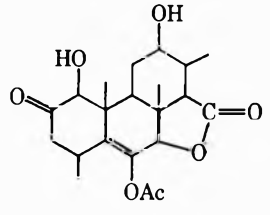
1a, 5α H, R = H
b, 5α H, R = Ac
c, 5β H, R = H



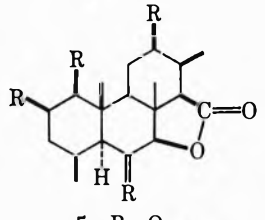
2a, R = H
b, R = Ac

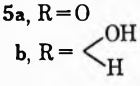


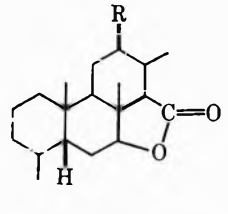
3a, R = H
b, R = Ac



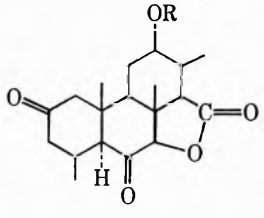
4



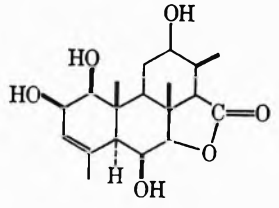
5a, R = O
b, R = 
c, R = O



6a, R = HOH
b, R = HOAc
c, R = O



7a, R = H
b, R = Ac



8

The saturated ketone in **1a** is located at position 6, since it is easily enolized in alkaline medium to give a conjugated enolate, typified by its uv absorption. The location of a ketone at C-6 is further confirmed by treatment of **1a** with acetic anhydride in pyridine at room temperature. An enol acetate (**3a**) resulted. Its ir still shows OH absorption (see Experimental Section) but, besides the γ-lactone band, there appeared a strong absorption corresponding to an enol acetate, also confirmed by uv (see Experimental Section).

When eurycomalactone (**1a**) is treated with acetic anhydride in pyridine solution at reflux temperature, the triacetate **3b** is obtained. However, reaction of **1a** with acetyl chloride gives exclusively the diacetate **1b**. Similarly, treatment of dihydroeurycomalactone (**2a**) with acetyl chloride furnished the diacetoxy derivative **2b**.

These results seem to indicate that the basicity of pyridine enolizes the 6-keto grouping, which is then more readily esterified than the hydroxyls at C-1 and C-12. Indeed, further acetylation of **3a** with acetic anhydride in pyridine for 9 hr on the steam bath affords the triacetate **3b**.

The presence of two secondary hydroxyl groups in eurycomalactone (**1a**) is also shown by chromic acid oxidation[6] of dihydroeurycomalactone (**2a**) which provided the tetraketolactone **5a**. The ir spectrum of **2a** is devoided of hydroxyl absorption.

Clemmensen reduction[7] of **2a** gives the monohydroxy derivative **6a**, which forms a monoacetate (**6b**). Oxidation of **6a** affords the ketolactone **6c**, which forms a 2,4-dinitrophenylhydrazone.

The presence of an α-ketol grouping in **1a** and **2a** is easily detected by ir spectroscopy.[8] Furthermore, the tetrol **5b**, obtained by reduction of **2a** with sodium borohydride, is readily oxidized with periodic acid, hence showing the presence of an α-glycol function in **5b**. Conversely, reaction of **1a** or **2a** with periodic acid is very slow.

When dihydroeurycomalactone (**2a**) is treated with zinc and acetic acid, the hydroxyl at C-1 is eliminated to afford the monohydroxy diketolactone **7a**, which is readily acetylated with acetyl chloride to give **7b**. Finally, Clemmensen reduction[7] of **7a** also provides the monohydroxy derivative **6a**.

The γ-lactone grouping of eurycomalactone (**1a**), easily identified by ir and nmr (*vide supra*), is quite stable, even under alkaline conditions.[9] However, the γ-lactone ring can be reduced with lithium aluminum hydride, as shown below.

The conjugated α-ketol shown to be present in eurycomalactone (**1a**) (*vide supra*) is common in simaroubolides, such as glaucarubinone,[10] chaparrinone,[10] ailanthone,[11] samaderine B,[12] and related compounds.[13] By similar reasoning the vinylic methyl group in **1a** is located at position C-4, thus explaining the uv of **1a**, which is in reasonable agreement with the calculated value.[14]

Since the α-ketol **2a** can be converted into the tetraketone **5a**, the hydroxyl at C-1, as well as all other hydroxyls present in the molecule, must be secondary. As indicated previously, on the basis of the easy formation of enol acetates (**3a**,**b**), as well as the facile isomer-

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

(7) See E. L. Martin, *Org. Reactions*, **1**, 155 (1942).

(8) L. Toris and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **90**, 4599 (1968).

(9) This observation has some precedent; *cf.* (a) Le-Van-Thoi and J. Ourgaud, *Bull. Soc. Chim. Fr.*, 761 (1955); (b) A. J. Birch, D. J. Collins, S. Muhammad, and J. P. Turnbull, *J. Chem. Soc.*, 2762 (1963); (c) J. Romo, L. Rodríguez-Hahn, P. Joseph-Nathan, M. Martínez, and P. Crabbé, *Bull. Soc. Chim. Fr.*, 1276 (1964).

(10) T. A. Geissman and K. R. Chandorkar, *J. Org. Chem.*, **26**, 1217 (1961).

(11) J. Polonsky and J. L. Fourrey, *Tetrahedron Lett.*, No. 52, 3983 (1964).

(12) (a) J. Polonsky, J. Zylber, and R. O. B. Wijesekera, *Bull. Soc. Chim. Fr.*, 1715 (1962); (b) J. Zylber, J. Polonsky, and C. Mitra, *ibid.*, 1322 (1963).

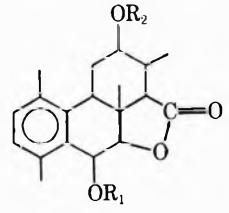
(13) (a) J. Polonsky and N. Bourguignon-Zylber, *ibid.*, 2793 (1965); (b) A. Gaudemer, J. L. Fourrey, and J. Polonsky, *ibid.*, 1676 (1967); (c) A. Gaudemer, *ibid.*, 406 (1967).

(14) (a) R. B. Woodward, *J. Amer. Chem. Soc.*, **64**, 76 (1942); (b) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Co., New York, N. Y., 1959, p 19.

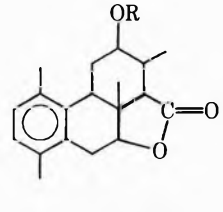
ization of the asymmetric center at C-5 (*vide infra*), the second ketone is located at position 6.

The hydroxylactone **6a** was obtained by two different routes, *i.e.*, either by Clemmensen reduction of dihydroeurycomalactone (**2a**) or from **7a** (*vide supra*). This indicates that the second OH group is somewhat hindered. Therefore, it is located at C-12 (*vide infra*).

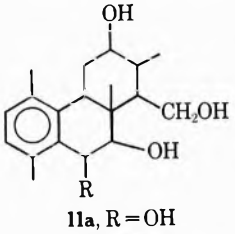
Sodium borohydride reduction of eurycomalactone (**1a**) affords a tetrol (**8**), which is noncrystalline, probably owing to a mixture of isomers at C-2, C-5, and C-6. Acid treatment of this tetrol gives the rearranged aromatic compound eurycomol (**9a**). Similar results are shown by other simaroubolides.[15]



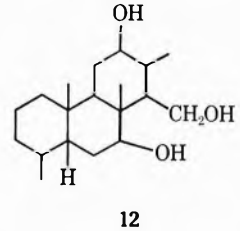
9a, $R_1 = R_2 = H$
b, $R_1 = Ac$; $R_2 = H$
c, $R_1 = R_2 = Ac$



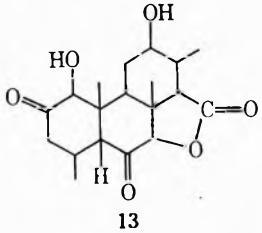
10a, R = H
b, R = Ac



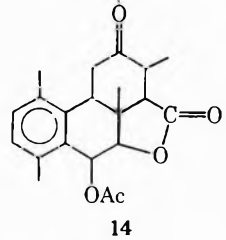
11a, R = OH
b, R = H



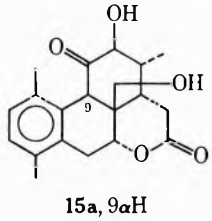
12



13



14



15a, 9αH
b, 9βH

The structure of eurycomol (**9a**) is supported by its uv and ir spectra (see Experimental Section). While acetylation of **9a** under vigorous conditions affords the corresponding diacetate **9b**, the monoacetate **9c** can be obtained under rather mild reaction conditions. The nmr spectra of **9b** and **9c** clearly indicate two aromatic methyls, besides the aromatic protons.

(15) (a) E. A. Ham, H. M. Schafer, R. G. Denkewalter, and N. G. Brink, *J. Amer. Chem. Soc.*, **76**, 6066 (1954); (b) J. Polonsky and A. Gaudemer, *Bull. Soc. Chim. Fr.*, 1432 (1961); (c) J. Polonsky, C. Fouquey, and A. Gaudemer, *ibid.*, 1255 (1962); 169 (1963); (d) T. A. Geissman and K. R. Chandorkar, *J. Org. Chem.*, **26**, 1217 (1961); (e) T. A. Geissman and G. A. Ellestad, *Tetrahedron Lett.*, No. 23, 1083 (1962); (f) T. A. Davidson, T. R. Hollands, and P. de Mayo, *ibid.*, No. 23, 1089 (1962); (g) T. A. Davidson, T. R. Hollands, P. de Mayo, and M. Nisbet, *Can. J. Chem.*, **43**, 2996 (1965).

Since eurycomol (**9a**) is unreactive toward periodic acid, in contrast to the high reactivity of tetrol **8**, one can conclude that at least one of the hydroxyls eliminated during conversion of **8** into **9a** belongs to the α-glycol group of ring A. Moreover, the methyl migration from C-10 to C-1 supports the hypothesis that one hydroxyl is located at position 1 in eurycomalactone (**1a**).

Treatment of eurycomol (**9a**) with platinum in acetic acid solution provides deoxyeurycomol (**10a**), which formed an acetate (**10b**). The elimination of one hydroxyl during the reaction indicates that this alcohol group must be benzylic, thus further confirming the presence of a ketone at C-6 in **1a**. Indeed, lithium aluminum hydride reduction of **10a** affords the triol **11b**, which does not react with periodic acid. The same applies to the triol **12** obtained by $LiAlH_4$ reduction of hydroxylactone **6a**.

Lithium aluminum reduction of eurycomol (**9a**) furnishes the tetrol **11a**. The tetrol **11a** reacts rapidly with periodic acid, thus showing the presence of an α-glycol group at C-6 and C-7. This also defines the position of the γ-lactone group in eurycomalactone (**1a**) and its derivatives.

The above experiments established the structure of rings A and B of eurycomalactone (**1a**). By analogy with other simaroubolides such as quassin,[16] simarolide,[16j,17] kalineanone,[13a] amarolide,[18] etc., the second tertiary methyl is situated at position 8. For similar reasons, supported by experimental evidence (*vide supra*), the γ-lactone function is located between positions 7 and 14.

A feature which is common to most simaroubaceous bitter principles is a methyl (or an equivalent oxidized entity) situated at C-13. Therefore, the secondary methyl in eurycomalactone (**1a**) is located at C-13.

Acetylation and reduction experiments performed on eurycomalactone (**1a**) and its derivatives indicate that the last secondary alcohol grouping is less reactive than the other hydroxyls present in the molecule. This may be attributed to steric hindrance, allowing the third alcohol group to be located at position C-12 (*vide infra*).

Eurycomalactone (**1a**) is easily isomerized by dilute acid to its 5β isomer, isoeurycomalactone (**1c**). When **1c** is treated with acetic anhydride in pyridine for several hours at 90°, compound **3b** is formed, clearly demonstrating that C-5 is the only asymmetric center involved in these transformations.

Catalytic reduction of isoeurycomalactone (**1c**) gives dihydroisoeurycomalactone (**13**), which is isomeric with **2a**. Enolization of the carbonyl at C-6 in dihydroiso-

(16) (a) E. P. Clark, *J. Amer. Chem. Soc.*, **59**, 927, 2511 (1937); (b) E. London, A. Robertson, and H. Worthington, *J. Chem. Soc.*, 3431 (1950); (c) R. J. S. Beer, D. B. G. Jaquiss, A. Robertson, and W. E. Savige, *ibid.*, 3672 (1954); (d) K. R. Hanson, D. B. G. Jaquiss, J. A. Lamberton, A. Robertson, and W. E. Savige, *ibid.*, 4238 (1954); (e) R. J. S. Beer, K. R. Hanson, and A. Robertson, *ibid.*, 3280 (1956); (f) R. J. S. Beer, B. G. Dutton, D. B. G. Jaquiss, A. Robertson, and W. E. Savige, *ibid.*, 4850 (1956); (g) Z. Valenta, S. Papadopoulos, and C. Podĕsva, *Tetrahedron*, **15**, 100 (1961); (h) Z. Valenta, A. H. Gray, D. E. Orr, S. Papadopoulos, and C. Podésva, *ibid.*, **18**, 1433 (1962); (i) R. M. Carman and D. A. Ward, *Tetrahedron Lett.*, No. 10. 317 (1961); (j) W. A. C. Brown and G. A. Sim, *Proc. Chem. Soc.*, 293 (1964).

(17) J. Polonsky, *ibid.*, 292 (1964); (b) J. Polonsky, *Bull. Soc. Chim. Fr.*, 1546 (1959); (c) S. C. Nyburg, G. L. Walford, and P. Yates, *Chem. Commun.*, No. 10, 203 (1965).

(18) C. G. Casinovi, V. Ballavita, G. Grandolini, and P. Ceccherelli, *Tetrahedron Lett.*, No. 27, 2273 (1963).

eurycomalactone (**13**) also occurs, affording an enol acetate (**4**) when treated with acetic anhydride in pyridine solution at room temperature. Clemmensen reduction of **13** affords **6a**, thus indicating the 5β configuration in **6a** and its derivatives **6b** and **6c**.

The circular dichroism (CD) curve of eurycomalactone (**1a**) exhibits a negative maximum[19] at *ca.* 400 mμ and a positive maximum[19] at *ca.* 370 mμ. This resembles the Cotton effect curve of chaparrinone[20] in this spectral region, and a marked negative Cotton effect at *ca.* 300 mμ, indicative of the homoconjugation existing between the unsaturated and the saturated keto chromophores. In isoeurycomalactone (**1c**) the negative Cotton effect at *ca.* 400 mμ is substantially decreased.

Dihydroeurycomalactone (**2a**) shows a "double humped" CD curve, with a negative maximum at 304 mμ and a positive maximum at 275 mμ (see Experimental Section). This Cotton effect strongly supports the 5α configuration in **2a**, since the 5β isomer would be expected to exhibit a very intense negative Cotton effect[19] in the 300-mμ region (summation of 2 ketone and 6 ketone in a 5β compound).

Oxidation of the acetoxy alcohol **9b** affords the acetoxy ketone **14**, which exhibits a negative Cotton effect in the 300-mμ region.

It has been shown earlier in the chaparrin series[20] that treatment of chaparrol (**15a**) with pyridine affords neochaparrol (**15b**) and that the inversion of configuration at C-9 is accompanied by a change in sign of the Cotton effect. Compound **15b** shows a very intense positive rotatory dispersion (RD) curve ($a = +250$).[19] In the 9β compound **15b** the nonbonded interactions between the 1-methyl group and the 11 ketone are substantially reduced, when compared with those in the 9α isomer **15a**, thus explaining the ease of isomerization.[21]

When the acetoxy ketone **14** was refluxed in pyridine, the starting material was recovered unchanged. This excludes the location of the keto group at C-11 in **14**; hence the secondary alcohol has to be situated at C-12 in eurycomalactone (**1a**) and its derivatives.

Further work will be performed in order to establish firmly the complete stereochemistry of eurycomalactone, when conditions will allow us to collect more starting material.

Experimental Section[22]

Extraction of the Bark of *Eurycoma longifolia*.—Dried bark (8 kg) was extracted with petroleum ether for a period of 7 days. After concentration *in vacuo*, 12 g of oily material were obtained. Petroleum ether (100 ml) was added, and the insoluble material was dissolved in benzene–hexane (1:1) and chromatographed over neutral alumina.

Elution with petroleum ether afforded 2.3 g of an oil which crystallized with methanol. Further recrystallizations from methanol gave 800 mg of β-sitosterol: mp 140°; $[\alpha]_D$ −36°; ν_{max}^{KBr} 3570 and 1650 cm^{-1}.

Anal. Calcd for $C_{29}H_{50}O$: C, 83.98; H, 12.15. Found: C, 83.88; H, 12.10.

Acetylation of 100 mg of β-sitosterol with 2 ml of acetic anhydride in pyridine gave the corresponding acetate, which was recrystallized from methanol: mp 129°; $[\alpha]_D$ −40°; ν_{max} 1724 and 1242 cm^{-1}.

Anal. Calcd for $C_{31}H_{52}O_2$: C, 81.51; H, 11.47. Found: C, 81.41; H, 11.40.

Further elution of the column gave 920 mg of a white substance which was purified further by crystallization from acetone to furnish pure campesterol: mp 157°; $[\alpha]_D$ −35°; ν_{max}^{KBr} 3571 and 1652 cm^{-1}.

Anal. Calcd for $C_{28}H_{48}O$: C, 83.93; H, 12.07. Found: C, 83.87; O, 12.12.

Acetylation as above provided the corresponding acetate, which was recrystallized from ethanol: mp 139°; $[\alpha]_D$ −38°; ν_{max}^{KBr} 1730 and 1259 cm^{-1}.

Anal. Calcd for $C_{30}H_{50}O_2$: C, 81.38; H, 11.38. Found: C, 81.28; H, 11.28.

2,6-Dimethoxybenzoquinone.—After extraction with petroleum ether, the bark was dried in the open air and then extracted with boiling water for 48 hr. This extraction was repeated until the water extracts did not show any bitterness. The water extracts were treated with lead acetate (30% water solution). The solution was filtered and the filtrate was treated with carbon. The bitter principles were adsorbed. The carbon was filtered and dried. The aqueous extracts were chromatographed on 400 g of magnesium silicate and Celite. Elution with chloroform afforded 2.04 g of an oily product which crystallized from methanol. Recrystallizations furnished a pure sample of 2,6-dimethoxybenzoquinone: mp 250–252° (in sealed tube); ν_{max}^{KBr} 1701, 1645, 1623, and 1592 cm^{-1}; λ_{max}^{EtOH} 287 mμ (log ϵ 4.29) and 380 (2.78).

Eurycomalactone (1a).—The carbon recovered from the previous extraction was dried in the open air for 3 days, and then for several hours at 50–60°. It was then extracted with chloroform. The chloroform extracts were concentrated under reduced pressure to afford 20 g of a bitter product. Chromatography on 400 g of magnesium silicate–Celite (2:1) gave 3 g of material by elution with benzene. Recrystallizations from methanol furnished 2 g of pure eurycomalactone (**1a**): mp 268–270°; $[\alpha]_D$ +100° ($CHCl_3$), +75° (MeOH), −4° (pyridine); CD (c 0.002, dioxane) $[\theta]_{398-404}$ −1710°; $[\theta]_{375-377}$ +700°, $[\theta]_{366}$ +815°, $[\theta]_{292-307}$ −17,750°; ν_{max}^{KBr} 3571, 3509, 1770, 1709, 1679, and 1621 cm^{-1}; $\nu_{max}^{CHCl_3}$ 3571, 3497, 1773, 1712, 1667, and 1629 cm^{-1}. ν_{max}^{Nujol} 3571, 3509, 1764, 1712, 1667, and 1618 cm^{-1}; λ_{max}^{MeOH} 241 mμ (log ϵ 3.85) and 290 (2.24); nmr 1.16 (d, J = 7 cps, 13-CH_3), 1.25, 1.55 (8-CH_3, 10-CH_3), 1.94 (4-CH_3), 6.1 (vinylic H), 3.10–3.20 and 4.30–4.40 (OH), and 4.80 ppm (HCO); mass spectrum *m/e* 348 (M^+).

Compound **1a** can exist at least partially in the enol form. The CD is solvent and concentration dependent; its uv absorption in alkaline medium is at λ_{max} 288 mμ (log ϵ 3.65), reminiscent of the uv of **3a** and **3b** (*vide infra*).

Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 65.43; H, 6.88.

The mono-2,4-dinitrophenylhydrazone derivative was obtained as yellow crystals, mp 125°, λ_{max}^{EtOH} 358 mμ (log ϵ 4.62).

Anal. Calcd for $C_{25}H_{28}O_9N_4$: N, 10.60. Found: N, 10.15.

The bis-2,4-dinitrophenylhydrazone derivative was obtained as red crystals, mp 150°, λ_{max}^{EtOH} 368 mμ (log ϵ 4.51).

Anal. Calcd for $C_{31}H_{32}O_{12}N_8$: N, 15.80. Found: N, 15.42.

Isoeurycomalactone (1c).—Treatment of 100 mg of eurycomalactone (**1a**) with 40 ml of a 1 *N* solution of H_2SO_4 at reflux temperature for 3 hr is followed by the usual extraction procedure. Chromatography over magnesium silicate–Celite (2:1) afforded 10 mg of recovered starting material. Elution with $CHCl_3$ gave 50 mg of isoeurycomalactone (**1c**): mp 255–258° (from ethanol–water); $[\alpha]_D$ ±0°; CD (*c* 0.009, dioxane) $[\theta]_{394-404}$ −726°; ν_{max}^{KBr} 3509, 3378, 1754, 1724, 1683, and 1629 cm^{-1}; λ_{max}^{EtOH} 232 mμ (log ϵ 3.92), 290 (3.20), and 334 (3.03); nmr (DMSO-d_6) 1.03 (d, J = 6 cps, 13-CH_3), 1.20, 1.36 (8-CH_3, 10-CH_3), and 1.48 (4-CH_3).

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Anal. Calcd for $C_{19}H_{24}O_6$: C, 65.50; H, 6.94. Found: C, 64.99; H, 6.92.

Compound **1c** was also obtained by treatment of **1a** with hydrogen chloride or with concentrated formic acid.

Dihydroeurycomalactone (2a).—A solution of 100 mg of **1a** in 20 ml of methanol was stirred in a hydrogen atmosphere in the presence of 100 mg of 10% Pd–C. After 1 equiv of hydrogen was taken up, the reaction mixture was filtered to give 98 mg of dihydroeurycomalactone (**2a**). Crystallization from methanol provided an analytical sample: mp 247–248°; $[\alpha]_D$ +23°; CD (c 0.001, dioxane) $[\Theta]_{309-313}$ −2.600°, $[\Theta]_{304}$ −2.780°, and $[\Theta]_{273-278}$ +2.450°, ν_{max}^{KBr} 3571, 3448, 1783, and 1706 cm^{-1}; λ_{max}^{EtOH} 280 mμ (log ε 1.83); nmr 0.95 ppm (d, J = 7 cps, 4-CH_3).

Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.47. Found: C, 65.00; H, 7.52.

The 2,4-dinitrophenylhydrazone derivative was obtained, mp 251°, λ_{max}^{EtOH} 355 mμ (log ε 4.54).

Anal. Calcd for $C_{31}H_{34}O_{12}N_8$: N, 15.70. Found: N, 14.93.

Enol Acetate 3a.—A solution containing 200 mg of **1a** and 5 ml of acetic anhydride in 3 ml of pyridine was left at room temperature for 15 hr. After work-up, followed by chromatography, 170 mg of **3a** was obtained: mp 272–273° (from benzene); $[\alpha]_D$ −98°; ν_{max}^{KBr} 3546, 1779, 1754, 1672, and 1681 cm^{-1}; λ_{max}^{EtOH} 285 mμ (log ε 4.66); mass spectrum m/e 388 (M^+).

Anal. Calcd for $C_{21}H_{26}O_7 \cdot {}^1/_2H_2O$: C, 63.01; H, 6.80. Found: C, 62.78; H, 6.50.

The same substance (**3a**) was obtained by treatment of **1a** with acetic anhydride in presence of sodium acetate.

Triacetate 3b.—When a pyridine solution of **1a** was heated for 9 hr at 90° in the presence of acetic anhydride (same proportions as above), a small amount of **3a** was isolated, but the major compound was the triacetate **3b**. Recrystallization from methanol furnished an analytical sample: mp 248°; $[\alpha]_D$ −95°; ν_{max}^{KBr} 1792, 1742, 1672, 1613, and 1285 cm^{-1}; λ_{max}^{EtOH} 285 mμ (log ε 4.37).

Anal. Calcd for $C_{25}H_{30}O_9$: C, 63.28; H, 6.37. Found: C, 63.68; H, 6.27.

Eurycomalactone Diacetate (1b).—A mixture of 200 mg of eurycomalactone **1a** in 10 ml of acetyl chloride was heated under reflux for 3 hr. The residue (170 mg) obtained at the end of the reaction was chromatographed to afford the diacetate **1b**: mp 267° (from ethanol); $[\alpha]_D$ +32°; ν_{max}^{KBr} 1786, 1739, 1721, 1678, and 1629 cm^{-1}; λ_{max}^{EtOH} 238 mμ (log ε 3.51) and 285 (2.53).

Anal. Calcd for $C_{23}H_{28}O_8$: C, 63.80; H, 6.52. Found: C, 63.63; H, 6.64.

Enol Acetate of Dihydroeurycomalactone (4).—Acetylation of **2a** with acetic anhydride in pyridine solution, followed by the usual work-up, gave a 90% yield of enol acetate **4**: mp 290° dec (from benzene); $[\alpha]_D$ −30°; ν_{max}^{KBr} 3597, 3333, 1779, 1742, 1712, and 1628 cm^{-1}; λ_{max}^{EtOH} 285 mμ (log ε 2.55).

Anal. Calcd for $C_{21}H_{28}O_7$: C, 64.27; H, 7.19. Found: C, 64.38; H, 7.12.

Dihydroeurycomalactone Diacetate (2b).—A mixture of 200 mg of **2a** and 10 ml of acetyl chloride was heated on the steam bath for 10 hr. The reaction mixture was evaporated to dryness and the residue (195 mg) was chromatographed over 4 g of magnesium silicate–Celite (2:1). Elution with petroleum ether furnished the diacetate **2b**: mp *ca.* 275–280° dec (from ethanol); $[\alpha]_D$ −36°; ν_{max}^{KBr} 1786, 1739, 1718, and 1277 cm^{-1}; λ_{max}^{EtOH} 285 mμ (log ε 2.52).

Anal. Calcd for $C_{23}H_{30}O_8$: C, 63.58; H, 6.95. Found: C, 63.40; H, 7.01.

Tetraketolactone 5a.—Chromic acid oxidation[6] of 100 mg of **2a** at room temperature was followed by usual work-up to provide 75 mg of tetraketone **5a**: mp 275° (from ethanol); $[\alpha]_D$ −57°; ν_{max}^{KBr} 1779, 1724, and 1718 cm^{-1}; λ_{max} 292 mμ (log ε 2.03).

Anal. Calcd for $C_{19}H_{22}O_6$: C, 65.88; H, 6.40. Found: C, 65.70; H, 6.30.

Preparation of the Monohydroxylactone 6a and Its Acetate 6b.—A solution containing 100 mg of **6a**, 500 mg of zinc amalgam, 1 ml of hydrochloric acid, 3 ml of water, and 10 ml of toluene was heated under reflux for 80 hr. The reaction mixture was cooled to room temperature, the organic layer separated, and the aqueous layer extracted with chloroform. The organic extracts were washed with sodium bicarbonate and water, dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. This gave 90 mg of a product which was purified by chromatography. Elution with petroleum ether–benzene (1:1) furnished the hydroxylactone **6a**: mp 220° (from petroleum ether–benzene); $[\alpha]_D$ +40°; ν_{max}^{KBr} 3448 and 1745 cm^{-1}; mass spectrum m/e 306 (M^+).

Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.46; H, 9.86. Found: C, 74.31; H, 9.70.

Acetylation of **6a** by the usual techniques gave the corresponding acetate **6b**: mp 135° (from ethanol); $[\alpha]_D$ +30°; ν_{max}^{KBr} 1779, 1739, and 1228 cm^{-1}.

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.41; H, 9.19.

Ketolactone 6c.—To a solution of 100 mg of **6a** in 5 ml of 90% acetic acid, a solution of 100 mg of chromic anhydride in 3 ml of 90% acetic acid was added dropwise. The reaction was allowed to stand at room temperature for 2 hr. Water was added, and the organic compound was extracted with chloroform. The organic layer was washed, dried, filtered, and evaporated to dryness, furnishing 90 mg of ketolactone **6c**: mp 198–200° (from ethanol); $[\alpha]_D$ −75°; ν_{max}^{KBr} 1786 and 1721 cm^{-1}; λ_{max}^{EtOH} 300 mμ (log ε 1.76).

Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.30. Found: C, 74.59; H, 9.43.

The 2,4-dinitrophenylhydrazone derivative was obtained as yellow-orange crystals, mp 135°, λ_{max}^{EtOH} 358 mμ (log ε 3.85).

Anal. Calcd for $C_{25}H_{32}O_6N_4$: N, 11.56. Found: N, 11.04.

Tetrahydroxylactone 5b.—Sodium borohydride (200 mg) was added in small portions to 100 mg of **2a** in 10 ml of methanol. Stirring was continued for 3 hr. Water was added, and the solution was neutralized with dilute sulfuric acid. Extraction with chloroform afforded 60 mg of noncrystalline tetrol **5b**, which showed no keto band in the ir.

Treatment of 100 mg of **5b** in dioxane solution with 10 ml of 0.25 *M* periodic acid showed that the cleavage of α-glycol is complete after 4 hr.

Hydroxydiketolactone 7a and Its Acetate 7b.—To a solution of 100 mg of **2a** in 10 ml of glacial acetic acid, 300 mg of zinc powder and 2 ml of concentrated hydrochloric acid were added. The reaction mixture was gently refluxed for 6 hr, 1 ml of concentrated hydrogen chloride being added after 3 hr. The solution was cooled, extracted with chloroform, washed, dried, filtered, and concentrated *in vacuo*. The hydroxydiketolactone **7a** (90 mg) was recrystallized from ethanol: mp 262°; $[\alpha]_D$ +11°; ν_{max}^{KBr} 3424, 1779, and 1706 cm^{-1}; λ_{max}^{EtOH} 282 mμ (log ε 1.84).

Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.83. Found: C, 68.50; H, 7.97.

Acetylation of **7a** with acetyl chloride under the conditions described previously provided the corresponding acetate **7b**: mp 135–140° (from ethanol); $[\alpha]_D$ −11°; ν_{max}^{KBr} 1779, 1745, 1715, and 1231 cm^{-1}; λ_{max}^{EtOH} 280 mμ (log ε 2.61).

Anal. Calcd for $C_{21}H_{28}O_6$: C, 67.00; H, 7.49. Found: C, 67.32; H, 7.60.

Clemmensen Reduction of 7a.—A solution of 100 mg of **7a**, 10 ml of toluene, 1 ml of concentrated hydrochloric acid, 3 ml of water, and 500 mg of zinc amalgam was heated under reflux for 80 hr. After the usual work-up, there was obtained 90 mg of hydroxylactone **6a**: mp 220°; $[\alpha]_D$ +40°; identical in all aspects with the compound obtained above.

Eurycomol (9a).—600 mg of sodium borohydride was slowly added, with stirring, to a solution of 300 mg of **1a** in 40 ml of methanol containing 600 mg of boric acid. Stirring was continued for 2 hr after addition was finished. Water was added, and the solution was neutralized with dilute sulfuric acid. Extraction with chloroform furnished 150 mg of noncrystalline **8**: $[\alpha]_D$ −25°; ν_{max}^{KBr} 3462, 3360, 1752, 1650, and 1625 cm^{-1}.

This material was used as such for the rearrangement reaction, which was performed as follows. **8** (200 mg) was treated with 40 ml of 10% sulfuric acid at reflux temperature for 3 hr. The reaction mixture was cooled, water was added, and the compound was extracted with chloroform. The organic layer was washed, dried, filtered, and evaporated, thus affording 150 mg of a yellow compound which was chromatographed over 3 g of magnesium silicate–Celite (2:1).

Elution with 200 ml of benzene gave eurycomol (**9a**), which was recrystallized from ethyl alcohol: mp 265°; $[\alpha]_D$ +14°; RD (c 0.001, dioxane) $[\Phi]_{600}$ +244°, $[\Phi]_{350}$ +367°, $[\Phi]_{296}$ +215°, $[\Phi]_{291}$ ±0°, $[\Phi]_{282}$ −380°, $[\Phi]_{273}$ −123°, $[\Phi]_{240}$ −5460°, and $[\Phi]_{232}$ −3240°; ν_{max}^{KBr} 3571, 3424, 1754, 1655, and 1628 cm^{-1}; λ_{max}^{EtOH} 224 mμ (log ε 4.08), 270 (2.68), 279 (2.57), and 308 (1.55).

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.64. Found: C, 72.00; H, 7.50.

Eurycomol Monoacetate (9b) and Diacetate (9c).—A solution containing 200 mg of **9a**, 3 ml of pyridine, and 4 ml of acetic anhydride was heated on the steam bath for 10 hr. The reaction mixture was then evaporated to dryness *in vacuo*. The

residue (190 mg) was chromatographed over 4 g of magnesium silicate–Celite (2:1).

Elution with petroleum ether–benzene (1:1) afforded the diacetate **9c**: mp 235–240° (from ethyl alcohol); $[\alpha]D$ +20°; ν_{max}^{KBr} 1764, 1724, and 1234 cm^{-1}; λ_{max}^{EtOH} 223 mμ (log ε 3.48), 270 (2.72), 274 (2.68), and 279 (2.71).

Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.04. Found: C, 68.68; H, 7.00.

Further elution with benzene furnished the monoacetate **9b**: mp 255–260° (from ethyl alcohol); $[\alpha]D$ +40°; ν_{max}^{KBr} 3472, 1754, 1724, 1650, 1625, and 1234 cm^{-1}; λ_{max}^{EtOH} 223 mμ (log ε 3.44), 270, (2.27), 274, (2.22), and 279 (2.24); nmr 0.95 (8-CH_3), 1.35 (d, J = 6 cps, 13-CH_3), 2.05 (6-OAc), 2.31 (1-CH_3), 2.67 (4-CH_3), and 6.98 ppm (2 aromatic H).

Anal. Calcd for $C_{21}H_{26}O_5$: C, 70.36; H, 7.31. Found: C, 70.10; H, 7.14.

Reduction of Eurycomol (9a) with Lithium Aluminum Hydride.—To a solution of 1 g of $LiAlH_4$ in 40 ml of anhydrous tetrahydrofuran, cooled at 0°, 100 mg of **9a** in tetrahydrofuran was slowly added. The reaction mixture was stirred for 3 hr. Ethyl acetate was then slowly added. After filtration and extraction with chloroform, an amorphous material was obtained: ν_{max}^{KBr} 3570, 1656, and 1626 cm^{-1}; λ_{max}^{EtOH} 248 mμ (log ε 2.74), 254 (2.77), 260 (2.79), 269 (2.82), and 279 (2.76).

When compound **11a** was treated with periodic acid under the conditions described above for the tetrahydroxylactone **5b**, the cleavage of the α glycol was achieved in less than 5 hr.

Deoxyeurycomol (10a) and Its Acetate (10b).—A solution of 80 mg of eurycomol (**9a**) in 20 ml of acetic acid was treated in a hydrogen atmosphere with 80 mg of prereduced platinum oxide. After taking up 1 mol of hydrogen, the catalyst was filtered, water was added, and the product was extracted with chloroform. The organic layer was washed, dried, filtered, and concentrated under reduced pressure to give deoxyeurycomol (**10a**): mp 215° (chloroform); $[\alpha]D$ +25°; ν_{max}^{KBr} 3424, 1754, 1658, and 1628 cm^{-1}; λ_{max}^{EtOH} 224 mμ (log ε 4.10), 261 (2.38), 270, (2.42), and 279 (2.36).

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.96; H, 8.05. Found: C, 76.01; H, 8.15.

Acetylation of **10a** under usual conditions furnished the corresponding acetate **10b**: mp 110°; $[\alpha]D$ +27°; ν_{max}^{KBr} 1779, 1742, 1634, 1618, and 1231 cm^{-1}; λ_{max}^{EtOH} 224 mμ (log ε 4.05), 270 (2.09), and 279 (2.04).

Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.65; H, 7.65. Found: C, 73.38; H, 7.50.

Preparation of Triol 11b.—A solution of 100 mg of **10a** in 20 ml of anhydrous tetrahydrofuran was reduced with 1 g of $LiAlH_4$ in 20 ml of the same solvent. At the end of the reaction, the excess of reagent was decomposed by careful addition of ethyl acetate. Addition of water and then 20% sulfuric acid was followed by extraction with chloroform. After washing and drying, evaporation of the solvents afforded 85 mg of triol **11b**: mp 190° (from chloroform); ν_{max}^{KBr} 3333 and 1484 cm^{-1}.

Anal. Calcd for $C_{19}H_{34}O_3$: C, 73.50; H, 11.03. Found: C, 73.14; H, 11.09.

Preparation of Triacetate 3b.—A solution containing 200 mg of isoeurycomalactone (**1c**), 4 ml of acetic anhydride, and 3 ml of pyridine was heated on the steam bath for 8 hr. The reaction mixture was then evaporated to dryness *in vacuo*. The amorphous residue was chromatographed to afford 120 mg of triacetate **3b**: mp 245° (from ethyl alcohol); $[\alpha]D$ −95°; ν_{max}^{KBr} 1792, 1742, 1672, 1613, 1285, and 1227 cm^{-1}; λ_{max}^{EtOH} 285 mμ (log ε 4.35).

Anal. Calcd for $C_{25}H_{30}O_9$: C, 63.28; H, 6.37. Found: C, 63.55; H, 6.24.

Dihydroisoeurycomalactone (13).—Catalytic reduction of **1c** (90 mg) with 180 mg of palladium on carbon (10%) in 10 ml of methanol in a hydrogen atmosphere furnished the saturated compound **13**: mp 230° (from methanol); $[\alpha]D$ +20°; ν_{max}^{KBr} 3521, 3448, 1757, and 1712 cm^{-1}; λ_{max}^{EtOH} 278 mμ (log ε 2.22).

Anal. Calcd for $C_{19}H_{26}O_6$: C, 65.12; H, 7.47. Found: C, 65.10; H, 7.51.

Hydroxylactone 6a.—When dihydroisoeurycomalactone (**1c**) was reduced under the Clemmensen reaction conditions described above, the hydroxylactone **6a** was isolated. Recrystallization from petroleum ether afforded the analytical sample: mp 220°; $[\alpha]D$ +40°; ν_{max}^{KBr} 3496, 1754, and 1458 cm^{-1}. This compound was shown to be identical with the substance obtained from **2a**. The melting points and $[\alpha]D$ values were identical, and the ir curves were superimposable.

Preparation of the Acetoxy Ketone 14.—Oxidation of the acetoxy alcohol **9b** with chromic acid in the usual manner[16] afforded the acetoxy ketone **14**: mp 225° (from ethanol); CD (c 0.0014, dioxane) $[\theta]_{298-301}$ −3800°; $[\theta]_{294-296}$ −3930°.

When **14** was dissolved in pyridine and the solution was heated to reflux, no change was observed. The starting material was recovered.

Registry No.—**1a**, 23062-24-0; **1a** bis-2,4-dinitrophenylhydrazone, 23102-76-3; **1b**, 23062-25-1; **1c**, 23062-26-2; **2a**, 23042-48-0; **2a** 2,4-dinitrophenylhydrazone, 23042-49-1; **2b**, 23102-77-4; **3a**, 23042-50-4; **3b**, 23042-51-5; **4**, 23042-52-6; **5a**, 23042-53-7; **6a**, 23042-54-8; **6b**, 23042-55-9; **6c**, 23042-56-0; **6c** 2,4-dinitrophenylhydrazone, 23042-57-1; **7a**, 23042-58-2; **7b**, 23042-59-3; **8**, 23042-60-6; **9a**, 23102-78-5; **9b**, 23042-61-7; **9c**, 23042-62-8; **10a**, 23042-63-9; **10b**, 23102-79-6; **11a**, 23042-64-0; **11b**, 23042-65-1; **13**, 23042-48-0; **14**, 23042-67-3; β-sitosterol, 83-46-5; β-sitosterol acetate, 915-05-9; campesterol, 474-62-4; campesterol acetate, 3037-45-4; 2,6-dimethoxybenzoquinone, 530-55-2.

Acknowledgments.—We express our sincere gratitude to Professors G. Ourisson (University of Strasbourg), R. Ryhage (University of Stockholm), H. C. Beachell (University of Delaware), and D. Lavie (Weizmann Institute of Science) for numerous physical and spectroscopic measurements. We should like to thank especially Professor P. Crabbé (Universidad Nacional Autónoma de México) for the interpretation of various spectroscopic properties, for stimulating discussions, and for his assistance in the preparation of this paper.

Parthemollin, a New Xanthanolide from *Parthenice Mollis* Gray[1]

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Received July 24, 1969

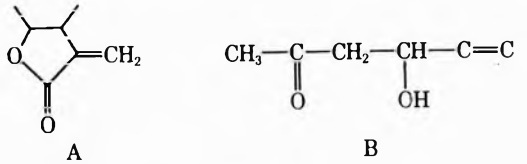
The structure of parthemollin, a new xanthanolide from *Parthenice Mollis* Gray, has been elucidated. Absolute configurations have been assigned to three of the four asymmetric centers.

The discovery of pseudoguaianolides in both *Ambrosia* and *Parthenium* species[2,3] was of interest because of the debate on the position of *Ambrosia* and its relatives, the ragweeds, in the general taxonomic scheme of the *Compositae*.[4] Since that time the distribution of sesquiterpene lactones in *Ambrosia* and related genera has received considerable attention[4,5] because of the possible utility of such knowledge in clarifying evolutionary relationships[6] within the group. However, in addition to the hints given by chemical examination of a few *Parthenium* species,[7] there are reasons based on morphology for suspecting that genera of the *Melampodiinae* may be on the road to the ragweeds.[8] As part of a general chemical investigation of this notion we now report the results of our study of *Parthenice mollis* Gray.[9]

P. mollis, although containing a relatively large sesquiterpene lactone fraction, afforded only one chemically characterizable entity in approximately 0.05% yield which we have called parthemollin. Parthemollin, $C_{15}H_{20}O_4$, mp 116–118°, $[\alpha]D$ −130.0°, had one hydroxyl group (infrared band at 3580 cm^{-1}, formation of monoacetate **1b**) and a conjugated γ-lactone (ir bands at 1775 and 1655 cm^{-1}, very strong end absorption at 205 nm). The presence of a second carbonyl function and a second double bond, probably not conjugated because of the uv spectrum, was suggested by ir bands at 1705 and 1620 cm^{-1}.

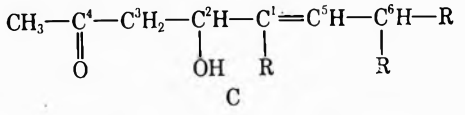
Although catalytic hydrogenation of parthemollin yielded a complex mixture, treatment with 1 mol equiv of sodium borohydride produced a crystalline dihydro derivative **2** whose uv and ir spectrum (see Experimental Section) indicated retention of the α,β-unsaturated lactone and reduction of the carbonyl group originally responsible for the ir band at 1705 cm^{-1}. Treatment of parthemollin with excess borohydride resulted in a tetrahydro derivative **3** by reduction of the carbonyl group and saturation of the lactone.

In the nmr spectra (Table I) the transformation of **1a** to **2** was attended by the appearance of an additional one-proton multiplet near 4.1 ppm signifying the formation of a new secondary hydroxyl group; this was accompanied by the conversion of a sharp three-proton singlet near 2.2 into a three-proton doublet at 1.16 ppm superimposed on a methyl doublet already present in the precursor **1a**. Evidently the reaction involved the reduction of a methyl ketone. The nmr spectra also confirmed the presence of partial structure A already indicated by the facile formation of a pyrazoline. **1a**, **1b**, and **2** exhibited the typical doublet of the conjugated exocyclic methylene group, whereas **3** displayed a third methyl doublet due to the reduction of A.



A

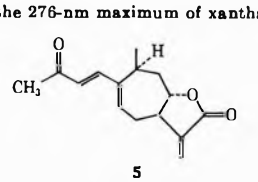
B



C

Manganese dioxide oxidation of parthemollin established the allylic nature of the hydroxyl group. The spectral properties of the product **4** [λ_{max} 294 and 210 nm (ϵ 16,200 and 17,500), ir bands at 1760, 1660 and 1600 cm^{-1}] were, however, not those expected from superposition of α,β-unsaturated ketone absorption on that of an α,β-unsaturated lactone. Instead the extended conjugation indicated by the uv spectrum and a positive ferric chloride test made likely the presence in **4** of an extended enolic β-diketone chromophore produced by oxidation of partial structure B. The conversion of **1b**, on treatment with basic alumina, to dienone **6** [λ_{max} 277 and 205 nm (ϵ 17,500 and 15,500[10])] provided further chemical support for this postulate.

The nmr spectra were in harmony with reactions based on partial structure B and permitted elaboration to C. Oxidation of **1a** to **4** resulted in disappearance of



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(1) Supported in part by a grant from the U. S. Public Health Service (GM-05814).

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(7) *Parthenium hysterophorus* L., ref 3 and A. Romo de Vivar, E. A. Bratoeff, and T. Rios, *J. Org. Chem.*, **31**, 673 (1966); *Parthenium incanum* HBK, ref 3; *Parthenium alpinum* var. *tetraneuris* (Barneby) Rollins, H. Rüesch and T. J. Mabry, *Tetrahedron*, **25**, 805 (1969); *P. hispidum* Raf., and *P. integrifolium* L., W. Herz, unpublished work.

(8) Private communication from Dr. W. W. Payne, University of Illinois, Urbana, Ill.

(9) The monotypic genus *Parthenice* stands next to *Parthenium* in subtribe *Melampodiinae*, tribe *Helianthеae*. The range of its single genus *P. mollis* Gray is Southern Arizona and Northern Mexico.

(10) Compare with the 276-nm maximum of xanthatin (**5**).[11]

(11) T. A. Geissman, P. G. Deuel, E. K. Bonde, and F. A. Addicott, *J. Amer. Chem. Soc.*, **76**, 685 (1954); P. G. Deuel and T. A. Geissman, *ibid.*, **79**, 3778 (1959); L. Dolejs, V. Herout, and F. Šorm, *Collect Czech. Chem. Commun.*, **23**, 504 (1958); T. A. Geissman, *J. Org. Chem.*, **27**, 2692 (1962).

TABLE I

NUCLEAR MAGNETIC RESONANCE SPECTRA OF PARTHEMOLLIN AND ITS DERIVATIVES[a]

Compd	H-2	H-3	H-5	H-6	H-7	H-13	C-4 Me	C-10 Me	Misc
1a	4.7 (t, br) (6.5)	2.62 (d) (6.5)[b]	5.75 (m)[c]	5.57 (ddd) (9,3,1.5)	3.1 (c)	6.31 (d) (3) 5.60 (d) (3)	2.23	1.16 (7)	
1b	5.56[d]	2.69 (m)[b]	5.56[d]	5.40 (d, br) (9)	3.16	6.30 (d) (3) 5.56 (d) (3)	2.17	1.18 (d) (7)	2.04[e]
2	4.58 (m)	*f*	5.78 (m)	5.48 (m)	3.1 (c)	6.30 (d) (3) 5.60 (d) (3)	1.24 (d) (7)	1.12 (d) (7)	4.10 (m)[g]
3	4.40 (m)	*f*	5.70 (m)	5.2 (m)	2.7 (c)	*h*	*h*	*h*	4.08 (m)[g]
4		5.60	6.07 (dd) (3.5, 0.5)	5.47 (m)	3.1 (c)	6.29 (d) (3) 5.60 (d) (3)	2.10	1.20 (d) (7)	
6	7.12 (d) (16)	6.34 (d) (16)	6.03 (dd) (3.5, 0.5)	5.45 (m)	3.25 (c)	6.29 (d) (3) 5.62 (d) (e)	2.28	1.20 (d) (7)	
9	4.65 (m)	2.04 (d) (6)[b]	5.84 (m)	5.48 (m)	2.9 (c)	6.31 (d) (3)	1.87	1.20 (d) (6.5)	

[a] Spectra were determined in deuteriochloroform solution on a Varian A-60 spectrometer using tetramethylsilane as internal standard. Chemical shifts are in parts per million. Signals are denoted in the usual way: d, doublet; t, triplet; m, multiplet; c, complex band whose center is given; br, somewhat broadened singlet; unmarked signals are singlets. Numbers in parentheses are line separations in hertz. Signals in the first six columns correspond to one proton unless marked otherwise, in seventh and eighth columns to three protons. [b] Two protons. [c] Apparent quintet; line separations, ~1 Hz. [d] Superimposed on other signal. [e] Acetate. [f] Obscured by other signals. [g] H-4. [h] Three methyl doublets at 1.16, 1.14, and 1.05 (7).

a broadened triplet at 4.7 (H-2 of C, exhibits the usual paramagnetic shift on acetylation to **1b**) and a two-proton doublet at 2.62 ppm (H-3) and introduced a one-proton singlet at 5.60 ppm (vinyl proton α to carbonyl). Simultaneously a narrowly split multiplet, found near 5.8 in the nmr spectra of **1a**, **1b**, **2**, and **3**, clearly the

signal of a third vinyl proton (H-5, disappears on hydrogenation), moved downfield and simplified to a doublet[12] whose chemical shift was consonant with its new position at the terminus of a conjugated system and whose multiplicity suggested that it was adjacent to a methinyl group. Conversion of **1b** into **6** effected the same change in chemical shift and appearance of the H-5 signal. In addition the appearance in **6** of an AB system characteristic of two *trans*-oriented vinyl hydrogens α and β to a carbonyl group at 6.34 and 7.12 ppm (J = 16 Hz) could be noted. The absence of other

(12) The additional small splitting shown in Table I was tentatively ascribed to allylic coupling (for verification *vide infra*).

vinylic signals and the lack of further coupling in the components of the AB system required the substitution depicted in C.

Since the empirical formula required that parthemollin be monocyclic, since partial formulas A and C accounted for 12 of the 15 carbon atoms, and since the nmr spectrum (see Table I) had revealed the presence of a secondary methyl group and another low field proton at 5.47 ppm plausibly associated with the lactone oxygen, it was logical to formulate parthemollin as **1a** (exclusive of stereochemistry).[13] Carbon atoms 8, 9, and 10 not represented in A and C were accounted for by degradation of parthemollin to (*S*)-(+)-α-methylglutaric acid (**7**) in the manner previously described for parthenin.[3] This result allowed only two possible expressions for parthemollin, **1a**, and the biogenetically highly implausible **12**.

A decision between these two possibilities was reached by spin-decoupling experiments at 90 MHz, whose results are given in Table II.[21]

TABLE II

90-MHz SPECTRUM OF PARTHEMOLLIN[a]

H-2	4.67 (t, br)[b]	$J_{2,3} = 6$, $J_{2,5} = 1.2$, $J_{2,6} = 1.5$, $J_{2,10} \leqq 0.5$
H-3	2.59 (d)[c,d]	$J_{3,2} = 6$
H-5	5.71 (m)[e]	$J_{5,2} = 1.2$, $J_{5,6} = 3$, $J_{5,10} = 1$
H-6	5.54 (ddd, br)	$J_{6,2} = 1.5$, $J_{6,5} = 3$, $J_{6,7} = 8.5$, $J_{6,10} = 0.5$
H-7	3.02 (c)	$J_{7,6} = 8.5$
H-8, H-9[f]	1.13–1.30 (c)	
H-10	2.6 (c)[g]	
H-13a	6.25 (d)	$J_{7,13a} = 3$
H-13b	5.58 (d)	$J_{7,13a} = 2.8$
H-14[h]	2.19	
H-15[h]	1.15 (d)	$J_{10,15} = 7$

[a] Symbols are those in Table I. Values of J are accurate to ±0.3 Hz. [b] Components of triplet resemble a broad triplet. [c] Two protons. [d] Superimposed on broad signal of H-10. [e] Resembles 1:2:2:2:1 quintuplet. [f] Four protons. [g] Superimposed on doublet of H-3. [h] Three protons.

Identification of the signal due to H-7 was achieved by irradiating at the frequencies of the narrow doublet of the exocyclic methylene group. This caused simplification of a multiplet at 3.02 ppm (H-7). Conversely, irradiation at 3.02 collapsed the doublet at 6.25 and 5.58 (H-13a and H-13b) and affected a series of signals corresponding to four protons in the region of 1.13–1.30, probably the methylene protons of the ring portion giving rise to α-methylglutaric acid. Simultaneous simplification of a multiplet at 5.54 ppm to a narrowly split slightly broadened doublet of doublets (line separation 3 and 1.5 Hz) showed that this signal had been correctly assigned to H-6.

Irradiation at the frequency of H-6 affected the signal of H-7, collapsed the multiplet of H-5 at 5.71 to a broad singlet, and sharpened the broad triplet of H-2 at 4.67 ppm. Hence H-2 and H-6 were coupled homoallylically. In turn, irradiation at the frequency of H-2 reduced the H-6 signal to a slightly broadened doublet of doublet separated by 8.5 ($J_{6,7}$) and 3 Hz ($J_{5,10}$), collapsed a two-proton doublet at 2.59 superimposed on a broad one-proton multiplet to a singlet, and sharpened the multiplet of H-5 to a doublet of doublets separated by 3 ($J_{5,6}$) and 1 Hz ($J_{5,10}$). Hence the two-proton multiplet at 2.59 ppm represented H-3, and H-2 and H-5 were coupled allylically ($J \sim 1.2$ Hz).

Irradiation at the frequency of the methyl doublet (1.15 ppm) produced a change in the broad one-proton multiplet at 2.6 ppm underlying the signal of H-3. Hence the origin of this signal could be attributed to the methinyl group present also in the degradation product α-methylglutaric acid. Now irradiation at the frequency of H-7 had produced no change in the 2.6-ppm region and, conversely, irradiation at 2.6 ppm, while collapsing the signals of H-2 and the secondary methyl group and affecting the signals in the methylene region,[22] did not exert any influence on the signal of H-7. Hence formula **12** was ruled out and parthemollin was correctly represented by **1a**.

As concerns stereochemistry, isolation of (*S*)-(+)-α-methylglutaric acid by degradation of parthemollin showed that the absolute configuration at C-10 was C-10 methyl β and therefore identical with the absolute configuration of other xanthanolides and pseudoguaianolides isolated from related species. The absolute configuration of C-2 was found by application of Horeau's method of asymmetric esterification[23] which has been found applicable to sesquiterpene lactones.[24] Reaction of parthemollin with an excess of (±)-α-phenylbutyric anhydride resulted in recovery of (−)-α-phenylbutyric acid. Hence the configuration at C-2 was *S*, or –OH α.

If one assumes, as is plausible, that the absolute configuration of the C-7 side chain is β as in all other sesquiterpene lactones of established stereochemistry, the remaining problem was elucidation of the stereochemistry of C-6. Since examination of molecular models showed that knowledge of the coupling constants $J_{2,5}$ (1.2 Hz), $J_{2,6}$ (1.5), $J_{5,6}$ (3), and $J_{6,7}$ (8.5) was not suffi-

(13) Compounds of this type, all of them, however, with the lactone ring closed to C-8, have been described[14] as xanthanolides because of their prevalence in *Xanthium* and related species: xanthinin and xanthatin,[11] xanthumin,[15] xanthanol,[16] isoxanthanol,[16] and ivalbin.[17] Some other members of this class have been isolated from species in the tribe Inuleae: carabrone,[18] gafrinin,[19] and griesenin.[20]

(14) T. G. Waddell, W. Stöcklin, and T. A. Geissman, *Tetrahedron Lett.*, 1313 (1969).

(15) H. Minato and I. Horibe, *J. Chem. Soc.*, 7009 (1969).

(16) T. E. Winters, T. A. Geissman, and D. Safir, *J. Org. Chem.*, **34**, 153 (1969).

(17) W. Herz, H. Chikamatsu, N. Viswanathan, and V. Sudarsanam, *ibid.*, **32**, 682 (1967).

(18) H. Minato, S. Nosaka, and I. Horibe, *J. Chem. Soc.*, 5503 (1964); H. Minato and I. Horibe, *ibid.*, 2131 (1968); E. Diaz T., *Bol. Inst. Quim. Unix. Nac. Auton. Mex.*, **20**, 84 (1968).

(19) L. A. P. Anderson, W. T. de Kock, and K. G. R. Pachler, *ibid.*, **24**, 1701 (1968).

(20) W. T. de Kock, K. G. R. Pachler, W. F. Ross, P. L. Wessels, and I. C. DuPreez, *Tetrahedron*, **24**, 6037 (1968).

(21) These were carried out on a Bruker 90-MHz nmr spectrometer purchased with the aid of a grant from the National Science Foundation for which we express our thanks. Chemical shifts on the 90-MHz instrument differed slightly from the values given in Table I, which were obtained on a Varian A-60 instrument, because of small calibration errors.

(22) Irradiation at the frequency of H-10 also simplified the signal of H-5 to a doublet of doublets, showing that H-5 was allylically coupled to H-10 ($J \sim 1$ Hz) as well as to H-2 and removed a very small coupling (≤ 0.5 Hz) from the signal of H-6. Hence H-6 was homoallylically coupled to H-10 as well as to H-2. Because the components of the broad H-2 triplet were only sharpened, but not resolved into doublets by irradiation of H-5 or H-6, H-2 was apparently coupled ($J \leqq 0.5$ Hz) to another proton, probably H-10. An attempt to demonstrate this by irradiation of H-10 failed since H-3 and H-10 had very nearly the same chemical shift.

(23) A. Horeau, *Tetrahedron Lett.*, 506 (1961); 965 (1962).

(24) W. Herz and H. B. Kagan, *J. Org. Chem.*, **32**, 216 (1967).

cient to decide unambiguously between a *cis* or *trans* fusion of the lactone ring,[25] information bearing on the stereochemistry at C-6 was sought.

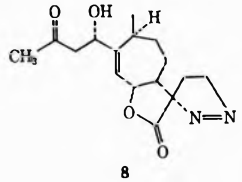
It has been suggested recently[14] that the sign of the lactone Cotton effect of a sesquiterpene lactone which incorporates partial structure A offers a clue to the solution of this problem. The generalization has been made[14] that, regardless of structural type, *cis*-fused lactones closed to C-8 exhibit negative Cotton effects, and that in *trans*-fused lactones closed to C-8 the Cotton effect is positive. The reverse situation prevails in lactones closed to C-6: *cis*-fused lactones display positive Cotton effects; *trans*-fused lactones show negative values. The strongly negative Cotton effect exhibited by parthemollin [λ_{max} 255 nm (θ −3400)] comparable in magnitude with the Cotton effect of other xanthanolides[14] would on this basis require a *trans*-lactone fusion (H-6 β).

Because all C-6 closed pseudoguaianolides previously isolated from *Parthenium* and related species are *cis*-lactones (H-6 α)[4-7,29-34] and might conceivably[12] be related to parthemollin through a common guaianolide intermediate, and because several exceptions to the generalization had been noted,[14] independent verification of the existence of a *trans*-fused lactone ring fusion in parthemollin seemed desirable. Accordingly we investigated the possibility of applying to parthemollin the modified Hudson–Klyne rule[35] which had proved serviceable in establishing the C-6 stereochemistry of parthenin.[3]

Protection of the lactone function by thiaketalization to **9** and sodium borohydride reduction of the latter afforded a lactone **10**, $[\alpha]_D$ −34.0°. Lithium aluminum hydride treatment of **10** gave the triol **11**, $[\alpha]_D$ −13.7°. The observed change in rotation indicated that, if the rule were applicable, parthemollin should be a *cis*-fused lactone with H-6 α, a result directly contradictory to the conclusion reached earlier by considering the CD curve of parthemollin.

Attempts to resolve this contradiction and to ascertain the correct stereochemistry of parthemollin at C-6 will be the goal of future studies. In the meantime, the isolation from *P. mollis* of a xanthanolide which appears to stem from the same precursor as the pseudoguaianolides of *Ambrosia* species seems to support the postulate of a relatively close relationship between the two genera.

(25) Conformations for both *cis*- and *trans*-fused Dreiding models of parthemollin are possible which appear to satisfy the dihedral angle requirement imposed by the magnitude of the vicinal coupling constant $J_{6,7}$, the allylic coupling constant[26] $J_{2,5}$, and the homoallylic coupling[26] constant $J_{2,6}$. Inspection of these models indicates that regardless of the configuration at C-6, formation of a pyrazoline by reaction of parthemollin with diazomethane should occur primarily, if not exclusively, by attack of the reagent from the α side to give **8**. On the basis of a recently deduced relationship[27] between



8

absolute configuration of such pyrazolines and the sign of their Cotton effect, one would expect a strongly negative CD curve for **8**. This was indeed observed, the value [λ_{max} 318 nm (θ −23,400)] being comparable in sign and magnitude with that reported for coronopilin,[27] damsin,[27] ambrosiol,[28] and psilostachyin C.[28] This provides excellent support for the postulated β orientation of the C-7 side chain.

(26) For leading references, see G. P. Newsoroff and S. Sternhell, *Tetrahedron Lett.*, 6117 (1968).

(27) G. Snatzke, *Riechst., Aromen, Koerperpflegem.*, **19**, 98 (1969); M. Suchy, L. Dolejs, V. Herout, F. Šorm, G. Snatzke, and J. Himmelreich, *Collect. Czech. Chem. Commun.*, **34**, 229 (1969).

(28) Private communication from Dr. W. Stöcklin.

(29) T. A. Geissman and F. P. Toribio, *Phytochemistry*, **6**, 1563 (1967).

(30) N. K. Fischer and T. J. Mabry, *Tetrahedron*, **23**, 2529 (1967).

(31) T. A. Geissman and S. Matsueda, *Phytochemistry*, **7**, 1623 (1968).

(32) F. P. Toribio and T. A. Geissman, *ibid.*, **7**, 1623 (1968).

(33) J. Romo, A. Romo de Vivar, A. Velez, and E. Urbino, *Can. J. Chem.*, **46**, 1535 (1968).

(34) E. Bianchi, C. C. J. Culvenor, and J. W. Loder, *Aust. J. Chem.*, **21**, 1108 (1968).

(35) V. Sykora and M. Romanuk, *Collect. Czech. Chem. Commun.*, **22**, 1909 (1957).

Experimental Section[36]

Isolation of Parthemollin.—Powdered above-ground *Parthenice mollis* Gray, wt 10.4 kg, collected by Mr. R. Barr on Sept 10, 1968 (Barr #68-573, on deposit in herbarium of Florida State University), along a wash, 1 mile south of Tubac, Santa Cruz County, Ariz., was extracted with chloroform in the usual manner.[37] The crude gum, wt 135 g, was chromatographed over 1.3 kg of silicic acid, 800-ml fractions being collected. Fractions 1–28 (benzene) and 29–40 (benzene–chloroform, 2:1) eluted noncrystallizable gums. Fractions 41–44 (benzene–chloroform, 1:2) eluted approximately 15 g of semicrystalline material which yielded 5.0 g of pure parthemollin after recrystallization from ethyl acetate. The more polar fractions (chloroform and chloroform–methanol, 9:1) eluted gums which could not be induced to crystallize and represented mixtures (tlc) subject to polymerization.

Pure parthemollin melted at 116–118°: $[\alpha]^{24}D$ −130.0° (c 4.285); ir 3580, 1775, 1705, 1655, and 1620 cm^{-1}; uv end absorption (ϵ 13,200 at 205 nm); CD curve (1-cm cell) λ_{max} 255 nm (θ −3400).

Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; O, 24.21. Found: C, 68.12; H, 7.60; O, 24.05.

Acetylation of 0.25 g of **1a** with acetic anhydride–pyridine at room temperature and work-up in the usual manner gave crude acetylparthemollin (**1b**) which was purified by filtration through silica gel and recrystallization from ethyl acetate–petroleum ether. Pure **1b** was obtained in a 0.20-g yield: mp 103–104°; $[\alpha]^{24}D$ −135.0° (c 5.0); ir 1755, 1735, 1720, 1655, and 1625 cm^{-1}; uv end absorption (ϵ 18,300 at 206 nm).

Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24; O, 26.11. Found: C, 66.42; H, 7.31; O, 26.35.

To a solution of 0.09 g of **1a** in 10 ml of tetrahydrofuran was added 10 ml of an ethereal diazomethane solution. After 3 days in the refrigerator the solvents were removed. The residue (**8**) was recrystallized from ethyl acetate and methanol: mp 117–119° dec; CD curve (1-cm cell) λ_{max} 318 nm (θ −23400).

Anal. Calcd for $C_{16}H_{22}O_4N_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.35; H, 7.19; N, 9.01.

A solution of 0.094 g of **1a** in 25 ml of ethyl acetate was reduced at atmospheric pressure with prereduced 10% Pd–C. Hydrogen uptake ceased after absorption of 2.6 mol equiv of hydrogen (partial hydrogenolysis). The product was a mixture of four components (tlc) which could not be obtained in crystalline form.

Reduction of Parthemollin with Sodium Borohydride. A.—To a solution of 0.508 g of **1a** in 25 ml of methanol was added with stirring 0.180 g of $NaBH_4$ in 5 ml of methanol at 0°. Stirring was continued for 1 hr, the reaction mixture was acidified with dilute hydrochloric acid, the solvent was removed at reduced pressure, and 10 ml of water was added to the residue. The mixture was extracted with chloroform and the washed and dried extract was evaporated. The solid residue (**2**) was purified by preparative tlc and by recrystallization from ethyl acetate: yield 0.175 g; mp 153–156°; ir 3582, 3480, 1758, 1659, and 1600 cm^{-1}; uv end absorption (ϵ 16,500 at 205 nm).

(36) Melting points are uncorrected. Rotations were run in chloroform, ultraviolet spectra in 95% ethanol on a Cary Model 14 recording spectrophotometer, infrared spectra in chloroform on a Perkin-Elmer Model 257 grating spectrophotometer, and CD curves in methanol on a Jasco ORD/UV-5 recording spectrophotometer. Petroleum ether was low boiling (30–60°). Analyses were performed by F. Pascher, Bonn, Germany.

(37) W. Herz and G. Högenauer, *J. Org. Chem.*, **27**, 905 (1962).

Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33; O, 24.03. Found: C, 67.21; H, 8.37; O, 24.46.

B.—Reduction of 0.279 g of **1a** with 0.265 g of $NaBH_4$ in the manner described in the previous paragraph gave a noncrystalline product (**3**) which was purified by preparative tlc: $[\alpha]^{24}D$ −41.4° (*c* 5.8); ir bands at 3580, 3480, 1760, and 1600 cm^{-1}.

Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01; O, 23.85. Found: C, 67.09; H, 9.18; O, 23.48.

Dehydroparthemollin (4).—A solution of 0.243 g of **1a** in 25 ml of dry chloroform was stirred with 2.4 g of activated manganese dioxide at room temperature for 4 days and filtered, the precipitate being washed thoroughly with chloroform. The combined filtrate and washings were evaporated at reduced pressure and the residual gum purified by preparative tlc. This gave 0.13 g of **4** and 0.1 g of recovered starting material. The product was recrystallized from ethyl acetate–petroleum ether: mp 95–97°; ir 1760, 1660, and 1600 cm^{-1}; uv λ_{max} 294 and 210 nm (ϵ 16,200 and 17,550).

Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92; O, 24.40. Found: C, 68.22; H, 7.05; O, 24.84.

Anhydroparthemollin (6).—A solution of 0.15 g of **1b** in benzene was chromatographed over a column of basic alumina. The eluate was evaporated and recrystallized from ethyl acetate–petroleum ether to give 0.065 g of **6**: mp 78–80°; ir 1760, 1708, 1665, and 1595 cm^{-1}; uv λ_{max} 277 and 205 nm (ϵ 17,500 and 15,500). The material polymerized on standing.

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37; O, 19.49. Found: C, 73.05; H, 7.21; O, 19.32.

Oxidation of Parthemollin to α-Methylglutaric Acid.—A solution of 1.0 g of **1a** in 100 ml of ethyl acetate was ozonized at 0° for 1 hr. After addition of 20 ml of water the mixture was warmed on the water bath for 0.5 hr. The solvents were removed at reduced pressure. The residue was taken up in 100 ml of 5% sulfuric acid and a solution of 5 g of $KMnO_4$ in 120 ml of water was added dropwise in 4 hr. The precipitate of manganese dioxide was reduced with sulfur dioxide solution in water. The clear solution was concentrated to 20 ml of at reduced pressure and extracted with ether. The washed and dried ether extract was evaporated and the residual gum was chromatographed over acid-washed alumina. Elution with chloroform–methanol (9:1) gave 0.35 g of gum which was dissolved in acetone and mixed with cyclohexylamine. The precipitated cyclohexylamine salt was recrystallized from ethanol–acetone and then melted at 168–171°. Decomposition of the salt with dilute hydrochloric acid, extraction with ether, washing, drying, and evaporation of the ether extract yielded 0.21 g of (*S*)-(+)-α-methylglutaric acid which was recrystallized from ethyl acetate–petroleum ether, mp 80–82°, $[\alpha]^{24}D$ +21.6° (ethanol, *c* 5.3). The melting point was undepressed on admixture of an authentic sample of mp 78–80°, $[\alpha]^{24}D$ +18° (*c* 1.24) and their ir spectra (Nujol) were superimposable.

Anal. Calcd for $C_6H_{10}O_4$: C, 49.31; H, 6.90. Found: C, 49.25; H, 6.90.

Preparation of 9, 10, and 11.—A solution of 0.310 g of **1a** and 0.8 ml of ethanedithiol in 10, ml of ether was mixed with 1.2 ml of boron trifluoride etherate and allowed to stand at room temperature. After 15 min concentrated aqueous potassium carbonate solution was added and the product was extracted with ether. Evaporation of the washed and dried extract gave crystalline **9**: mp 128–131°; $[\alpha]^{25}D$ −61.7° (c 2.02); ir 3410, 1750, and 1653 cm^{-1}.

A solution of 0.15 g of **9** in 10 ml of methanol–dioxane (1:1) were reduced with $NaBH_4$ as described in the preparation of **3**. The noncrystalline product **10** was purified by preparative tlc: $[\alpha]^{24}D$ −34.0° (*c* 5.62); ir 3420 and 1762 cm^{-1}.

A solution of 0.10 g of **10** in 10 ml of tetrahydrofuran was added dropwise with stirring to a slurry of 0.240 g of $LiAlH_4$ at 0°. Stirring was continued overnight at room temperature. Excess reducing agent was decomposed by addition of ethyl acetate. The mixture was acidified and the solvents were removed. The residue was taken up in chloroform. The washed and dried extract was evaporated and the noncrystalline product **11** was purified by preparative tlc, wt 30 mg, $[\alpha]^{24}D$ −13.7° (c 2.9).

Reaction of 1a with Phenylbutyric Anhydride.—The method of ref 22 was employed, using 211 mg (6.8×10^{-4} mol) of α-phenylbutyric anhydride and 61 mg (2.27×10^{-4} mol) of **1a**. The recovered α-phenylbutyric acid weighed 133 mg (constant weight after drying *in vacuo*, pure on tlc), $\alpha^{24}_{546.1}$ −0.064° (5 ml of benzene, 4-ml tube, measured on a Bendix Type 143A automatic polarimeter), $[\alpha]^{24}_{546.1}$ −5.97°. This corresponded to an optical yield of 25–30% ($[\alpha]D$ of α-phenylbutyric acid is ±96.5°, but a specimen of optically pure acid for determination of the rotation at the $Hg_{546.1}$ line was not available).

Registry No.—**1a**, 23264-32-6; **1b**, 23264-33-7; **2**, 23264-34-8; **3**, 23263-98-1; **4**, 23263-99-2; **6**, 23282-28-2; **7**, 1115-82-8; **8**, 23264-01-9; **9**, 23264-02-0; **10**, 23264-03-1; **11**, 23264-04-2.

The Absolute Configuration of α-*t*-Butylphenylacetic Acid and Some Derivatives[1]

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Received August 5, 1969

The absolute configurations of α-isopropylphenylacetic acid and α-*t*-butylphenylacetic acid have been established as *R*-(−) by relating them chemically to (*S*)-(+)-hydratropic acid through (*R*)-(−)-2-methyl-3-phenylbutane (**2**) and (*S*)-(−)-2,2-dimethyl-3-cyclohexylbutane (**8**). (+)-*t*-Butylphenylcarbinol (**16**) and (+)-β-*t*-butyl-β-phenylpropionic acid (**13**) have been related to α-*t*-butylphenylacetic acid (**9**) and shown to have the *R* configuration. These experiments resolve the uncertainties concerning the configurations of these compounds. The method of configurational correlation of these and related compounds is outlined in formulas **1–16**.

There has been considerable controversy concerning the absolute configuration of α-isopropylphenylacetic acid[2–4] (**3**). Červinka and Hub[2] reported a method for correlating configurations of α-substituted phenylacetic acids, which involved the reaction of an excess of the racemic acid with the chiral amine (*S*)-(+)-1-phenyl-2-methylaminopropane, and measuring the optical rotation of the recovered, unreacted acid. They concluded that the α-alkylphenylacetic acids which they tested[5] had the absolute *S*-(+) configuration with the exception of α-isopropylphenylacetic acid which had the *S*-(−) configuration. These experiments were repeated by Halpern and Westley[3] who failed to confirm this latter exception and concluded that all these α-substituted phenylacetic acids had the *S*-(+) configuration including the α-isopropyl derivative. We

(1) We acknowledge with thanks support of these studies by the National Science Foundation, Grant NSF GP 9452.

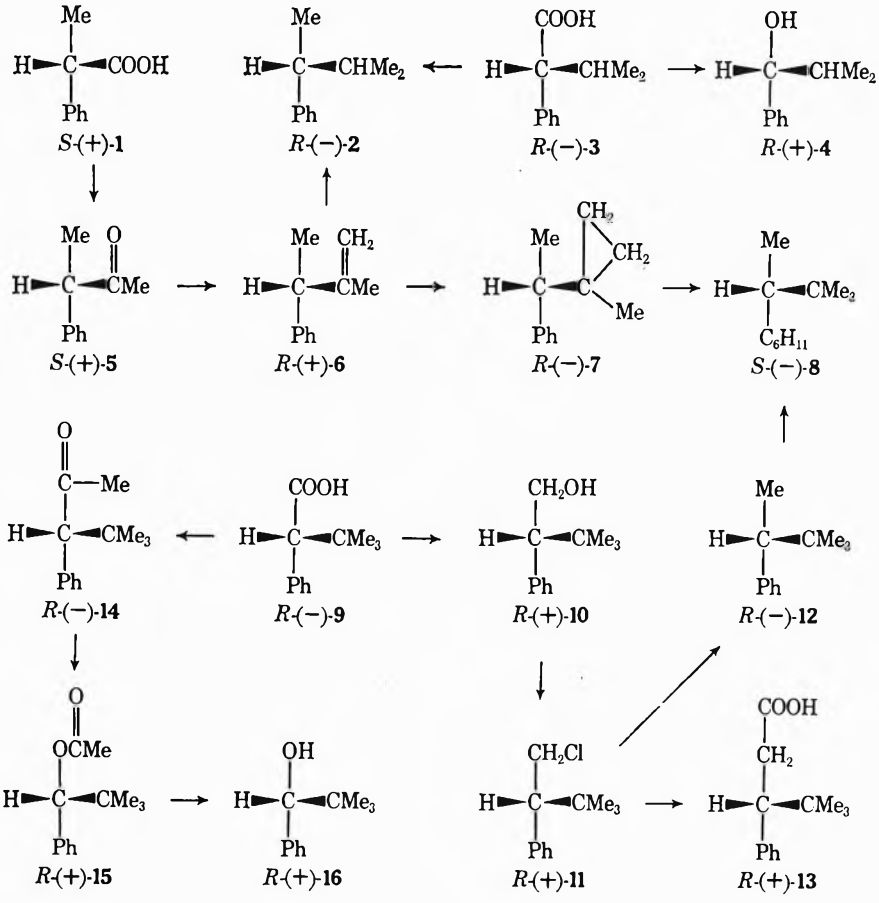
(2) (a) O. Červinka and L. Hub, *Chem. Commun.*, 761 (1966); (b) *Collect. Czech. Chem. Commun.*, **32**, 2295 (1967).

(3) B. Halpern and J. Westley, *Chem. Commun.*, 237 (1967).

(4) C. Aaron, D. Dull, J. L. Schmiegel, D. Jaeger, Y. Ohashi, and H. S. Mosher, *J. Org. Chem.*, **32**, 2797 (1967).

(5) The alkyl groups included methyl, ethyl, *n*-propyl, *n*-butyl, *n*-amyl, *n*-hexyl, iso-propyl, iso-butyl, benzyl, and allyl.

Scheme I



also had concluded,[4] on the basis of the optical rotatory shifts of a series of acid derivatives according to the Freudenberg method,[6] and on the basis of the optical rotatory dispersion (ORD) curves of the thionamide derivatives[7] of these acids, that all of these α-alkylphenylacetic acids, including α-isopropyl- and α-t-butyl- had the S-(+) configuration.[8]

However Červinka and Hub[9] subsequently claimed to have chemically interrelated (−)-isopropylphenylacetic acid and hydratropic acid (**1**) of known configuration *via* the common intermediate (−)-2-methyl-3-phenylbutane (**2**) in such a way as to confirm their original assignment of S-(−) to **3**.

Horeau and Guetté[10] then related (−)-isopropylphenylacetic acid (**3**) to (+)-isopropylphenylcarbinol (**4**), the configuration of which is generally accepted as *R* based on several lines of indirect but very reliable evidence,[11] and deduced therefrom that (−)-isopropylphenylacetic acid had the *R* configuration.

The configurations of isopropylphenylcarbinol and t-butylphenylcarbinol[11] are based on much the same evidence. Recently the generally accepted S-(−) configuration of the latter has been challenged[12] based on asymmetric synthesis studies.

We have made extensive use of α-isopropyl- and α-t-butylphenylacetic acids and of isopropyl- and t-butylphenylcarbinols in our asymmetric reduction studies;[13] it was therefore essential that we determine the absolute configurations of these compounds with certainty. We have therefore undertaken a direct chemical correlation in order to resolve this problem. The interconversions are summarized by formulas **1**–**16**.

Results

We have interrelated (−)-α-t-butylphenylacetic acid (**9**) and S-(+)-hydratropic acid (**1**) of known absolute configuration by converting them into the common intermediate 2,2-dimethyl-3-cyclohexylbutane (**8**). The process used involves conversion of the carboxyl group of acid **9** into a methyl group, and that of acid **1** into a t-butyl group *via* hydrogenolysis of a cyclopropane intermediate by the general procedure first reported by Schleyer and coworkers.[14]

(S)-(+)-3-Phenyl-2-butanone (**5**) was prepared by the action of methyllithium on (S)-(+)-hydratropic acid[15] (**1**) (Scheme I). This ketone was converted into (R)-(+)-3-phenyl-2-methyl-1-butene (**6**), *via* a Wittig

(6) K. Freudenberg, "Die Stereochemie," Franz Deuticke, Leipzig and Vienna, 1933, p 693.

(7) J. Burakevich and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 51 (1965).

(8) (+)-α-Trifluoromethylphenylacetic acid, which is configurationally related to the other (S)-(+)-α-alkylphenylacetic acids, is designated R-(+) because CF_3 takes nomenclatural preference over carboxyl according to the Cahn–Ingold–Prelog sequence rule contrary to the other alkyl groups.

(9) (a) O. Červinka and L. Hub, *Z. Chem.*, 423 (1967); (b) *Collect. Czech. Chem. Commun.*, **33**, 1911 (1968); (c) private communication, 1968.

(10) A. Horeau and J. Guetté, *C. R. Acad. Sci. Paris, Ser. C.*, **267**, 257 (1968).

(11) R. MacLeod, F. Welch, and H. S. Mosher, *J. Amer. Chem. Soc.*, **82**, 876 (1960).

(12) O. Červinka, O. Belovský, A. Fabryová, V. Dudek, and K. Grohman, *Collect. Czech. Chem. Commun.*, **32**, 2618 (1967).

(13) J. L. Schmiegel, Ph.D. Thesis, Stanford University, Stanford, Calif., 1967.

(14) (a) C. Woodworth, V. Buss, and P. v. R. Schleyer, *Chem. Commun.*, 569, 570 (1968); (b) J. Jacobus, Z. Majerski, K. Mislow, and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **91**, 1998 (1969).

(15) K. Mislow and J. Brenner, *ibid.*, **75**, 2318 (1953).

reaction using triphenylmethylene phosphorylide. The Simmons–Smith reaction was carried out with the modified procedure of Shank and Schechter[16] to give (*R*)-(−)-1-methyl-1-(α-phenylethyl)-cyclopropane (**7**). Extensive attempts to hydrogenolyze the cyclopropane ring without reducing the aromatic moiety with a variety of catalysts and conditions were unsuccessful. It was therefore necessary to bring about the correlation *via* the cyclohexyl derivative **8**, rather than the phenyl derivative **12**. Cyclopropane **7** was hydrogenated with PtO_2 at 55° in glacial acetic acid to (*S*)-(−)-2,2-dimethyl-3-cyclohexylbutane (**8**).

The second stage of the correlation was completed by reducing (*R*)-(−)-α-*t*-butylphenylacetic acid (**9**) with lithium aluminum hydride to (*R*)-(+)-3,3-dimethyl-2-phenyl-1-butanol (**10**) which gave (*R*)-(+)-3,3-dimethyl-2-phenyl-1-chlorobutane (**11**) upon treatment with thionyl chloride and pyridine. The Grignard reagent was prepared and decomposed with water to give (*R*)-(−)-2,2-dimethyl-3-phenylbutane (**12**), reduction of which with Rh–Al_2O_3 furnished levorotatory hydrocarbon **8**, with the same sign of rotation as that obtained from the (*S*)-(+)-hydratropic acid (**1**).

The configurations of (−)-α-isopropylphenylacetic acid (**3**) and (−)-α-*t*-butylphenylacetic acid (**9**) were linked together through the olefin **6** and its reduction to hydrocarbon **2**. α-Isopropylphenylacetic acid (**3**), enantiomerically pure, was reduced with $LiAlH_4$ to the primary alcohol, treatment of which with thionyl chloride and pyridine produced the chloride. The Grignard reagent was prepared and decomposed with water to give (*R*)-(−)-2-methyl-3-phenylbutane (**2**). Hydrogenation of olefin **6** in the presence of PtO_2 gave the identical hydrocarbon, **2**.

The *R*-(−) acid **9** was converted into (*R*)-(−)-2,2-dimethyl-3-phenyl-4-pentanone (**14**), with methyllithium. We recovered only starting material from the Baeyer–Villiger reaction on this hindered ketone using perbenzoic acid, *m*-chloroperbenzoic acid, or trifluoroperacetic acid. However, (*R*)-(+)-*t*-butylphenylcarbinyl acetate (**15**) was isolated after reaction with persulfuric acid,[17] although it was a minor product. This acetate was cleaved with $LiAlH_4$ to form (*R*)-(+)-*t*-butylphenylcarbinol, (**16**), thus interrelating this carbinol *via* acid **9** and hydrocarbon **8** with hydratropic acid of proven configuration.

In addition, the ORD curves[18] were obtained for the two ketones (+)-**5** and (−)-**14**. These curves are almost exact mirror images, showing that the ketones of opposite configuration give opposite ORD curves in spite of the difference in steric effect of the methyl *vs.* *t*-butyl groups.

To correlate the homologated acid, the Grignard reagent prepared from the (+)-chloride **11** was carbonated to form (*R*)-(+)-β-phenyl-β-*t*-butylpropionic acid[19,20] (**13**).

Discussion

Since (−)-α-*t*-butylphenylacetic acid (**9**) gives (−) hydrocarbon **8**, which in turn is made from known (*S*)-(+)-hydratropic acid (**1**) by a sequence which does not alter the chirality of the asymmetric center, (−)-**9** must have the *R* configuration, and (−)-**8** the *S* configuration as shown in Scheme I. This proves that the previously assigned[4,6] *R* configuration for the (−)-α-*t*-butylphenylacetic acid (**9**) is correct. If the rotations of hydrocarbon **8** prepared by the two routes are adjusted for the enantiomeric purity of the starting acids **1** and **9**, the following result is obtained: **8** from **1**, $\alpha^{24}D$ − 24.2° (neat); **8** from **9**, $\alpha^{23}D$ −22.6° (neat). A similar comparison for **2** gives the rotations following: **2** from **3**, $[\alpha]^{23.5}D$ −27.2° (CC_4), $[\alpha]^{23.5}D$ −20.4° (CH_3OH); and **2** from **6**, $[\alpha]^{23.5}D$ −29.2° (CCl_4). This compares with a value of $[\alpha]D$ −20.6° (CH_3OH), obtained by Červinka and Hub[9] for the same hydrocarbon **2** made from **3** by a slightly different route. The satisfactory agreement of all these values indicates that all the reactions involved in the correlation of these acids have gone with stereochemical integrity.

The interrelation of acid *R*-(−)-**9** to (+)-*t*-butylphenylcarbinol (**16**) by the sequence shown, confirms its *R* configuration as previously assigned by us.[11] The incorrect *R*(−) assignment[12] was based upon an interpretation of the steric course of an asymmetric synthesis which is unwarranted.

The chemical proof of the *R* configuration of the (+)-propionic acid **13** confirms that previously assigned by Almy, Uyeda, and Cram[17] based on the similarity of ORD curves for a derivative of this acid and of a derivative of the known (*R*)-(−)-3-phenylbutyric acid.

The configurational interconnections outlined in the chart also prove the configurations of (*R*)-(+)-isopropylphenylcarbinol as shown and as previously assigned[10,11] and prove that the configuration of α-isopropylphenylacetic acid is *S*-(+) contrary to previous reports,[2,21] but in accord with Horeau's[10] prior assignment.[4] Now that two more α-alkylphenylacetic acids have been proven to have the *S*-(+) configuration, it is almost certain that the configurations of the remaining α-alkyl-substituted phenylacetic acids[4] have been assigned correctly.

Experimental Section

(*S*)-(+)-**3-Phenyl-2-butanone** (**5**).—This ketone was prepared by the method of Mislow and Brenner[15] from hydratropic acid (**1**) which had $[\alpha]^{27}D$ +88.3° (benzene, C 2.96) corresponding to 95.5% excess of the (+) enantiomer. However, the distilled product was found to be impure, and was chromatographed on a silica gel column. The ketone was eluted with benzene and was distilled (102.5–103.5°, 15 mm) to give (*S*)-(+)-3-phenyl-2-butanone (**5**): $[\alpha]^{24}D$ +368° (benzene, C 1.76); ORD maximum $[\theta]_{2180}$ −25,000°, $[\theta]_{2950}$ +25,200° (cyclohexane).

(*R*)-(+)-**2-Methyl-3-phenyl-1-butene** (**6**).—To a solution of 0.0068 mol of *n*-butyllithium in 50 ml of dry ether was added 2.41 g (0.0068 mol) of triphenylmethylphosphonium bromide, and the mixture was stirred at 25° under dry N_2 gas for 3.5 hr. A solution of 1.00 g (0.0068 mol) of ketone **5**, $[\alpha]^{25}D$ +368° (benzene, c 1.76), in 10 ml of dry ether was added dropwise. The thick mixture was stirred mechanically and refluxed for 40 hr. Solids were then removed by filtration and washed with ether. The combined filtrates were extracted with water and dried

(16) R. Shank and H. Schechter, *J. Org. Chem.*, **24**, 1825 (1959).

(17) R. Robinson and L. Smith, *J. Chem. Soc.*, 371 (1937).

(18) We wish to thank Dr. Bunnenberg for these ORD measurements which are reported in the experimental section.

(19) J. Almy, R. T. Uyeda, and D. J. Cram, *J. Amer. Chem. Soc.*, **89**, 6768 (1967).

(20) We wish to thank Mr. Robert Whitson for preliminary experiments on this reaction.

(21) By private communication from O. Červinka and L. Hub we are now informed that their sequence[2] actually proves the *S*-(+) configuration and not the *S*-(−) configuration as previously reported.[2] This mistake arose from the presence of an impurity of olefin **6** of opposite rotation in hydrocarbon **2**. NOTE ADDED IN PROOF.—*Cf.* O. Červinka, V. Dudek, and L. Hub, *Z. Chem.*, **9**, 267 (1969).

(Na_2SO_4); solvent was removed under vacuum. The liquid residue was distilled at 95–105° (15 mm) to give 0.70 g of colorless liquid. This mixture of olefin and ketone was separated by preparative glpc on a 6 ft × 0.25 in. 20% Carbowax 4000 column at 170° to give 0.20 g (20% yield) of pure (*R*)-(+)-2-methyl-3-phenyl-1-butene (**6**), $[\alpha]^{25}D$ + 76° (benzene, *c* 1.55). On a later run, a yield of 31% was obtained.

Anal. Calcd for $C_{11}H_{14}$: C, 90.35; H, 9.65. Found: C, 90.39; H, 9.76.

(*R*)-(−)-**2-Methyl-3-phenylbutane** (**2**). **A. From (*R*)-(−)-α-Isopropylphenylacetic Acid**[4,13] (**3**).—Acid **3**, $[\alpha]^{24}D$ −62.35° ($CHCl_3$, *c* 4.46), 100% enantiomerically pure, was converted into hydrocarbon **2** by the same method that α-*t*-butylphenylacetic acid (**9**) was converted into 2,2-dimethyl-3-phenylbutane (**12**). The compounds had the followng rotations: (*R*)-(−)-3-methyl-2-phenyl-1-butanol, $\alpha^{22}D$ −11.66° (neat); (*R*)-(−)-3-methyl-2-phenyl-1-chlorobutane, $\alpha^{23}D$ −0.73° (neat); *R*-(−)-2-methyl-3-phenylbutane (**2**), $\alpha^{28}D$ −23.23° (neat), $[\alpha]^{28.5}D$ −27.2° (CCl_4, *c* 2.39), $[\alpha]^{23.5}D$ −20.4° (MeOH, *c* 1.27).

B. From (*R*)-(+)-2-Methyl-3-phenyl-1-butene (**6**).—Butene (**6**), 0.12 g, $[\alpha]^{26}D$ +68.5° (benzene, *c* 1.67) in 5 ml of absolute ethanol was added to 0.20 g of prereduced PtO_2 (83.5%, Engelhard Industries) in 10 ml of absolute ethanol and stirred under 1 atm of H_2 for 24 hr at 25°. Filtration and concentration followed by preparative glpc on a 20 ft × 3/8 in. 20% Carbowax 20M TPA at 190°, helium flow rate 60 ml/min, gave 0.055 g of (*R*)-(−)-2-methyl-3-phenylbutane (**2**), retention time 27 min, $[\alpha]^{26}D$ −25.4° (CCl_4, *c* 1.44). Reinjection on the same column indicated less than 0.2% impurity of the olefin **6** in this product which had an ir spectrum identical with that of the same hydrocarbon made by method A.

(*R*)-(−)-**1-Methyl-1-(α-phenylethyl)cyclopropane** (**7**).—Zinc–copper couple,[16] 1.25 g (0.0192 mol), 5.15 g (0.0192 mol) of methylene iodide, and 25 ml of ether were heated to reflux and several crystals of I_2 were added. After this mixture refluxed for 30 min, 1.40 g (9.6 mmol) of olefin **6**, $[\alpha]^{28}D$ +75.4° (benzene, *c* 1.76), $\alpha^{28}D$ +61.98° (neat), was added, and the mixture refluxed overnight. Solids were removed from the cold mixture by filtration through a Celite Super Cel pad. The filtrate was extracted with 5% HCl (3 times with 20 ml) and 10% $NaHCO_3$ (twice with 30 ml) and then dried (Na_2SO_4). The reaction was incomplete as shown by glpc analysis; therefore the ether solution was resubjected to the original reaction conditions with the same amounts of reagents. After the mixture had been heated overnight under reflux and subjected to the same work-up, the product was distilled under vacuum, and purified by preparative glpc on a 10 ft × 3/8 in. 20% Ucon HB 5100 column at 130°, to give 0.60 g (40% yield) of pure **7**, $\alpha^{25}D$ −51.40° (neat).

Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 89.54; H, 10.07.

(*S*)-(−)-**2,2-Dimethyl-3-cyclohexylbutane** (**8**).—A mixture of 0.30 g of **7**, $\alpha^{25}D$ −51.40° (neat), 1.0 g of PtO_2 (83.5%), and 30 ml of glacial acetic acid was shaken under 40 psi of H_2 and heated to 55° for 4 days. The catalyst was removed by filtration and ether was added to the filtrate. This solution was extracted with 10% NaOH and dried (Na_2SO_4), ether was removed under reduced pressure, and the resulting yellow liquid was purified by preparative glpc on a 20 ft × 3/8 in. 30% SE-30 column at 175°, to give **8**, $\alpha^{24}D$ −23.02° (neat).

(*R*)-(+)-**3,3-Dimethyl-2-phenyl-1-butanol** (**10**).[19]—To 5.50 g (0.145 mol) of $LiAlH_4$ in 100 ml of ether was added dropwise at 25° 26.2 g (0.136 mol) of (*R*)-(−)-α-*t*-butylphenylacetic acid (**9**), $[\alpha]^{26}D$ −9.79° [$CHCl_3$, *c* 7.05, 15.6% excess of (−) enantiomer] dissolved in 100 ml of dry ether. The mixture was stirred at 25° for 4 days. Excess hydride was decomposed with saturated Na_2SO_4 solution and 100 ml of 10% NaOH was added. The ether layer was combined with ether extracts, dried ($MgSO_4$), and evaporated under vacuum to leave 24 g (99%) of crude (*R*)-(+)-3,3-dimethyl-2-phenyl-1-butanol (**10**). This carbinol was used without further purification. On a later run, from (+) acid **9** of $[\alpha]^{26}D$ +41.5° ($CHCl_3$, *c* 5.32), 66.3% excess (+) enantiomer, was obtained (−)-carbinol **12** of $[\alpha]^{23}D$ −2.1° ($CHCl_3$, *c* 5.65), mp 75–90°.

(*R*)-(+)-**3,3-Dimethyl-2-phenyl-1-chlorobutane** (**11**).—(*R*)-(+)-3,3-Dimethyl-2-phenyl-1-butanol (**10**) (24.0 g, 0.135 mol), was dissolved in 40 ml of dry pyridine. To this solution was added slowly at 5–10° 14 ml of thionyl chloride. After stirring in an ice bath for 4 hr, the mixture was heated to 90°, and finally to 116° until gas evolution was complete. The mixture was cooled, poured onto ice, and extracted with ether; the ether extracts were washed with saturated $NaHCO_3$ solution and water. The ether layer was dried ($MgSO_4$) and evaporated under vacuum to leave 18.7 g (71%) of crude chloride **11**. This particular sample was distilled after being stored over $NaHCO_3$ for 3.5 years, bp 79–82° (1 mm), to give colorless (*R*)-(+)-3,3-dimethyl-2-phenyl-1-chlorobutane (**11**), $\alpha^{26}D$ +4.56° (neat).

(*R*)-(−)-**2,2-Dimethyl-3-phenylbutane** (**12**).—To 0.144 g (0.0059 g-atom) of sublimed magnesium shavings under dry N_2 was added 1.00 g (0.0051 mol) of (*R*)-(+)-3,3-dimethyl-2-phenyl-1-chlorobutane (**11**), $\alpha^{26}D$ +4.56° (neat), and 20 ml of dry ether. The mixture was heated to reflux and three 0.010-ml portions of 1,2-dibromoethane were added. After refluxing for 3 hr, the reaction was stopped and 4 ml of water was cautiously added. This was followed by 6 ml of 7% HCl. The layers were separated, the aqueous layer was extracted with ether, and the combined ether solutions were dried (Na_2SO_4), and evaporated to 2 ml. The product was isolated by preparative glpc on a 5 ft × 0.25 in. 20% Carbowax 4000 column at 160°, to give 0.57 g (69%) of *R*-(−)-2,2-dimethyl-3-phenylbutane (**12**), $\alpha^{28}D$ −3.42° (neat).

Anal. Calcd for $C_{12}H_{18}$: C, 88.82; H, 11.18. Found: C, 89.06; H, 11.37.

(*S*)-(−)-**2,2-Dimethyl-3-cyclohexylbutane** (**8**).—A mixture of 1.47 g of (*R*)-(−)-2,2-dimethyl-3-phenylbutane (**12**), $\alpha^{28}D$ −3.42° (neat), 1.5 g of 5% Rh–Al_2O_3, and 10 ml of acetic acid–ethanol (1:9) was shaken under 3 atm of H_2 at 25° for 2 days. The catalyst was removed by filtration, and ether was added to the filtrate, which was extracted with 10% NaOH and water. The ether layer was dried (Na_2SO_4) and concentrated under vacuum; the product was isolated by preparative glpc to give 0.50 g (30%) of (*S*)-(−)-2,2-dimethyl-3-cyclohexylbutane (**8**), $\alpha^{23}D$ −3.52° (neat), retention time 9.7 min on a 6 ft × 0.25 in. 20% poly-*m*-phenyl ether 5 ring at 165°; helium flow rate 75 ml/min.

Anal. Calcd for $C_{12}H_{24}$: C, 85.63; H, 14.37. Found: C, 85.87; H, 14.30.

(*R*)-(−)-**4,4-Dimethyl-3-phenyl-2-pentanone** (**14**).—*R*-(−)-α-*t*-Butylphenylacetic acid (**9**), 1.0 g (0.0052 mol), $[\alpha]^{22}D$ −48.2° (absolute EtOH, *c* 1.68), 100% excess (−) enantiomer, was dissolved in 25 ml of dry ether and added slowly to a solution of 0.0176 mol of methyllithium in 20 ml of ether at 25°. After the mixture was stirred at 25° for 20 min and then refluxed for 45 min, it was poured into ice–water. The ether layer was washed rapidly with cold water until neutral and dried (Na_2SO_4), and the solvent was removed under vacuum to leave 0.70 g (70%) of (*R*)-(−)-4,4-dimethyl-3-phenyl-2-pentanone (**14**), >95% pure, $[\alpha]^{25}D$ −275° (CCl_4, *c* 0.835). On a 10 ft × 3/8 in. 20% silicone SE-30 glpc column at 200° and 95 ml/min He, this ketone had a retention time of 44 min. The recovered acid was racemic. Ketone **14** from another run had $[\alpha]^{23}D$ −248° (CCl_4, *c* 1.95); ORD max $[\theta]_{2140}$ +15,800°, $[\theta]_{2060}$ −19,400 (cyclohexane).

(*R*)-(+)-**Phenyl-*t*-butylcarbinyl Acetate** (**15**).—Potassium persulfate (3.98 g, 0.015 mol) was added to a stirred solution of 9.8 g of 98% sulfuric acid and 1.85 g of water at 0°. To this mixture was added 8 ml of absolute ethanol, followed by 0.50 g (0.026 mol) of (*R*)-(−)-4,4-dimethyl-3-phenyl-2-pentanone (**14**), $[\alpha]^{23}D$ −248° (CCl_4, *c* 1.95), in 2.5 ml of absolute ethanol. This mixture was stirred at 0° for 1 hr, then at 25° for 4.5 hr. Water was added, and the solution was extracted with ether. The ether layer was dried (Na_2SO_4) and concentrated under vacuum to give a complex mixture which was separated by preparative glpc on 6 ft × 0.25 in. 20% silicone SF96 at 130°, 90-ml/min helium flow rate. The components of the mixture (at 190°) follow: (retention time, relative area) phenyl *t*-butyl ketone (2.5 min, 3); phenyl-*t*-butylcarbinol (**16**) (3 min, 1); ketone **14** (3.5 min, 1); acetate **15** (3.8 min, 2); and an unidentified solid (7 min, 2). (*R*)-(+)-Phenyl-*t*-butylcarbinyl acetate (**15**), $[\alpha]^{27}D$ +42.3° ($CHCl_3$, *c* 1.66), and the carbinol **16**, $[\alpha]^{28}D$ +11.4° ($CHCl_3$, *c* 2.30), were isolated.

(*R*)-(+)-**Phenyl-*t*-butylcarbinol** (**16**).—(*R*)-(+)-Phenyl-*t*-butylcarbinyl acetate (**15**), 0.035 g (0.00017 mol), $[\alpha]^{27}D$ +42.3° ($CHCl_3$, c 1.66), was added to 0.030 g (0.00079 mol) of $LiAlH_4$ in 3 ml of dry ether. The mixture was refluxed 1.5 hr, 10% HCl was added, the layers were separated, and the aqueous phase was extracted with ether. The combined ether extracts were dried (Na_2SO_4) and concentrated to give 0.023 g (82%) of (*R*)-(+)-phenyl-*t*-butylcarbinol (**16**), $[\alpha]^{28}D$ +22.9° ($CHCl_3$, *c* 2.30).

(*R*)-(+)-**β-Phenyl-β-*t*-butylpropionic Acid**[20] (**13**).—Sublimed magnesium, 0.145 g (0.0060 g-atom), and 0.50 g (0.0025 mol) of

R-(+)-3,3-dimethyl-2-phenyl-1-chlorobutane (**11**), $\alpha^{26}D$ +4.54° (neat), were mixed with 15 ml of dry ether and 0.25 ml (0.55 g, 0.0029 mol) of 1,2-dibromoethane was added to start the reaction. After 1.5 hr of reflux, dry CO_2 gas was bubbled through the mixture for 10 min, HCl (10% solution) was added, and the aqueous layer was extracted with ether. The ether extracts were then extracted with 10% NaOH. Acidification of the aqueous layer, extraction with ether, and removal of solvent under vacuum after drying (Na_2SO_4) gave 0.072 g (12%) of crude acid. Sublimation at 85° (0.6 mm) yielded (*R*)-(+)-β-phenyl-β-*t*-butylpropionic acid (**17**), $[\alpha]^{25}D$ +1.74° ($CHCl_3$, *c* 3.16), mp 110–112.5°, reported[22] 114–116°. The nmr spectrum of this material was compatible with the assigned structure.

Registry No.—**2**, 23406-51-1; **5**, 23406-52-2; **6**, 23406-53-3; **7**, 23439-89-6; **8**, 23406-54-4; **9**, 13491-16-2; **11**, 23406-56-6; **12**, 23406-57-7; **14**, 23406-58-8; **15**, 23439-90-9; **16**, 23439-91-0; **17**, 23406-59-9; (*R*)-(−)-3-methyl-2-phenyl-1-butanol, 23406-60-2; (*R*)-(−)-3-methyl-2-phenyl-1-chlorobutane, 23406-61-3.

(22) C. C. Koelsch, *J. Amer. Chem. Soc.*, **65**, 1640 (1943).

Sulfur-Containing Polypeptides. XII. Studies on the Scope and Limitations of the Sulfenylthiocyanate Method as a Route to Cystine Peptides[1,2]

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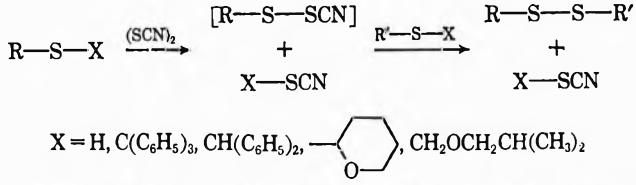
Received August 6, 1969

The sulfenylthiocyanate method of disulfide synthesis has been applied to the preparation of 13 cystine peptides containing various amino acid residues. In general no significant side reactions were observed; however, acidic solvents were required for a histidine-containing cystine peptide, and the ω-nitro protective group was necessary for an arginylcystine derivative.

Among the remaining obstacles to the unambiguous synthesis of complex polypeptides is the problem of the "correct pairing" of the sulfur–sulfur bonds of the cystine residues in synthetic polypeptides. At present the final stage of all synthetic routes to polypeptides containing several cystine residues has involved the simultaneous removal of S-protecting groups from cysteine residues and subsequent one-step oxidation. This approach appears to lead to complex mixtures and diminished biological activity.

Several years ago we reported[5] that cystine derivatives could be prepared by employing the sulfenylthiocyanate method discovered by Lecher and Wittwer.[6] These workers had used thiocyanogen to oxidize thiols, and the subsequent recognition that the oxidation could also be performed on appropriate thio ethers[5,7–10] and hemithioacetals[5,11] greatly enhanced the flexibility and apparent applicability of the method to the synthesis of polypeptides containing several cystine residues.



Although these experiments suggest that certain open-chain and cyclic cystine peptides can be prepared *via* the sulfenylthiocyanate method, no information was available on the compatibility of thiocyanogen or the sulfenylthiocyanates of cysteine derivatives with other amino acids. For example, thiocyanogen is known to decompose slowly in the presence of water or alcohols;[12,13] thiocyanogen[14] and sulfenylthiocyanates[15] are also known to react with aliphatic amines to yield amine thiocyanates. In addition, *para*-substituted aromatic amines and phenols undergo ring substitution with thiocyanogen and provide the corresponding 2-iminobenzoazoxoles or 2-iminobenzothioxoles.[12] Although the hydroxyl, phenolic, and amine side chains could always be protected during the preparation of a polypeptide, ring substitution and possible subsequent reactions in tyrosine, tryptophan, and histidine side chains would be a definite possibility. For example, tyrosine, tryptophan, and histidine peptides are cleaved by electrophiles, particularly bromine, N-bromosuccinimide, and cyanogen bromide.[16] Various sulfenyl halides react at the indole 2 position of tryptophan in peptides and proteins but not with the side chains of other amino acids.[17] Finally, methionine is known[16] to suffer cleavage by certain electrophiles, notably cyanogen bromide, and this possibility also warranted examination using thiocyanogen and sulfenylthiocyanates.

In order to evaluate the effects of side chains on the formation of cystine peptides with sulfenylthiocyanates or thiocyanogen, a series of 13 cystine derivatives were prepared; with two exceptions these were of the general structure IV (Table I). The sulfenylthiocyanates II

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(2) Supported by Research Grants GM-07966 and AM-03416 from the Institute of General Medical Science and the Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service.

(3) Abstracted in part from the Ph.D. dissertation of B. F. Ward, Jr., submitted in partial fulfillment of the requirements for the Ph.D. degree to the University of North Carolina, June 1969.

(4) Ethyl Corp. Fellow, 1968–1969.

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TABLE I
CONDITIONS FOR SYNTHESIS AND PROPERTIES OF UNSYMMETRICAL CYSTINE PEPTIDE DERIVATIVES

Z·CysOMe | Z·Cys·(AA)OR, (AA)OR	Concn, *M*	Time, hr	Purification[b]	Yield, %	Mp, °C	$[\alpha]^{25}D$, deg	Calcd, %				Found, %			
							C	H	N	S	C	H	N	S
GlyOEt (IVa)	0.3	22	F	58	123–124	−106.4 (*c* 0.5, MeOH)	53.27	5.63	6.90	10.53	53.39	5.69	6.84	10.58
SerOCH$_3$ (IVb)	0.08	5	F	84, 71[c]	100–101	+42.7 (*c* 1.0, $CHCl_3$)	51.99	5.33	6.73	10.28	51.95	5.42	6.68	10.21
AsnOEt (IVc)	0.07	9	A	74, 80[c]	161–162	−93.6 (*c* 0.5, MeOH)	52.54	5.46	8.43	9.65	52.36	5.46	8.24	9.49
AlaOEt (IVd)	0.06	12	G[d]	70	85–86	+35.7 (*c* 1.0, $CHCl_3$)	54.09	5.68	6.76	10.31	54.19	5.65	6.67	10.49
PheOEt (IVe)	0.08	11	D[d]	66	131–132	+43.6 (*c* 1.0, $CHCl_3$)	58.52	5.60	6.02	9.19	58.48	5.56	5.87	9.36
TyrOEt (IVf)	0.08	11	G[d]	77, 70[c]	81–83	+25.5 (*c* 1.0, $CHCl_3$)	57.21	5.51	5.88	8.98	57.01	5.50	5.87	9.02
MetOEt (IVg)	0.10	12	H[d]	75, 72[c]	83–85	+32.8 (*c* 1.0, $CHCl_3$)	52.84	5.76	6.16	14.11	53.00	5.77	6.21	14.09
HisOCH$_3$ (IVh)	0.10	12	I[e]	82, 68[c]	115–116	−67.9 (*c* 1.0, acetone)	53.47	5.24	10.40	9.52	53.24	5.22	10.28	9.66
TrpOEt (IVi)	0.15	12	J[d]	54, 62[c]	78–80	−46.4 (*c* 1.0, acetone)	58.68	5.47	7.60	8.70	58.57	5.32	7.40	8.89
ThrOCH$_3$ (IVj)	0.08	10	K[f]	61	51–53	+25.2 (*c* 0.5, $CHCl_3$)	52.73	5.53	6.59	10.06	52.90	5.47	6.54	10.32
NO_2 | ArgOEt (IVk)	0.10	8	L[g]	74, 75[c]	152–154	+12.6 (*c* 0.5, $CHCl_3$)	48.83	5.33	13.29	8.69	49.18	5.37	13.17	8.47
VI	0.05	15	F	31	70–72	−52.0 (*c* 1.0, acetone)	49.41	5.67	11.52	8.78	49.24	5.72	11.59	8.89
VII	0.14	8	M	70	167–168	−87.4 (*c* 0.5, MeOH)	54.37	5.99	7.93	9.07	54.41	6.09	8.18	9.00

[a] Solvents for IVh, VI, and VII were ethyl acetate–trifluoroacetic acid (1:1, v/v); all other reactions were conducted in ethyl acetate. [b] F = acetone–ether; A = ethyl acetate; G = ethyl acetate–ether; D = chloroform–ether (3:2, v/v); H = acetone–ether–hexane; I = ethyl acetate–hexane; J = acetone–cyclohexane; K = ether–hexane; L = ethyl acetate–ether–hexane; M = methanol. [c] Yield of disulfide *via* V. [d] Chromatographed prior to recrystallization using chloroform–ether (3:2, v/v). [e] Using chloroform–methanol (9:1, v/v). [f] Using ether. [g] Using ethyl acetate.

were generated by the action of thiocyanogen on I; the S-trityl component III (Table II) was then added to II in a suitable solvent. Alternatively the S-trityl peptide III could be treated with thiocyanogen to generate

the sulfenylthiocyanate V, which could then be treated with I to produce IV. Both reactions in either sequence could be monitored by tlc, and the products were isolated by column chromatography and/or crystallization.

The anticipated products, IV, were obtained in reasonable yield from II and derivatives of III containing glycine (a), serine (b), asparagine (c), alanine (d), phenylalanine (e), tyrosine (f), methionine (g), tryptophan (i), and threonine (j) (Table I). The reactions were performed in ethyl acetate. The cystine derivatives IVb, IVc, IVg, and IVi were prepared in similar yield by the reverse process (Table I). The nmr spectra of all cystine derivatives were in agreement with the indicated structures. These results suggest that the reaction of thiocyanogen or a sulfenylthiocyanate with these S-trityl thioethers proceeds rapidly and cleanly without detectable side reactions involving the other side chains. When the tyrosyl peptide IVf was prepared by the reverse process, tlc of the reaction mixture indicated the presence of the corresponding symmetrical disulfide; however, no product owing to ring substitution of thiocyanogen was evident.

The preparation of the histidine-containing peptide IVh led to somewhat different results. When the reaction between II and IIIh was carried out in ethyl acetate, no reaction occurred and IIIh was recovered unchanged after work-up of the reaction mixture. However, when the reaction was carried in ethyl acetate–acetic acid (1:1, v/v) a 24% yield of IVh was obtained; the presence of IIIh was noted in the reaction mixture. Assuming that a reaction of II and the basic nitrogen atoms of IIIh was responsible for the lowered yield, the reaction was repeated in ethyl acetate–trifluoroacetic acid (1:1, v/v); under these conditions IVh was obtained in 82% yield and no IIIh could be detected.

The effect of a basic side chain was also noted in the preparation of the arginyl cystine peptide VI. When methyl N-carbobenzoxy-L-arginyl-S-benzhydryl-L-cysteinate (VII) was allowed to react with II in ethyl acetate–trifluoroacetic acid (1:1, v/v), a low yield (31%) of VI resulted and VII was not completely consumed. However, when the ω-nitro protective group was employed for the guanidino side chain, IVk was obtained in 74% yield; IVk could also be obtained in good yield *via* the reverse reaction.

The production of IVb from II and IIIb was used to determine which types of polar solvents might be used

TABLE II

CONDITIONS FOR SYNTHESIS AND PROPERTIES OF VARIOUS CYSTEINE PEPTIDE DERIVATIVES

Tr | Z-Cys-AAOR, AAOR	Reaction solvent[a]	Crystallization solvent[b]	Yield, %	Mp, °C	$[\alpha]_D$, deg	Calcd, % C	H	N	S	Found, % C	H	N	S
GlyOEt (IIIa)[c]													
SerOCH$_3$ (IIIb)[d]	L	O[e]	76	62–66	+24.0[f]	68.22	5.72	4.68	5.35	68.03	5.79	4.62	5.32
AsnOEt (IIIc)[d]	N	Q[e]	43	103–105	+36.6[f]	67.58	5.83	6.57	5.01	67.84	5.89	6.37	4.94
AlaOEt (IIId)[d]	N	O[e]	72	46–50	+21.8[f]	70.44	6.08	4.70	5.37	70.46	6.24	4.67	5.33
PheOEt (IIIe)[d]	L	O[e]	71	47–50	+29.4[f]	73.18	5.99	4.16	4.77	73.04	5.91	4.17	4.76
TyrOEt (IIIf)[d]	N	P[e]	84	68–71	+33.1[g]	71.50	5.87	4.07	4.65	71.54	5.96	4.18	4.35
MetOEt (IIIg)[d]	L	O[e]	92	110–111	+28.4[f]	67.65	6.14	4.27	9.93	67.68	6.16	4.29	9.77
HisOCH$_3$ (IIIh)[h]	M	R	67	152–154	+58.7[g]	68.49	5.59	8.64	4.94	68.32	5.83	8.40	4.98
TrpOEt (IIIi)[d]	M	S[e]	62	65–70	+13.1[g]	72.55	5.81	5.90	4.50	72.79	6.10	5.73	4.04
ThrOCH$_3$ (IIIj)[d] NO$_2$ |	N	T[e]	68	60	+ 6.2[i]	68.60	5.92	4.57	5.23	68.88	6.26	4.41	4.93
ArgOEt (IIIk)[d] Bzh |	N	U[e]	61	91–95	+ 6.4[i]	62.34	5.66	11.76	4.50	62.52	5.71	11.72	4.63
Z-Arg-CysOCH$_3$ (VII)[k] ·HCl Bzh |	N	V[e]	22	97–99	−10.7[i]	57.63	6.29	11.20	5.13	57.93	6.44	10.96	5.18
Z-Val-Cys-GlyOEt (IX)[l]	L	W	82	165–167	−13.1[i]	65.43	6.49	6.94	5.29	65.32	6.44	7.03	5.50

[a] L = methylene chloride; M = methylene chloride–methanol (1:1, v/v); N = methylene chloride–DMF (2:1, v/v). [b] O = ether–cyclohexane; P = ethyl acetate; Q = ethyl acetate–ether; R = acetone; S = ether–hexane; T = acetone–ether–cyclohexane; U = chloroform–hexane; V = methanol–ether; W = ethyl acetate–hexane. [c] L. Zervas and I. Photaki, *J. Amer. Chem. Soc.*, 84, 3887 (1962). [d] Coupled to Z·(Tr)Cys$^-$ DEA$^+$ using 1-ethyl-3-(3′-*N*,*N*-dimethylaminopropyl)carbodiimide hydrochloride. [e] Chromatographed using ethyl acetate prior to crystallization. [f] $[\alpha]^{25}D$ (*c* 1, $CHCl_3$). [g] $[\alpha]^{21}D$ (*c* 1, $CHCl_3$). [h] Coupled to Z·(Tr)CysOSu. [i] $[\alpha]^{22}D$ (c 1, acetone). [j] $[\alpha]^{22}D$ (*c* 0.5, $CHCl_3$). [k] Prepared from H·(Bzh)Cys·OCH$_3$ by coupling with DCC. [l] Prepared from H·(Bzh)Cys·GlyOEt by coupling with 1-ethyl-3(3′-N,N-dimethylaminopropyl)carbodiimide hydrochloride.

TABLE III

SYNTHESIS OF Z·CysOCH$_3$ Z·Cys·SerOCH$_3$ (IVb) IN VARIOUS SOLVENTS

$(SCN)_2$ Prepd in[a]	II added in	III added in	Yield, %
A	A	A	84
A	A	CH_2Cl_2	82
A	AcOH	AcOH	76
A	TFA	TFA	73
A	MeOH	MeOH–H_2O	67
A	TFE	TFE	75
A	MeOH–H_2O	MeOH	0
A	NaOMe–MeOH	MeOH	0
MeOH	MeOH	MeOH	0
A	A	C_5H_5N	0
A	A	B	0
A	HMPA	HMPA	0
A	A	HMPA	5

[a] A = ethyl acetate; B = pyridine–acetic acid, pH 6.3; TFE = β,β,β-trifluoroethanol; HMPA = hexamethylenephosphoramide.

for the sulfenyl thiocyanate method (Table III). Ethyl acetate appears to be the solvent of choice for the generation of thiocyanogen; acetic acid can also be used, but the formation of thiocyanogen is much slower; water or alcohols cannot be employed. Sulfenylthiocyanates appear to be more stable to water and alcohols; these intermediates are decomposed by amines and apparently some amides, since reactions of sulfenylthiocyanates in hexamethylenephosphoramide (HMPA), DMF, DMAc, and N-methylpyrrolidone have not been successful.

Thus the sulfenylthiocyanate method of disulfide synthesis may be applicable to the synthesis of large polypeptides containing several cystine residues. The advantages of the method appear to lie in the high degree of reactivity of thiols and certain thio ethers toward thiocyanogen and sulfenylthiocyanates. The disadvantages of this approach involve the thermal lability of the intermediate sulfenylthiocyanates and their reactivity with basic nitrogen atoms. The actual application of this system to an appropriate biologically active polypeptide containing several cystine residues should establish whether the problem of the "correct pairing" of cystine residues can be overcome by this route.

Experimental Section[18]

Methyl N-carbobenzoxyl-S-trityl-L-cysteinylglycinate (IIIa) was prepared by the procedure of Zervas and Photaki.[19]

General Procedure for the Preparation of N,O,S-Protected Di- and Tripeptides.—To a solution of 10 mmol of the appropriate cysteine derivative in 30 ml of methylene chloride was added 10 mmol of the appropriate protected amino acid in 20 ml of the indicated solvent. The solution was cooled to −10° and treated with 10.8 mmol of the indicated coupling reagent. The reaction mixture was allowed to stir at −10° for 2 hr, warmed to room temperature, and stirred for 12–15 hr. The reaction mixture was then diluted to 200 ml with methylene chloride and washed with 2 *N* sulfuric acid, water, and saturated brine. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to an oil which was purified by column chromatography and/or crystallization (Table II).

General Method of Preparation of Cystine Peptide Derivatives. A. In Ethyl Acetate.—A solution of 9 mmol of thio-

(18) Melting points are uncorrected. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Ill. The optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Column chromatography was performed on 0.05–0.20-mm silica gel; thin layer chromatography was conducted on silica gel G coated microscope slides. The amino acid ester hydrochlorides used to prepare the various dipeptides were purchased from the Sigma Chemical Co. Nuclear magnetic resonance spectra were recorded on a Varian Associates A-60 spectrometer.

(19) L. Zervas and I. Photaki, *J. Amer. Chem. Soc.*, **84**, 3887 (1962).

cyanogen in 35 ml of ethyl acetate was prepared in the usual manner in the dark at 0°. To this cold solution was added 7.2 mmol of I in 20 ml of ethyl acetate over at 15-min period. At this point tlc indicated that no thiol remained. The appropriate thioether (7.2 mmol) was dissolved in 25 ml of ethyl acetate and added in one portion to the reaction mixture. The solution was stirred in the dark for 2 hr at 0°, allowed to warm to room temperature, and stirred for an additional period of time (3–33 hr depending on the reaction progress as demonstrated by tlc). After reaction was complete the solution was diluted to 200 ml with ethyl acetate and washed with 5% sodium bicarbonate solution, water, and saturated brine. The organic extract was dried and evaporated *in vacuo*, and the residue was triturated with hexane to remove the trityl thiocyanate. The resulting powder was purified by recrystallization or chromatography followed by recrystallization. The reported yields (Table I) are based on the amount of purified product.

B. Acidic Solvents.—To a cold, stirred solution containing 9 mmol of thiocyanogen in 35 ml of ethyl acetate was added 7.2 mmol of I in 20 ml of trifluoroacetic acid (TFA). After 10 min, 7.2 mmol of the appropriate thio ether in 15 ml of TFA was added and the mixture was stirred at 0° for 3 hr and at room temperature for 5–12 hr. The reaction mixture was poured into 1200 ml of cold 5% sodium bicarbonate and the mixture was extracted with ethyl acetate. The organic layer was washed, dried, and evaporated *in vacuo*. Trituration with hexane afforded a powder which was purified by recrystallization.

Registry No.—IIIb, 23465-05-6; IIIc, 23465-06-7; IIId, 23465-07-8; IIIe, 23465-08-9; IIIf, 23465-09-0; IIIg, 23435-44-1; IIIh, 23435-45-2; IIIi, 23435-46-3; IIIj, 23435-47-4; IIIk, 23465-10-3; IVa, 23465-11-4; IVb, 23435-52-1; IVc, 23435-53-2; IVd, 23435-54-3; IVe, 23435-55-4; IVf, 23465-12-5; IVg, 23500-37-0; IVh, 23435-56-5; IVi, 23500-38-1; IVj, 23435-57-6; IVk, 23435-58-7; VI, 23435-48-5; VII, 23435-49-6; VII (HCl), 23435-50-9; IX, 23435-51-0.

Acknowledgment.—The authors are grateful to Mrs. Mary W. Pendergraft for the polarimetry measurements. Valuable discussions with Mr. E. B. Williams, Jr., concerning the effect of histidine residues on the thiocyanogen reaction are gratefully acknowledged.

The Photodimerization of Substituted Stilbenes

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Received June 6, 1969

Stilbenes with electron-donating groups on either of the aromatic moieties undergo rapid photodimerization. With dissimilar phenyl groups, two photodimers are obtained, and their structures have been elucidated by nmr and mass spectral studies. The extent of dimerization was measured by gel-permeation chromatography and a singlet mechanism is proposed for the photodimerization process.

The photochemistry of stilbene is well known and the three photochemical reactions are *cis–trans* isomerization, cyclization, and dimerization. Although the dimerization of stilbene has been discovered at the beginning of this century by Ciamician and Silber,[1] it is the least understood of the three reactions. Shechter and coworkers[2] have isolated two photodimers from *trans*-stilbene (27% conversion upon irradiation for 2 months) and their structures were assigned on the basis of nmr data. In our study directed toward the use of stilbene derivatives for photocross-linking of polymers,[3] we noticed considerable enhancement of dimerization if electron-donating groups are attached to the aryl groups.[4] The quantum yield of dimerization of **5** was found to be *ca.* 0.06. In Table I the previously unreported stilbene derivatives used in this study are listed. The photodimerization was conducted on the mono- and bismethyl carbamates of the mono- and diisocyanates in order to approximate the bonding generated in polymer systems. As ultraviolet sources a 100- and a 450-W mercury lamp have been used and benzene, ethyl acetate, and tetrahydrofuran were the solvents employed in the photodimerization experiments. The quantitative determination of dimerization was achieved using gel permeation chromatography (gpc) and the monomer was used for calibration. The dimer yields were verified by column chromatography, which also allowed separation of the isomeric photodimers.

The gpc method is accurate, nondestructive (room temperature assay), and convenient, *i.e.*, the reaction mixture can be directly injected into the chromatograph. For example, the rate of photodimerization can be followed, and a first-order rate law is observed in the photodimerization of **5** (10% concentration) up to *ca.* 70% conversion. The results of the photodimerization experiments are listed in Table II.

The results obtained in the photodimerization experiments (irradiation for 4 hr in ethyl acetate) show that electronic effects as well as steric effects are operative. For example, electron-donating groups, such as OCH_3, $NHCOCH_3$, and $NHCOOCH_3$, enhance dimerization (compare *trans*-stilbene with **14**, **2**, **3**, and **5**). The steric effects are also quite pronounced, as shown by the comparison of **15** (4,4′ substituted) with **9** (2,4′ substituted) and **12** (2,2′ substituted). Comparable yields were obtained using benzene, ethyl acetate, and tetrahydrofuran. However, highly polar solvents, such as N,N-dimethylformamide, lower the extent of dimerization. For example, irradiation of **5** in DMF for 4 hr, using a 450-W source, gave 68% photodimerization, while in tetrahydrofuran, under similar conditions, 91.3% dimerization was obtained. The extent of dimerization was not affected when the reaction was conducted in a nitrogen atmosphere.

No *cis*-stilbene or phenanthrene could be isolated, suggesting that, at the concentrations studied, only photodimerization is the major pathway. The extent of dimerization decreases with dilution (see compound **5** in Table II), meaning that at higher dilution isomeri-

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(2) H. Shechter, W. J. Link, and G. V. D. Tiers, *J. Amer. Chem. Soc.*, **85**, 1601 (1963).

(3) F. A. Stuber, H. Ulrich, D. V. Rao, and A. A. R. Sayigh, *J. Appl. Polym. Sci.*, **13**, 2247 (1969).

(4) This phenomenon appears to be general because we observed a similar effect in the photodimerization of coumarins and cinnamates: D. V. Rao, F. A. Stuber, H. Ulrich, and A. A. R. Sayigh, in press.

TABLE I

STILBENE DERIVATIVES[a]

Compd	R_1	R_2	R_3	R_4	R_5	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1[b]	CH_3O	H	H	H	NH_2	72	68–70	$C_{15}H_{15}NO$	79.97	6.71	6.22	79.89	6.67	6.28
2[c]	CH_3O	H	H	H	$NHCOOCH_3$	93	131–132	$C_{17}H_{17}NO_3$	72.06	6.05	4.94	72.22	6.17	5.02
3[d]	H	CH_3O	H	H	$NHCOOCH_3$	93	190–191	$C_{17}H_{17}NO_3$	72.06	6.05	4.94	71.90	6.14	4.83
4[e]	CH_3O	H	CH_3O	H	NH_2	99	91–92	$C_{16}H_{17}NO_2$	75.27	6.71	5.49	75.28	6.64	5.52
5	CH_3O	H	CH_3O	H	$NHCOOCH_3$	99	130–132	$C_{18}H_{19}NO_4$	68.99	6.11	4.47	68.96	6.33	4.57
6	H	H	H	NH_2	NH_2	86	105–107	$C_{14}H_{14}N_2$	79.96	6.71	13.32	79.78	6.76	13.28
7[f]	H	H	H	$NHCOOCH_3$	$NHCOOCH_3$	72	180–181	$C_{18}H_{18}N_2O_4$	66.24	5.56	8.58	66.32	5.77	8.73
8	H	CH_3O	H	NH_2	NH_2	100	153–155	$C_{15}H_{16}N_2O$			11.66			11.69
9[g]	H	CH_3O	H	$NHCOOCH_3$	$NHCOOCH_3$	57	207–208	$C_{19}H_{20}N_2O_5$	64.03	5.66	7.86	64.20	5.69	7.96
10	CH_3O	H	CH_3O	NO_2	NO_2	48	175–177	$C_{16}H_{14}N_2O_6$	58.18	4.27	8.48	58.31	4.16	8.33
11[h]	CH_3O	H	CH_3O	$NHCOCH_3$	$NHCOCH_3$		256–258	$C_{20}H_{22}N_2O_4$	67.78	6.25	7.91	67.72	6.45	7.82
12[g]	CH_3O	H	CH_3O	$NHCOOCH_3$	$NHCOOCH_3$	90	193–194.5	$C_{22}H_{22}N_2O_6$	62.16	5.74	7.25	62.16	5.72	7.30

[a] The acetyl derivatives were obtained from the corresponding amines and acetic anhydride and the methyl carbamates were prepared by refluxing the corresponding isocyanates in excess MeOH. [b] Acetyl derivative, mp 135–137°. [c] The isocyanate was obtained as a liquid according to the general method. [d] Isocyanate, mp 163–166°. [e] Acetyl derivative, mp 172–173°. [f] Diisocyanate, mp 95–98°. [g] The diamine was obtained as a liquid according to the general method. [h] The diamine was obtained as a light brown liquid according to the general method.

zation and cyclization compete with photodimerization. In the present investigation we have not examined this aspect of photochemistry.

The isolated stilbene photodimers are listed in Table III, and all compounds show the absence of the infrared band at 952–971 cm^{-1} which corresponds to the out-of-plane deformation of the olefinic CH bond in stilbenes. The mass spectra of the photodimers obtained from **5** show a molecular ion at *m/e* 626, which is in agreement with the dimer structure. Separation of both dimers derived from compounds **2**, **3**, and **5** could be accomplished by column chromatography. The high-melting photodimers (type B) gave a broad signal in their nmr spectra for the cyclobutane protons at δ 4.30–4.45 ppm. In contrast, the low-melting photodimers (type A), derived from **2** and **5**, show two symmetric multiplets centered at δ 4.30 and 4.33 ppm and 4.60 and 4.70 ppm, respectively. In the case of **3** both types of dimers gave a broad signal for the cyclobutane protons at δ 4.32.

The symmetric signals obtained for the four-ring protons correspond to an AA′BB′-type spectrum. Among the eleven possible isomers, six contain a symmetry element, but two isomers with all the substituents on the same side of the cyclobutane ring are unlikely for steric reasons; the remaining configurations are depicted in Chart I. Earlier studies by Shechter[2]

CHART I

16 **17** **18** **19** **20**

on unsubstituted stilbenes showed that the two dimers formed had the structures indicated in Chart I. The dissimilar substituents attached to the aryl moieties in our investigation complicate the structural assignment because of the possibility of formation of head-to-head and head-to-tail dimers. The formation of a dimer with structure **20** seems quite improbable, since isomerization of the *trans* to the *cis* monomer would have to occur during the reaction.

In order to determine the fine structure of the multiplets in case of the photodimers of **5**, 100-MHz nmr spectra were recorded. Theoretical spectra were calculated for each of the five configurations using coupling constants derived from similar substituted cyclobutanes described in the literature, *e.g.*, $^3J_{cis}$ = 10 Hz, $^3J_{trans}$ = 6.5 Hz, $^4J_{cis}$ = 0.6 Hz, $^4J_{trans}$ = −1.5 Hz, and $\nu_A\nu_B$ = 31 Hz.[5,6] Comparison of the observed spectrum and the calculated transitions indicates that **16** (Chart I and Figure 1) is the most probable structure for the low-melting dimer. However, the lack of fine structure in the case of the high-melting dimer prevents differentiation between structures **17** and **19**.

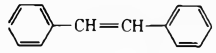
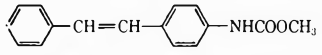
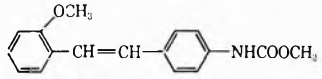
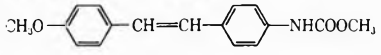
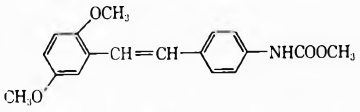
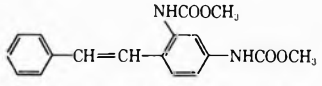
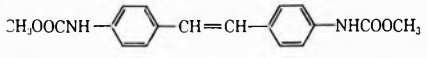
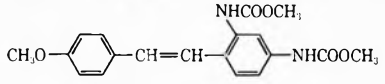
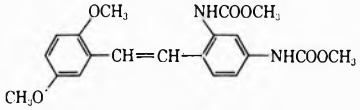
The fragmentation pattern in the mass spectrum should allow further differentiation, because in the case of **16** and **17** three stilbene ion fragments, [RCH=CHR]·⁺, [RCH=CHR′]·⁺, and [R′CH=CHR′]·⁺,

(5) C. H. Krauch, S. Farid, and G. O. Schenck, *Chem. Ber.*, **99**, 625 (1966).

(6) R. Steinmetz, W. Hartman, and G. O. Schenck, *ibid.*, **98**, 3854 (1965).

TABLE II

PHOTODIMERIZATION OF STILBENE METHYL CARBAMATES[a]

Structure of monomer	Compd	Concn, %	Extent of dimerization, %[b]
		10	11
	14	10	27
	2	10	51
	3	10	66
	5	10 3 1	74[c,d] 42 25
	7	10 3[e]	10 6
	15	3[e]	45
	9	10 3[d]	35 22
	12	10	22

[a] The experiments were conducted using ethyl acetate as the solvent, a 100-W mercury lamp as the light source, and an exposure time of 4 hr. [b] Determined by gel-permeation chromatography. Two photodimers were generally obtained, except with **9** and **15** which yielded only one photodimer. [c] The same yield was obtained in benzene. [d] The extent of dimerization of the N-acetyl derivative of the amine precursor of **5** was found to be 75%, using 10% concentration. [e] Tetrahydrofuran was used as solvent.

TABLE III

STILBENE PHOTODIMERS

Starting stilbene	Dimer	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found % C	Found % H	Found % N
2	A	102–105	$C_{34}H_{34}N_2O_6$	72.06	6.05	4.94	71.64	5.87	5.09
	B	219–221					72.16	6.07	4.75
3	A	116–118	$C_{34}H_{34}N_2O_6$	72.06	6.05	4.94	71.92	6.13	4.95
	B	220–222					71.90	6.04	4.83
5	A	103–105	$C_{36}H_{38}N_2O_8$	68.99	6.11	4.47	68.97	6.17	4.69
	B	223–224					68.72	6.21	4.49
15		194–195	$C_{36}H_{36}N_4O_8$	66.24	5.56	8.58	66.28	5.62	8.44
9		142–145	$C_{38}H_{40}N_4O_{10}$	64.03	5.66	7.86	63.79	5.28	7.50

are expected, whereas **18** and **19** could only produce $[RCH{=}CHR']\cdot^+$; the intensity of the fragment ions cannot be predicted *a priori*.

In the mass spectrum of the type A dimer of **5**, the main fragmentation sequence is formation of the monomer ion at *m/e* 313 followed by the loss of methanol leading to the base peak at *m/e* 281. Although the abundance of the ion at *m/e* 300 corresponding to a $[R'CH{=}CHR']\cdot^+$ [R′ = 2,5-$(CH_3O)_2C_6H_4$] fragment ion is only 3.3%, there is strong evidence from the nmr study that this dimer has structure **16**. Another peak of low intensity (0.5%) at *m/e* 262 corresponding to a fragment derived from $[RCH{=}CHR]\cdot^+$(R = 4-$CH_3OOCNHC_6H_4$) by the loss of two CH_3OH supports the proposed structure.

The pattern of fragmentation in the case of the type B dimer is very similar to that of the A dimer, since the favored process leads to the formation of the monomer ion at *m/e* 313. However, the peak at *m/e* 300 is of very low intensity and represents mainly the +2 isotope peak of *m/e* 298; the peak at *m/e* 298 corresponding to the loss of CH_2 from the *m/e* 313 ion. The absence of a fragment ion at *m/e* 300 suggests that all-*trans* dimer has structure **19**, because ring fragmentation gives only rise to the formation of $[RCH{=}CHR']\cdot^+$ fragments.

In order to understand the nature of the excited state from which dimerization occurs, several experiments were conducted. Irradiation of a benzene solution of **5** (0.016 *M*) with light of 366 nm in the presence of Michler's ketone (97% of incident light being absorbed by the ketone) produced no appreciable dimerization. In contrast, 67% dimerization occurred upon direct irradiation of **5** under similar conditions. This experiment suggests that either the triplet energy of **5** is greater than that of Michler's ketone (E_t = 61 kcal/mol[7]) and hence not favorable for energy transfer or that the dimerization occurs from an excited singlet

(7) N. J. Turro, "Molecular Photochemistry," W. A. Benjamin, Inc., New York, N. Y., 1967, p 131.

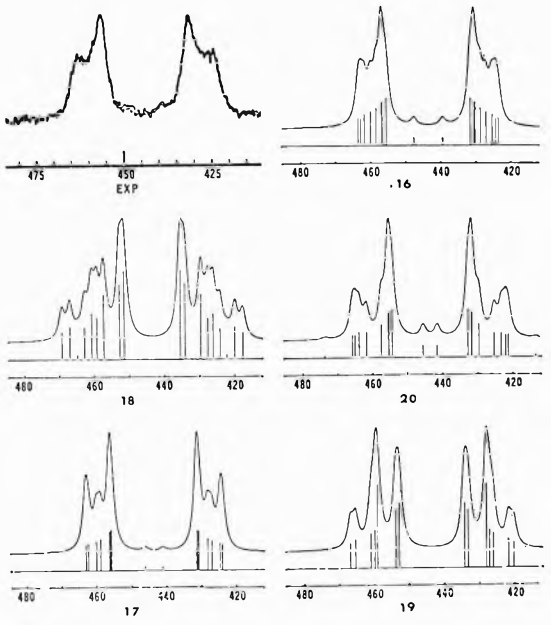


Figure 1.—Observed and calculated 100-MHz spectral bands for the protons in the four-membered ring of the low-melting dimer of **5**.

state. The triplet energies of *trans*- and *cis*-stilbene are reported to be 50 and 57 kcal/mol, respectively.[8] Attempts to observe the phosphorescence emission of **5** at 77°K in EPA failed. However, **5** exhibits fluorescence with an emission maximum at 410 nm, and the O–O band was located at 378 nm, corresponding to a singlet energy of E_s = 75.6 kcal/mol. The extent of dimerization was not affected by the presence of air. In contrast to **5**, 2,5-dimethoxy-4′-nitro-*trans*-stilbene does not undergo photodimerization and exhibits only weak fluorescence (emission maximum at 510 nm, O–O band at 445 nm). This can be explained by the effect of the NO_2 group, which is known to enhance intersystem crossing.[9] In EPA at 77°K 2,5-dimethoxy-4′-nitro-*trans*-stilbene exhibits phosphorescence with a maximum at 495 nm and the blue edge at 440 nm.

The above data seem to preclude the involvement of an excited triplet state in the photodimerization of substituted stilbenes and therefore strongly suggest the intermediacy of an excited singlet state.

Experimental Section

Melting and boiling points are uncorrected. Analyses were by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and Galbraith Laboratories, Knoxville, Tenn. Ir spectra were determined using a Beckman IR-8 spectrophotometer. Uv spectra were recorded on a Cary-14 spectrophotometer. Fluorescence emission spectra were obtained on an Aminco–Bowman spectrofluorometer. Nmr spectra were obtained from samples in deuteriochloroform or deuterated dimethyl sulfoxide solutions with a Varian A-60 instrument using tetramethylsilane as the internal standard. Mass spectra were determined using a MS 12 mass spectrograph. Glpc chromatography was conducted using a Waters instrument and authentic monomers and dimers were used for calibration. Column chromatographic separations were conducted over silica gel (100–200 mesh supplied by Bio-Rad Laboratories, Richmond, Calif.).

Reagents and General Procedures.—Benzene and ethyl acetate were spectral grade solvents and were used without further purification. Tetrahydrofuran was purified by refluxing over $LiAlH_4$ fcllowed by distillation. The following stilbene derivatives were prepared according to the literature: *trans*-4-isocyanatostilbene,[10] *trans*-2-methoxy-4′-nitrostilbene,[11] *trans*-4-methoxy-4′-aminostilbene,[11] *trans*-4-methoxy-2′,4′-dinitrostilbene,[12] *trans*-2,4-dinitrostilbene,[13] *trans*-4,4′-diisocyanatostilbene,[10] and *trans*-2,5-dimethoxy-4′-nitrostilbene.[14] The N-acetyl derivatives of the corresponding amines were obtained by treating the corresponding amines with acetic anhydride at room temperature. The methyl carbamates were obtained by refluxing the corresponding isocyanates with excess methanol.

***trans*-2,5-Dimethoxy-2′,4′-dinitrostilbene (10). General Procedure.**—The preparation of **10** exemplifies the procedure followed in the synthesis of the reported nitrostilbene derivatives. A mixture of 2,5-dimethoxybenzaldehyde (28.19 g, 0.168 mol) and 2,4-dinitrotoluene (27.0 g, 0.148 mol) in 200 ml of chlorobenzene containing 30 drops of piperidine was heated for 3 hr with azeotropic removal of water. Evaporation of the solvent under vacuum and addition of 200 ml of ethanol gave 17 g (35%) of **10**: mp 175–177° after recrystallization from ethyl acetate; ir ($CHCl_3$) 1342 (NO_2) and 966 cm^{-1} (olefinic CH).

***trans*-2,5-Dimethoxy-4′-aminostilbene (4). General Procedure.**—The preparation of **4** exemplifies the procedure followed in the reduction of the nitrostilbenes. To 6.0 g (0.023 mol) of *trans*-2,5-dimethoxy-4′-nitrostilbene[13] suspended in 250 ml of methanol 1.0 g of Raney nickel was added and the reaction mixture was hydrogenated using a Parr hydrogenator at 50 psi. After the uptake of the theoretical amount of hydrogen (5.5 lb), the reaction was stopped and filtration and evaporation yielded 5.3 g (99%) of **4**: mp 91–92° after recrystallization from 2-propanol; ir ($CHCl_3$) 3509, 3390 (NH_2), 1618 (C=C), and 966 cm^{-1} (olefinic CH); uv max (methanol) 345 nm (ϵ 2.10 × 10^4) and 220 (1.85 × 10^4); fluorescence emission λ_{max} (methanol) 415 nm; nmr ($CDCl_3$) δ 3.47 (s, 2, NH_2), 3.78 and 3.80 (2 s, 6, OCH_3), 7.0 and 7.28 (2 d, 2, J = 16 Hz, CH=CH), and 6.62–7.35 (m, 7).

***trans*-2,5-Dimethoxy-4′-isocyanatostilbene. General Procedure.**—The preparation of *trans*-2,5-dimethoxy-4′-isocyanatostilbene demonstrates the method of phosgenation used in the preparation of the isocyanatostilbenes. In a four-necked flask, provided with a stirrer, thermometer, dewar condenser with Dry Ice, and an inlet tube was placed 200 ml of dry chlorobenzene. At 0–2°, 1800 ml (0.08 mol) of phosgene was added followed by the dropwise addition of **4** (10.0 g, 0.039 mol) in 75 ml of chlorobenzene, while the temperature was maintained at 1–4°. After the addition, the dewar condenser was removed, an Allihn condenser was attached and the solution was heated at 90–95° for 1.5 hr while a gentle stream of phosgene was added. After excess phosgene had been removed with N_2 (2 hr), the solvent was removed under vacuum on a hot-water bath and the yellow residue crystallized after addition of 200 ml of ligroin. Thus 10.1 g (91%) of *trans*-2,5-dimethoxy-4′-isocyanatostilbene, mp 69.5–70.5° after recrystallization from benzene–ligroin (1:9, v/v), was obtained: ir (CCl_4) 2247 (NCO) and 966 cm^{-1} (olefinic CH); uv max (*n*-hexane) 342 nm (ϵ 1.72 × 10^4), 296 (2.35 × 10^4), 231 (1.37 × 10^4), and 219 (1.69 × 10^4); fluorescence emission λ_{max} (*n*-hexane) 402 and 383 nm; nmr (CCl_4) δ 3.72 and 3.75 (2 s, 6, OCH_3) and 6.9 and 7.30 (2 d, 2, J = 16 Hz, CH=CH).

Methyl Carbamate (5).—An amount of 8.0 g of *trans*-2,5-dimethoxy-4′-isocyanatostilbene, dissolved in 100 ml of methanol, was refluxed for 3 hr. After cooling, 8.8 g (99%) of **5**, mp 130–132°, was obtained: ir ($CHCl_3$) 3425 (NH), 1724 (C=O), and 969 cm^{-1} (olefinic CH); uv max (methanol) 343 nm (ϵ 2.44 × 10^4), 301 (2.37 × 10^4), 233 (1.00 × 10^4), and 217 (0.90 × 10^4); fluorescence emission λ_{max} (CH_3OH) 410 nm; nmr (DMSO-d_6) δ 3.72, 3.78, and 3.81 (3 s, 9, OCH_3-2, OCH_3-5, $COOCH_3$), 7.24 and 7.30 (2 d, 2, J = 17 Hz, CH=CH), and 9.70 (s, 1, NH).

Irradiation of the Methyl Carbamate (5) Derived from *trans*-2,5-Dimethoxy-4′-isocyanatostilbene. A. Benzene.—A solution of 2.0 g of **5** in 20 ml of benzene was irradiated in a 250-ml quartz flask provided with a water-cooled condenser using a 100-W Hanovia utility model mercury lamp (Type SH, 616A) for a period of 21 hr. The flask was placed at a distance of 8–10 cm

(8) L. M. Stephenson and G. S. Hammonn, *Angew. Chem.*, **81**, 279 (1969).
(9) M. Kasha, *Discuss. Faraday Soc.*, **9**, 14 (1950).
(10) V. H. Bertsch, E. Ulsperger, and M. Bock, *J. Prakt. Chem.*, **11**, 225 (1960).
(11) P. Pfeiffer, *Chem. Ber.* **48**, 1793 (1915).
(12) P. Pfeiffer, *Ann. Chem.*, **411**, 132 (1916).
(13) J. Thiele and R. Escales, *Chem. Ber.*, **34**, 2843 (1901).
(14) H. Ulrich and A. A. R. Sayigh, *J. Org. Chem.*, **31**, 4148 (1966).

from the uv source. The precipitated solid material was filtered, washed with excess benzene, and dried to yield 0.5 g (25%) of photodimer B: mp 220–223° (recrystallization from acetone or ethyl acetate rasised the melting point to 223–224°); ir ($CHCl_3$) 3378 (NH) and 1701 cm^{-1} (C=O); nmr (DMSO-d_6) 3.55 and 3.64 (2 s, 18, OCH_3, $NHCOOCH_3$), 4.45 (m, 4, cyclobutane H), 6.64–7.28 (m, 14), and 9.40 (s, 2, $NHCOOCH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 626 (*ca.* 0.01), 313 (27), 300 (0.15) 281 (100), and 238 (15.4).

The concentrated filtrate was chromatographed over silica gel and eluted with benzene, yielding 0.4 g (20%) of the starting material as evidenced by mixture melting point and ir comparison. Elution with benzene–ether (9:1 and 8:2, v/v) gave a light brown liquid material which upon trituration with ether–*n*-hexane yielded 0.7 g (35%) of photodimer A: mp 103–105° after recrystallization from chloroform–*n*-hexane; ir ($CHCl_3$) 3425 (NH) and 1724 cm^{-1} (C=O); nmr (DMSO-d_6) δ 3.52, 3.57, and 3.63 (3 s, 18, OCH_3, $NHCOOCH_3$), 4.33 and 4.65 (2 m, 4, cyclobutane H), 6.65–7.28 (m, 14), and 9.40 (s, 2, $NHCOOCH_3$); mass spectrum (70 eV) *m/e* (rel intensity) 626 (*ca.* 0.01), 313 (44), 300 (3.3), 281 (100), 262 (0.5), and 238 (15.5).

A quantitative determination of dimerization (by gpc) gave a value of 73.3% when a 10% solution of **5** was irradiated for 4 hr.

B. Ethyl Acetate.—Irradiation of a 10% solution of **5** in ethyl acetate for 4 hr yielded 74% photodimers as determined by gel-permeation chromatography.

C. Tetrahydrofuran.—A solution of 0.5 g of **5** in 5 ml of tetrahydrofuran was placed in a quartz test tube which was taped to the quartz probe (19434, supplied by Hanovia Lamp Division) containing a water-cooled immersion-type 450-W Hanovia mercury lamp (Type L, 679A). The entire system was controlled at 15–17° and the uv light was filtered through a Pyrex 7740 filter sleeve. After irradiation for 4 hr the photodimer content was determined by gpc to be 91.3%. Repeating the experiment under nitrogen gave a photodimer yield of 91.8%.

Irradiation of the Methyl Carbamate (2) Derived from *trans*-2-Methoxy-4′-isocyanatostilbene.—A solution of 2.0 g of **2** in 20 ml of benzene was irradiated for 4 hr using the 100-W Hanovia lamp as described above. On standing, 0.51 g (25.5%) of a crude photodimer, mp 89–92°, precipitated. Recrystallization from benzene and from chloroform–*n*-hexane gave photodimer A: mp 102–105°; ir ($CHCl_3$) 3425 (NH) and 1724 cm^{-1} (C=O); nmr (DMSO-d_6) δ 3.56 and 3.62 (2 s, 12, OCH_3 and $NHCOOCH_3$), 4.30 and 4.70 (2 m, 4, cyclobutane H), and 9.40 (s, 2, $NHCOOCH_3$).

The benzene filtrate was concentrated and chromatographed over silica gel (55 g) and the following fractions were obtained. Benzene gave 0.8 g (40%) of starting material. Benzene–ether (9:1 and 8:2, v/v) gave 0.45 g (22.5%) of photodimer B: mp 219–221° after recrystallization from benzene; ir ($CHCl_3$) 3425 (NH) and 1724 cm^{-1} (C=O); nmr (DMSO-d_6) δ 3.62 and 3.65 (2 s, 12, OCH_3 and $NHCOOCH_3$), 4.48 (m, 4, cyclobutane H), and 9.40 (s, 2, $NHCOOCH_3$).

A quantitative determination of photodimerization by gpc indicated a 51% yield of photodimers. In tetrahydrofuran, using the 450-W Hanovia lamp, a 75% yield of photodimers was realized.

Irradiation of the Methyl Carbamate (3) Derived from *trans*-4-Methoxy-4′-isocyanatostilbene.—A solution of 2.0 g of **3** in 20 ml of ethyl acetate was irradiated for 4 hr using the 100-W Hanovia lamp. The reaction mixture was evaporated, dissolved in benzene, and chromatographed over silica gel. Elution with benzene gave 0.3 g (15%) of starting material. Elution with benzene–diethyl ether (8:2, v/v) gave a mixture of photodimers from which 0.4 g (20%) of photodimer B, mp 220–222° after recrystallization from benzene, was precipitated with diethyl ether: ir (KBr) 3311 (NH) and 1695 cm^{-1} (C=O); nmr (DMSO-d_6) δ 3.62 (s, 12, OCH_3 and $NHCOOCH_3$), 4.32 (m, 4, cyclobutane H), and 9.36 (s, 2, $NHCOOCH_3$).

Concentration of the filtrate and addition of *n*-hexane precipitated 0.66 g (33%) of photodimer A: mp 116–118° after recrystallization from chloroform–*n*-hexane; ir ($CHCl_3$) 3425 (NH) and 1712 cm^{-1} (C=O); nmr (DMSO-d_6) δ 3.60 and 3.63 (2 s, 12, OCH_3 and $NHCOOCH_3$), 4.32 (m, 4, cyclobutane H), and 9.36 (s, 2, $NHCOOCH_3$).

Quantitative determination of photodimerization by gpc indicated a 66% yield of photodimers.

Irradiation of the Bismethylcarbamate (9) Derived from *trans*-4-Methoxy-2′,4′-diisocyanatostilbene.—A solution of 1.4 g of **9** in 14 ml of ethyl acetate was irradiated for 4 hr using the 100-W Hanovia lamp. Evaporation of the solvent and addition of benzene caused precipitation of 0.4 g (28%) of starting material. The benzene filtrate was chromatographed over silica gel, and elution with benzene–diethyl ether (8:2, v/v) afforded more starting material and an unknown by-product. Elution with diethyl ether gave 0.3 g (21.4%) of the photodimer: mp 142–145° after repeated crystallization from aqueous methanol (4:1, v/v); ir ($CHCl_3$) 3425 (NH) and 1718 cm^{-1} (C=O). Quantitative determination of photodimerization by gpc indicated a 35% yield of photodimer.

Irradiation of the Bismethylcarbamate (15) Derived from *trans*-4,4′-Diisocyanatostilbene.—A solution of 0.6 g of **15** in 20 ml of tetrahydrofuran was irradiated for 4 hr using the 100-W Hanovia lamp. The resulting solution was repeatedly chromatographed over silica gel, and elution with benzene–acetone (8:2, v/v) gave a low yield of a photodimer: mp 194–195° after recrystallization from ethyl acetate; ir (Nujol) 3311 (NH) and 1695 cm^{-1} (C=O). Quantitative determination of photodimerization by gpc indicated a 45% yield of photodimer.

Irradiation of 2,5-Dimethoxy-4′-nitro-*trans*-stilbene.—A solution of 3.0 g of the above compound in 30 ml of ethyl acetate was irradiated for 4 hr with unfiltered light from the 100-W light source. The solution contained no photodimers as evidenced by thin layer chromatography on an Eastman silica gel plate using benzene–ether (4:1, v/v).

Quantum Yield Determination.—A rotating turntable assembly (Merry-Go-Round Model MGR-500, supplied by the Southern New England Ultraviolet Co.) with a centrally located light source (450-W medium-pressure lamp, Type L, using Pyrex and Corning CS-7-39 filters to isolate 366-nm region) was used to obtain quantitative data. Benzophenone–benzhydrol actinometry[15] was used and the solutions were irradiated in quartz test tubes (13 mm) after thoroughly degassing with prepurified nitrogen. A quantum yield of 0.6 was obtained from the intercept. Using this value the output of the lamp was calculated to be 8.21×10^{16} quanta/sec. Simultaneously, a 5-ml benzene solution of **5** (0.03 *M*) was irradiated, and from the percentage dimerization (34.3%), the quantum yield was found to be *ca.* 0.057.

Irradiation of 5 in the Presence of Michler's Ketone.—Two quartz test tubes (13 mm) containing in each 5 ml of benzene solution of **5** and Michler's ketone in concentration of 0.016 and 0.126 *M*, respectively, were degassed with prepurified nitrogen, stoppered with a rubber septum, and irradiated for 4 hr in the system used for quantum-yield measurements. Simultaneously, two tubes containing in each 5 ml of benzene solution of **5** (0.016 *M*) were irradiated. The amount of dimer formation was measured by gpc, and in the former not more than 5% dimer was observed, whereas in the latter the dimerization occurred to the extent of 67%.

Emission Spectra of 5.—The fluorescence emission spectrum of **5** was determined in methanol at room temperature using an excitation wavelength of 350 nm. The emission maximum occurred at 410 nm and the O–O band was chosen at the point of crossing of the excitation and emission spectra which occurs at 378 nm. The phosphorescence emission at 77°K in EPA could not be detected.

Registry No.—**1**, 23435-25-8; **1** (acetyl derivative), 23435-26-9; **2**, 23465-04-5; **2** (dimer A), 23435-27-0; **3**, 23435-28-1; **3** (isocyanate), 23435-29-2; **3** (dimer A), 23435-30-5; **4**, 23435-31-6; **4** (acetyl derivative), 23435-32-7; **5**, 23435-33-8; **5** (isocyanate), 23435-34-9; **5** (dimer A), 23435-35-0; **6**, 23435-36-1; **7**, 23435-37-2; **7** (diisocyanate), 23435-38-3; **8**, 23435-39-4; **9**, 23435-40-7; **10**, 23435-41-8; **11**, 23435-42-9; **12**, 23435-43-0.

Acknowledgment—The authors wish to express their appreciation to B. V. Cheney, The Upjohn Co., Biochemical Research, Kalamazoo, Mich., for the 100-MHz nmr spectra and computer simulation. The invaluable assistance of F. P. Recchia and A. R. Marchant of our laboratories in obtaining the gpc results is greatly appreciated.

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The Stereochemistry of Dehydrogenation of Δ^4-3-Keto Steroids by Chloranil[1]

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Received September 28, 1969

Dehydrogenation of androst-4-ene-3,17-dione-7β-*d* with chloranil gives androsta-4,6-diene-3,17-dione with almost complete retention of the deuterium. Taken with other evidence, this experiment establishes that chloranil abstracts the 7α hydrogen. The mass spectra of steroid 4,6-dien-3-ones show two important peaks corresponding to cleavage of the molecule in ring B. Allylic bromination of 3β-acetoxyandrost-5-en-17-one gives a mixture of the 7α- and 7β-bromo derivatives in approximately equal yield.

The dehydrogenation of Δ^4-3-keto steroids with chloranil to the corresponding 4,6-dien-3-ones was first described by Agnello and Laubach,[2] who proposed the presently accepted mechanism of hydride abstraction from C-7 of the 3,5-dien-3-ol.

Although the dehydrogenation had been shown to involve the loss of the 6β hydrogen atom,[3] the removal of the 7α hydrogen had not been established beyond doubt. The evidence for removal of the 7α hydrogen rested on the observation that, while 7β,17α-dimethyl-17β-hydroxyandrost-4-en-3-one (**1a**) reacts with chloranil in boiling *t*-butyl alcohol to form the 4,6-dien-3-one (**2a**), the 7 epimer (**1b**) reacts much more slowly, if at all, under the same conditions.[4] The presence of the 7-methyl groups, however, may cause disturbance of the ring geometry.

When 3β-hydroxyandrost-5-en-17-one is reduced with tritium gas, some tritium is introduced at the 7 position in the major product, 3β-hydroxy-5α-androstan-17-one. Having established that the tritium at the 6 position was entirely α oriented, Brodie, *et al.*,[3] showed that the C-7 tritium could be removed by dehydrogenation of the derived androst-4-ene-3,17-dione with chloranil. They cited the evidence of Campbell and Babcock[4] and suggested that, by analogy with the *trans* diaxial 1α,2β dehydrogenation of 3-keto steroids to the Δ^1-3 ketones by dichlorodicyanoquinone,[5] the chloranil reaction should remove the 7α axial hydrogen. The *trans* diaxial relation of the two hydrogens removed is, however, of little relevance, since the first step is the preferential[6] loss of the 2β and 6β protons to form the enols. The removal of the 1α hydrogen by dichlorodicyanoquinone could be due to an α-face attack on the Δ^2 enol and need not be due to its axial character. The evidence for removal of the 7α hydrogen during the chloranil reaction was therefore persuasive but not conclusive. Since this reaction was to be used in examining the stereochemistry of deuteron attack at C-7 on the 3α,5α-cycloandrost-6-ene system,[7] it was considered worthwhile to establish the stereochemistry of the chloranil reaction at the 7 position by synthesis and dehydrogenation of a 7-deuterioandrost-4-ene-3,17-dione of known configuration.

Results and Discussion

Treatment of 3β-acetoxyandrost-5-en-17-one (**3a**) with N-bromosuccinimide gave as a crystalline product a mixture of 3β-acetoxy-7α-bromoandrost-5-en-17-one (**3b**) and the 7β-bromo epimer (**3c**) as judged by the nmr spectrum. Recrystallization from ethyl acetate or from carbon tetrachloride gave the pure 7α-bromo isomer (**3b**). Recrystallization of the allylic bromide mixture from alcohols caused accelerated decomposition. The nmr spectrum of the product showed the 6-vinyl hydrogen as a sharp doublet at δ 5.85 ppm (J = 5 Hz) indicative[8] of coupling only to a 7β H, with a dihedral angle (6,7β H) of 40°. The singlet at δ 5.41 ppm (H-6) of the 7β-bromo derivative **3c** was now absent. The H-6–H-7α dihedral angle is *ca.* 80° and would correspond to $J < 1$ Hz. Reduction of the product with lithium aluminum deuteride gave, after crystallization, androst-5-ene-3β,17β-diol-7β,17α-d_2 (**4a**). Combined gas–liquid chromatography–mass spectrometry showed the product to consist of 6% d_1 and 94% d_2 species. The nmr spectrum of the derived diacetate differed from that of androst-5-ene-3β,17β-diol diacetate only in the absence of the H-17α triplet and the appearance of the 6-vinyl proton as a sharp singlet at δ 5.37 ppm ($W_{1/2}$ = 3 Hz), demonstrating that inversion of configuration at C-7 had occurred. Chromium trioxide oxidation of the diol **4a** gave androst-5-ene-3,17-dione-7β-*d*, showing again H-6 as a singlet in the nmr spectrum. Treatment with acid gave the conjugated androst-4-ene-3,17-dione-7β-*d* (**1c**, 96% d_1). During the chromium trioxide oxidation, androst-4-ene-3,6,17-trione containing no excess deuterium was obtained as a minor product. The absence of deuterium at C-7 in the trione, taken together with the observed presence of the vinyl hydrogen at the 6 position in the diol **4a** and in the nonconjugated dione, establishes that the deuterium atom had originally been present at C-7.

In a parallel series of reactions, 17-cycloethylenedioxyandrost-5-en-3β-ol acetate (**3d**) was converted into the bromo derivative **3e** and reduced with lithium aluminum deuteride to 17-cycloethylenedioxyandrost-5-en-3β-ol-*d* (**4b**). When sufficiently purified allylic bromide **3e** was used for the reduction, a by-product,

(1) This is publication No. 1368 of the Cancer Commission of Harvard University. This work was presented in part: Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, No. ORGN 55.

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(3) H. J. Brodie, S. Baba, M. Gut, and M. Hayano, *Steroids*, **6**, 659 (1965).

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(8) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

17-cycloethylenedioxyandrost-6-en-3β-ol-5α-*d*,[9] could not be detected. This by-product may therefore originate from the rearranged 5-bromoandrost-6-ene system. The Δ⁵ ketal **4b** was converted into androst-4-ene-3,17-dione-7β-*d* (**1c**, 100% d_1).

Dehydrogenation of two samples of androst-4-ene-3,17-dione-7β-*d* (**1c**, 96 and 100% d_1), with chloranil gave androsta-4,6-diene-3,17-dione-7-*d* (**2b**, 91 and 95% d_1, respectively), establishing that the dehydrogenation does indeed cause removal of the 7α rather than the 7β hydrogen. The 5% loss of deuterium may be due to 5% androst-4-ene-3,17-dione-7α-*d* in the starting material for the dehydrogenation. This level of contamination would not have been detected in the nmr spectra of the bromo or deuterio compounds. In the chloranil dehydrogenation of androst-4-ene-3,17-dione-7α-*t*, which Brodie *et al.*,[3] used to assign stereochemistry at the 7 position, all but 2% of the starting radioactivity was lost.

The mass spectrum of androsta-4,6-diene-3,17-dione (**2c**, Figure 1) shows two intense fragments at *m/e* 136 and 149. Since in the spectrum of the related 17 alcohol *m/e* 136 remains unchanged but *m/e* 149 has been replaced by a fragment of *m/e* 151, these two peaks may represent cleavage of the molecule at C-1–C-10 and C-7–C-8, *m/e* 136 being the AB end (+2 H) and *m/e* 149 the CD region (−1 H). Introduction of the 7-deuterium atom (**2b**, Figure 2) shifts *m/e* 136 to 137 but leaves *m/e* 149 unchanged.

Allylic bromination of cholesteryl benzoate has been noted[10] to give initially the 7β-bromo compound, which epimerizes to an equilibrium mixture with the 7α-bromo isomer. In an attempt to prepare directly androst-4-ene-3,17-dione-7α-*d*, the product of N-bromo succinimide bromination of androst-5-ene-3β,17β-diol diacetate was immediately evaporated to dryness at room temperature or below and reduced with lithium aluminum deuteride in tetrahydrofuran to give androst-5-ene-3β,17β-diol-7ξ-*d* (7% d_0, 78% d_1, 15% d_2). Oxidation, conjugation, and treatment of the product with chloranil gave androsta-4,6-diene-3,17-dione containing 54% d_1. The bromination product at the time of reduction was thus *ca.* a 1:1 mixture of the 7α- and 7β-bromo isomers. In order to determine whether the initial bromination product had been entirely the 7β-bromo compound which had partly epimerized while refluxing in tetrahydrofuran with lithium aluminum deuteride, 3β-acetoxyandrost-5-en-17-one in an nmr tube was brominated with N-bromosuccinimide and light. After 2 min of heating and irradiation, the nmr peak of the vinyl 6 hydrogen of 3β-acetoxyandrost-5-en-17-one had disappeared completely and had been replaced by the vinyl proton pattern characteristic of a mixture of approximately equal quantities of 7α-bromo- and 7β-bromo-3β-acetoxyandrost-5-en-17-one. This ratio remained unchanged on further irradiation. The presence of a 3β-benzoyloxy group had been claimed to affect the stability of the allylic bromides.[11] Repetition of the bromination using 3β-benzoyloxyandrost-5-en-17-one gave the 7α- and 7β-bromo derivatives in approximately the same ratio.

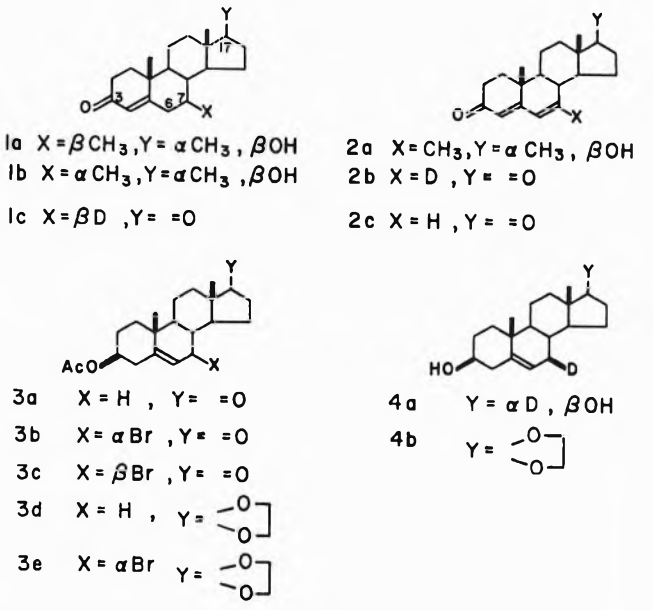

Figure 1.

It is probable that the isolation of 3β-benzolyloxy-7β-bromocholest-5-ene by Schaltegger[12] was due to its solubility characteristics rather than to selective 7β bromination.

Experimental Section

Combined gas–liquid chromatography–mass spectrometry was carried out on an LKB 9000 instrument with helium carrier gas, and OV-1 on Gas-Chrom Q (Applied Science Laboratories, State College, Pa.) at 200° as the stationary phase. Samples in the solid state, adsorbed on stainless steel gauze,[13] were injected into the flash heater at 230°. The molecular separator was maintained at 250° and the ion source at 270°. The mass spectrometer ionizing current was 50 μA, and the ionizing energy was 70 eV during the mass spectral scans. Melting points were determined on a Kofler block and are not corrected. Nmr spectra were measured on a Varian A-60 spectrometer in deuteriochloroform solution unless otherwise noted. Chemical shifts are reported in δ units with tetramethylsilane (δ 0.00 ppm) as internal standard. Evaporations were carried out under vacuum in a rotary evaporator with a bath temperature of *ca.* 45° unless otherwise noted.

3β-Hydroxy-7α-bromoandrost-5-en-17-one Acetate (3b).—3β-Hydroxyandrost-5-en-17-one acetate (10 g, 30.3 mmol) in refluxing carbon tetrachloride (70 ml) dissolved completely. N-Bromosuccinimide (5.35 g, 1.07 equiv) in carbon tetrachloride (30 ml) was added and the mixture was refluxed over a 150-W lamp for 8 min. The yellow solution was filtered to remove the crystalline succinimide and evaporated almost to dryness under reduced pressure without heating to give faintly yellow crystals. Three recrystallizations from carbon tetrachloride–ethyl acetate gave the 7α-allylic bromide (**3b**, 2.7 g, 6.6 mmol, 22% yield): mp 150–153° (lit.[12] mp 155°); nmr δ 5.85 (d, J = 5.0 Hz, H-6), 4.78 (d, J = 5.0 Hz, H-7β), 2.03 (acetate), 1.07 (C-19 H_3), and 0.90 ppm (C-18 H_3).

Androst-5-ene-3β,17β-diol-7β,17α-d_2 (4a).—3β-Hydroxy-7α-bromoandrost-5-en-17-one acetate (**3b**, 1.5 g) in dry tetrahydrofuran (120 ml) was refluxed for 5 hr with lithium aluminum deuteride (1.0 g, Alfa Inorganics, 99+% *d*). Thin layer chromatography showed the reduction to be complete. Water and ether were added, and the organic layer was separated. The aqueous layer was reextracted twice with ether, and the combined organic layers were washed with water and evaporated to a crystalline mass, which upon recrystallization gave androst-5-ene-3β,17β-

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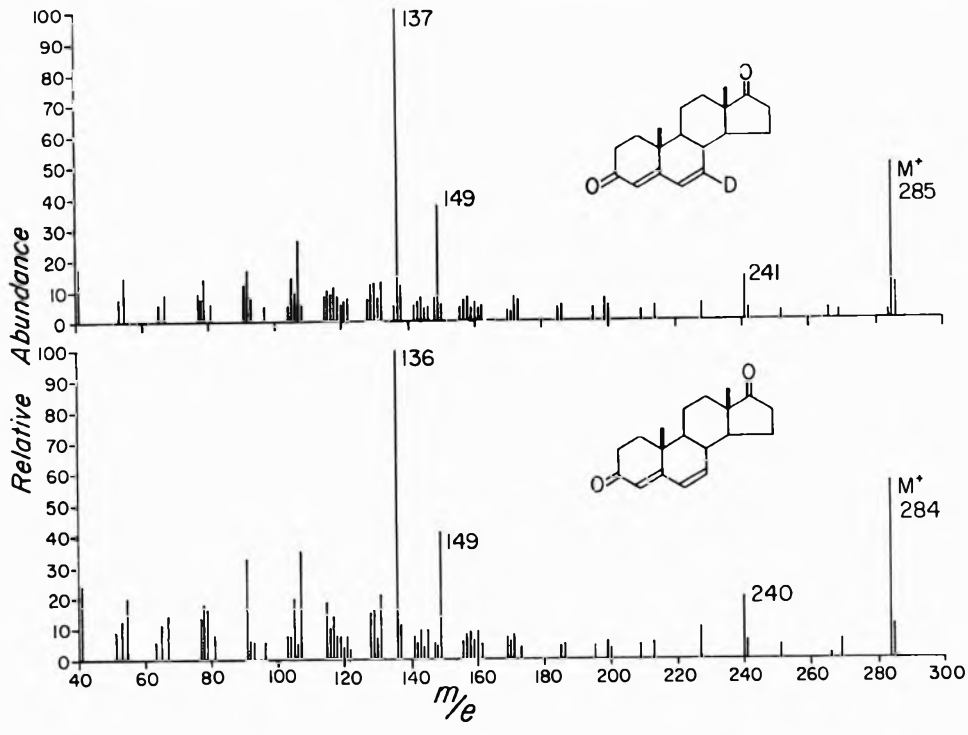

Figure 2.

diol-7β,17α-d_2 (**4a**, 800 mg): mp 178–180.5°, undepressed on mixing with an authentic sample of the unlabeled diol of mp 178–180°; mass spectrum m/e 292 (M^+). The nmr spectrum of the diol **4a** in chloroform was unsatisfactory owing to low solubility.

The derived diacetate, mp 159–162°, was undepressed on admixture with an authentic sample of androst-5-ene-3β,17β-diol diacetate, mp 159–162°. The nmr spectrum of androst-5-ene-3β,17β-diol-7β,17α-d_2 diacetate showed the absence of the H-17α triplet and showed a singlet at δ 5.37 ppm ($W_{1/2}$ = 3 Hz, H-6). The mass spectrum showed as the heaviest ion m/e 316 (M − 60); the fragmentation pattern corresponds closely to that expected on the basis of the nondeuterated diacetate.

Chromium Trioxide Oxidation of Androst-5-ene-3β,17β-diol-7β,17α-d_2 (4a).—The diol **4a** (100 mg, 0.35 mmol) in acetone was stirred with chromium trioxide (0.195 ml of 8 *N*, 1.4 equiv) in 1 *N* sulfuric acid for 5 min.[14] The brown chromate remained in excess. The solution was extracted with ethyl acetate–water, and the ethyl acetate layer was washed and evaporated to give a crystalline solid. The nmr spectrum showed this to be the nonconjugated androst-5-ene-3,17-dione-7β-*d*; the angular methyl groups (δ 1.21 and 0.88 ppm) and H-6 (δ 5.35 ppm) all appeared as singlets, giving no indication of contamination with the Δ^6 isomer.

Treatment of the nonconjugated dione with methanol (5 ml) containing concentrated hydrochloric acid (1 drop) at room temperature overnight and two recrystallizations from aqueous ethanol gave androst-4-ene-3,17-dione (**1c**): yield 12 mg; mp 172–174°, undepressed on mixing with authentic nonlabeled androst-4-ene-3,17-dione of mp 172–174°. Combined gas–liquid chromatography–mass spectrometry showed the product to be homogenous and to contain 96% d_1.[15] The abundant fragment at m/e 124 of ring A, C-6, C-19, and 2 H[16] was not shifted to m/e 125 and hence did not contain the deuterium. Glpc of the mother liquors revealed the presence of androst-4-ene-3,6,17-trione [m/e 300 (M^+)] as a minor component. The mass spectrum of his compound was identical with that of an authentic sample; it contained no excess deuterium.

7α-Bromo-17-cycloethylenedioxyandrost-5-en-3β-ol Acetate (3e).—17-Cycloethylenedioxyandrost-5-en-3β-ol acetate (17.7 g, 47.3 mmol) in carbon tetrachloride was heated on a steam bath. N-Bromosuccinimide (10.1 g, 1.1 equiv) was added and the mixture was refluxed over a 150-W lamp for 10 min. The solution was filtered and evaporated on a rotary evaporator in a water bath at *ca.* 25° under vacuum until crystals began to form. Ethyl acetate was added and the suspension was left in an ice bath.

Two recrystallizations of the crystalline product, by dissolving carbon tetrachloride, adding ethyl acetate, and rotary evaporation at room temperature or below, gave the allylic bromide **3e** (5.21 g): mp 164–165° (lit.[9] mp 148–151°); nmr δ 0.86 and 1.04 (sharp singlets with no evidence of impurity, angular methyl groups), 3.87 (ketal CH_2), 4.63 (H-7β), and 5.75 ppm (H-6).

17-Cycloethylenedioxyandrost-5-en-3β-ol-7β-*d* (4b).—The allylic bromide **3e** (2.73 g, 6.02 mmol) in tetrahydrofuran (200 ml, freshly distilled from lithium aluminum hydride) was refluxed overnight with $LiAl_4D$ (24 mmol). The solution was diluted with water, and *ca.* 150 ml of tetrahydrofuran were evaporated. The solution was further diluted with water and extracted with ether; the ether solution was washed and evaporated to give colorless crystals of **4b**, recrystallized from methanol, mp 165–168° (1.38 g, 69% yield). In the absence of an authentic nonlabeled sample, the mass spectrum alone does not allow calculation of the per cent deuterium; the peaks in the region of the molecular ion at m/e (rel intensity) 232 (8), 233 (100), and 234 (23) indicate that the material is substantially monodeuterated. The substance was homogenous both by glpc and tlc. The nmr spectrum again showed no peak corresponding to the angular methyl groups of the Δ^6 isomer:[9] δ 5.34 (s, H-6), 3.88 (ketal), and 1.01 and 0.86 ppm (angular methyl).

Androsta-4,6-diene-3,17-dione-7-*d* (2b).—Androst-4-ene-3,17-dione-7β-*d* (10 mg, 100% d_1) in benzene (10 ml) with chloranil (50 mg) was refluxed for 2 days. The benzene solution was washed with aqueous KOH and then with water until neutral. A portion of the benzene solution was applied directly to stainless steel gauze and injected into the combined glpc–mass spectrometer. The major glpc peak (85% of the total steroid peak area) corresponded in retention time and mass spectrum to androsta-4,6-diene-3,17-dione-7-*d* (**2d**, Figure 2). Three successive mass spectral scans taken over the peak showed 96.1, 95.2, and 94.2% d_1 (average 95% d_1).[15]

Similar dehydrogenation of the androst-4-ene-3,17-dione-7β-*d* (96% d_1) gave the diene dione **2b**, containing, on successive scans over the peak, 92.1, 91.6, 91.5, 91.5, 89.9, and 88.6% d_1 (average 91% d_1).

N-Bromosuccinimide Bromination of 3β-Benzoyloxyandrost-5-

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(15) As with all steroids so far examined by glpc–mass spectrometry on OV1, the deuterated steroid has a slightly shorter retention time than does the unlabeled molecule. This has been observed with greater clarity in the fatty acid series, where the predeuterated acid methyl esters have been separated completely from the unlabeled material: J. A. McCloskey, A. M. Lawson, and F. A. J. M. Leemans, *Chem. Commun.*, 285 (1967).

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en-17-one and of the Corresponding Acetate (3a).—The benzoate (0.10 mmol) in deuteriochloroform containing tetramethylsilane in an nmr tube was refluxed and irradiated after addition of N-bromosuccinimide (0.11 mmol). After 2 min, the doublet at 5.46 ppm (H-6) (7,7 H_2) had diminished while a doublet at δ 5.95 ppm (J = 5.1 Hz), H-6 (7α Br) and a singlet at δ 5.72 ppm (H-6) (7β Br), ratio 1.3:1, had appeared.

A similar bromination of 3β-acetoxyandrost-5-en-17-one (3a) in CCl_4 gave a ratio of 7α Br (3b) to 7β Br (3c) product of 1.2:1.

Registry No.—Chloranil, 118-75-2; **1c**, 23668-15-7; **2b**, 23668-16-8; **2c**, 633-34-1; **3b**, 23668-18-0; **3e**, 748-37-8; **4a**, 23668-20-4; **4a** diacetate, 23668-21-5; **4b**, 23688-22-6.

Acknowledgments.—This work was supported by U. S. Public Health Service (Grants CA02421 and CA01939) and a grant from the American Cancer Society (P95). The LKB 9000 combined glpc–mass spectrometer was purchased through a special grant from the American Cancer Society (Massachusetts Division). The authors are deeply indebted to Dr. L. L. Engel for encouragement and helpful discussion of this work.

The Addition of Coordinated Glycine to Acetaldehyde. Mechanism[1]

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Received October 3, 1969

The kinetics of the reaction of acetaldehyde with glycinatobis(ethylenediamine)cobalt(III) chloride in the presence of a tertiary amine in water solution to produce the threoninato complex ion has been studied. The rate of reaction is first order in aldehyde and one-half order in each the complex ion and the amine base. These results are consistent with a mechanism involving abstraction by base of an α proton of the glycine moiety followed by reaction of the resulting enolatelike ion with aldehyde.

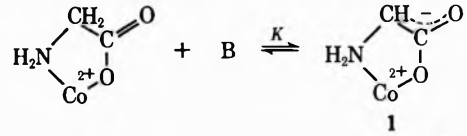
Aldehydes react with glycine coordinated with certain metal ions in the presence of base to produce hydroxy amino acids,[2-6] *e.g.*, eq 1, where en is ethylenediamine and gly and thr are glycine and threonine (allo and

$$(\text{Coen}_2\text{gly})^{2+} + \text{CH}_3\text{CHO} \xrightarrow[\text{H}_2\text{O}]{\text{base}} (\text{Coen}_2\text{thr})^{2+} \qquad (1)$$

threo) anions, respectively, coordinated with cobalt(III). If optically active glycinatobis(ethylenediamine)cobalt(III) ion is treated with acetaldehyde, an asymmetric synthesis of threonine and allothreonine can be effected.[6] The base most commonly used is sodium carbonate. The amino acids are obtained upon cleavage of the ligands from the metal ion.

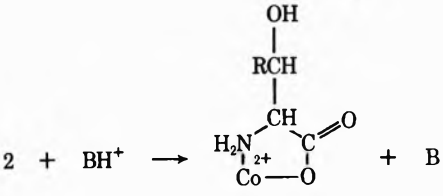
This paper reports the results of a kinetic study of reaction 1 with a tertiary amine, 1,4-diazabicyclo[2.2.2]-octane (dabco), serving as the base and glycinatobis-(ethylenediamine)cobalt(III) chloride and acetaldehyde serving as the reactants. Essentially complete conversion of glycine into the threonines occurs with this base. The results of this study are consistent with the mechanism of eq 2–4 where B is the base and the ethylenediamine ligands are omitted for clarity.

Reaction conditions (Table I) were chosen so that the reaction was pseudo first order in acetaldehyde and such that the competing aldol condensation[7] can be neglected. The spectrophotometric method developed for the determination of aldehyde concentration as a



(2)

(3)



(4)

function of time is described in the Experimental Section. Equation 5 describes the observed rate law at essentially constant ionic strength and chloride ion concentration for the reaction conditions investigated (Table I).

$$\frac{-\text{d}[\text{CH}_3\text{CHO}]}{\text{d}t} = k_1[\text{dabco}]^{1/2}[(\text{Coen}_2\text{gly})\text{Cl}_2]^{1/2}[\text{CH}_3\text{CHO}] \qquad (5)$$

This rate law is related to the above mechanism as shown in eq 6–9; K_B is the basic dissociation constant of

$$\frac{-\text{d}[\text{CH}_3\text{CHO}]}{\text{d}t} = k[\text{CH}_3\text{CHO}][1] \qquad (6)$$

$$= k[\text{CH}_3\text{CHO}]K[(\text{Coen}_2\text{gly})^{2+}][\text{B}]/[\text{BH}^+] \qquad (7)$$

$$[\text{BH}^+] = [^-\text{OH}] + [1] \qquad (8)$$

$$\text{or } [\text{BH}^+]^2 = [\text{B}]\{K_B + K[(\text{Coen}_2\text{gly})^{2+}]\} \qquad (9)$$

dabco. The contribution to $[BH^+]$ from the formation of $CH_3CH(OH)O^-$ can be neglected since the known values at 25° of the hydration constant[7] of acetaldehyde

(1) The support of this work by the U. S. Public Health Service, National Institute of Arthritis and Metabolic Diseases Grant AM 12262, is gratefully acknowledged.

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(6) M. Murakami and K. Takahashi, *ibid.*, **32**, 308 (1959).

(7) R. P. Bell and P. T. McTigue, *J. Chem. Soc.*, 2893 (1960).

TABLE I

RATE DATA FOR REACTION 1 AT 35.00°

Initial concentrations, M						
$[Coen_2gly]Cl_2$	Dabco[b]	CH_3CHO	KCl	10^4k_1,[a] sec^{-1}	$10^4k_1/[dabco]^{1/2}$	$10^4k_1/[(Coen_2gly)Cl_2]^{1/2}$
0.0797	0.379	*Ca.* 1.6×10^{-3}		2.50	41	
0.0797	0.733	*Ca.* 1.6×10^{-3}		3.22	38	
0.0797	1.36	*Ca.* 1.6×10^{-3}		5.52	47	
					Av 42	
0.0797	1.36	*Ca.* 1.6×10^{-3}	1.28	4.84		17
0.0428	1.36	*Ca.* 1×10^{-3}	1.28	3.33		16
0.0214	1.36	*Ca.* 1×10^{-3}	1.28	2.33		16
						Av 16.3

[a] Average of two or three determinations. Maximum deviation from the average for runs without KCl is 6.7%; with KCl, 2.5%. [b] Calculated values of concentration based on density measurements accurate to 1 or 2%.

and the acid dissociation constant[7] of $CH_3CH(OH)_2$ lead to a value much smaller than that[8] of K_B of eq 9. If K_B can be neglected compared with the other term on the right-hand side of eq 9, combination of eq 7 and 9 leads to an equation identical in form with eq 5.

Neglect of K_B in eq 9 requires that the acid dissociation constant for ionization of an α hydrogen of the glycine moiety be two or three orders of magnitude greater than the ion product constant of water. This is reasonable since the dipositive charge on the cobalt atom would be expected to increase the acidity compared with the neutral free ligand.

The concentrations in eq 5 refer to stoichiometric concentrations. Thus the observed pseudo-first-order rate constant will be a function of the hydration constant of acetaldehyde, the ion-pairing constant for glycinatobis(ethylenediamine)cobalt(III) chloride, and the chloride ion concentration. The ion-pair association constant for chloropentaamminecobalt(III) chloride at 25° and zero ionic strength is ten.[9] The same form for the rate equation will be obtained whether or not the ion pair undergoes reaction; this will also be true if hydroxide ion generated from the tertiary amine base and water serves as the base in eq 2.

Ultraviolet spectroscopy indicates that there is no interaction between dabco and the carbonyl group of acetaldehyde. The absorption due to the carbonyl group is the same for 0.019 M acetaldehyde in water containing no, 0.10 M, and 0.73 M dabco, respectively.

Additional evidence for intermediate **1** is found in previous reports by other workers. Nmr deuterium-exchange experiments[10,11] and mutarotation studies[11] have shown the lability of the α hydrogens of the amino acid moiety of $(Coen_2aa)^{2+}$ where aa is the amino acid anion of glycine and other compounds. The rate of exchange of the α hydrogen of alaninatobis(ethylenediamine)cobalt(III) ion in D_2O with NaOD at 34.3° was found[11] to be first order in ^-OD ion and first order in complex ion. These data may be used as follows to show that process 3 is slower than process 2 in the proposed mechanism. If the only function of the dabco were to generate hydroxide ion which then serves as the base in eq 2, then the calculated half-life for the exchange (based on the literature data for the basicity[8] of dabco and the exchange experiments using the alaninato moiety as a model for the glycinato moiety) is less than half of the half-life for the overall reaction with acetaldehyde (Table I). Dabco itself is an effective base for proton removal;[8] *e.g.*, the ratio of the second-order catalytic constants for deuteron abstraction from isobutyraldehyde-2-*d* is $k_{-OH}/k_{dabco} = 4.8$ in water solution at 35°. Since the dabco is in large excess to hydroxide ion in the present system, the half-life for exchange of the α hydrogen of the glycine moiety is expected to be even smaller than that calculated above.

Experimental Section

Materials.—Acetaldehyde was distilled and stored under nitrogen in a refrigerator. It was checked for absence of polymers and acetic acid by infrared spectroscopy before each use. 1,4-Diazabicyclo[2.2.2]octane (Aldrich Chemical Co.) was crystallized from 1:1 methanol–ethyl ether and stored in a desiccator over potassium hydroxide pellets: mp 155.3–158.1° (lit.[12] mp 155–157°). Glycinatobis(ethylenediamine)cobalt(III) chloride monohydrate, a gift of Dr. D. W. Cooke, was crystallized from aqueous ethanol. *Anal.*[13] Calcd for $(Coen_2gly)Cl_2 \cdot H_2O$: C, 21.06; N, 20.47; H, 6.48. Found: C, 21.14; N, 20.67; H, 6.49. Doubly distilled water was used throughout. The concentrations listed in Table I are for ambient temperature and are corrected for volume changes occurring upon mixing.

Reaction Products.—A solution of glycinatobis(ethylenediamine)cobalt(III) chloride monohydrate (0.40 g, 0.0012 mol), 1,4-diazabicyclo[2.2.2]octane (0.22 g, 0.0020 mol), and acetaldehyde (0.67 ml, 0.012 mol) in 25 ml of water was allowed to stand at room temperature for 3 days. Hydrogen sulfide was bubbled through the mixture until the filtrate from filtration of the resulting mixture was no longer orange. The filtrate was concentrated at reduced pressure and placed on a Dowex 50 (100–200 mesh, H form) column. The amino acids were eluted with 1:5 pyridine–water by volume. The eluate totaled 125 ml, the last 50-ml portion of which was alkaline. The eluate was evaporated to dryness by use of reduced pressure and heat. The residue was further purified by redissolving it in water and placing it on an ion-exchange column as above. Elution of the amino acids with 2 N ammonia was begun after the eluate from water elution was no longer colored. The alkaline eluate (50 ml) was evaporated to dryness as before. An nmr spectrum (Varian A-60 spectrometer) of the residue dissolved in deuterium oxide containing sodium 2,2-dimethyl-2-silapentanesulfonate as an internal standard was obtained. The spectrum corresponds to that of a mixture of authentic threonine and allothreonine. No glycine signals are present.[14]

Spectrophotometric Method for Acetaldehyde.—2,4-Dinitrophenylhydrazine (0.025 g), water (5 ml), and concentrated hydrochloric acid (0.1 ml) were dissolved in 95% ethanol to make a final volume of 50 ml to prepare the standard reagent (DNPH reagent). The reagent contained added amounts of concentrated hydrochloric acid (and water) required for neutraliza-

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(11) D. A. Buckingham, L. G. Marzilli, and A. M. Sargeson, *ibid.*, **89**, 5133 (1967).

(12) S. D. Ross, J. J. Bruno, and R. C. Petersen, *ibid.*, **85**, 3999 (1963).

(13) Galbraith Laboratories, Inc., Knoxville, Tenn.

(14) J. C. Dabrowiak of this department has shown that the ratio of authentic glycine:threonine allothreonine remains unchanged upon placement on and elution from the ion-exchange column.

tion of base contained in the aliquots from kinetic runs. The reagent is stable for several days. One milliliter of the DNPH reagent was pipetted into each of 25-ml volumetric flasks. An aliquot of the aldehyde containing solution (for amounts, see kinetic procedure) was added and the solution was allowed to stand for 1 day before dilution with 1:1 95% ethanol–water by volume. The absorbance of the solution at 374 mμ was determined with 1 ml of the DNPH reagent diluted to 25 ml as above serving as the blank solution with a Beckman Model DU spectrophotometer. A small decrease in the absorbance with time occurs; however, if a constant time interval passes from addition of the aldehyde solution until determination of the absorbance, the ratio of aldehyde concentrations in different samples is the same as the corresponding absorbance ratios.

Kinetic Procedure.—Ten milliliters (20 ml for runs listed in last two rows of Table I) of the appropriate dabco solution was pipetted into a polypropylene tube containing the glycinatobis(ethylenediamine)cobalt(III) chloride monohydrate and the resulting solution was equilibrated at 35.00 ± 0.01°. Cold acetaldehyde was transferred by a micropipet to 10 ml of cold dabco solution. One milliliter of this was added to the above equilibrated solution. After 15–20 min of further equilibration, a 1-ml aliquot (2 ml for runs listed in last two rows of Table I) of the reaction mixture was pipetted into a 25-ml volumetric flask containing 1 ml of DNPH reagent and the time was taken as zero time. Aliquots were then taken periodically and added to the DNPH reagent in volumetric flasks, and the absorbance was determined as described above.

Observed "infinity" absorbances were within experimental error of those calculated from the spectra of the complex ions involved. The visible spectrum is changed only slightly when glycine is replaced by threonine;[15,16] since the $(Coen_2gly)^{2+}$ is in large excess to the aldehyde under the reaction conditions, the difference is negligible. Calculated infinity values[17] were used to determine rate constants. The pseudo-first-order rate constants were calculated from the following equation: $\log (A - A_\infty) = -k_1 t/2.303 +$ constant. The slope was calculated by the method of least squares. The reaction was followed to two-thirds complete reaction.

The stability of the reactants under the reaction conditions was tested as follows. Acetaldehyde (*ca.* 2.9×10^{-3} *M*) in 0.96 *M* dabco solution was sampled periodically as described above (except 0.5-ml aliquots were used); an 8% decrease in absorbance occurred after 5 hr. Glycinatobis(ethylenediamine)cobalt(III) chloride monohydrate (0.190 *M*) in 1.36 *M* dabco was held at 35° for 3 days. The visible spectrum of a 1-ml aliquot diluted to 25 ml was identical with that of authentic material.

Registry No.—Acetaldehyde, 75-07-0; glycinatobis(ethylenediamine)cobalt(III) chloride, 14408-57-2.

(15) C. T. Liu and B. E. Douglas, *Inorg. Chem.*, **3**, 1356 (1964).
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(17) Determined from spectra obtained by use of a Cary Model 14 spectrophotometer.

Pyrimidines. IX. A New Synthesis of 8-Azapurines and *v*-Triazolo[4,5-*b*]pyridines[1]

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Received August 4, 1969

The 5-nitropyrimidines **1–5** and the 5-nitropyridines **6** react with sodium azide to furnish the 8-azapurines **14–18** and the *v*-triazolo[4,5-*b*]pyridines **19**, respectively. The first step of this new reaction leading to *v*-triazoles is probably attack of azide ion at position 6 of the 5-nitropyrimidines and -pyridines followed by cyclization and subsequent elimination of the nitro function as nitrous acid. With hydroxide, deuteroxide, and ethoxide ions as the nucleophiles, N-1 substituted derivatives of some of these nitroheterocycles form stable Meisenheimer-type adducts by reaction at position 6. A reaction with deuterium oxide in DMSO-d_6/D_2O concurrent with adduct formation is H–D exchange at position 6 of the N-1 substituted 5-nitro-2-oxo-pyrimidines and -pyridines, **1–3** and **6**. A carbanion mechanism is postulated for these H–D exchange reactions.

The chemistry of *v*-triazolo[4,5-*d*]pyrimidines[2] (8-azapurines) has developed in conjunction with biological studies on the antimetabolite activity of analogs of the nucleic acid purines.[3] Such compounds have been prepared previously by the action of nitrous acid on 4,5-diaminopyrimidines[4,5] and from substituted *v*-triazoles.[6,7] This report describes a new and facile synthesis of some 8-azapurines and 5-oxo-*v*-triazolo[4,5-*b*]-pyridines. The procedure consists of the treatment of certain 5-nitrooxopyrimidines and -pyridines with sodium azide, which results, overall, in the addition of the three-nitrogen fragment of the *v*-triazole ring to the 5,6 positions of the nitropyrimidine or -pyridine followed by elimination of the nitro function as nitrous acid. A preliminary report[8] on this reaction has appeared. The extent and mechanism of this process as well as its practical value are now further elaborated.

Results

The reaction with azide ion was achieved with the following types of compounds (Scheme I): 5-nitrouracils (**1**), 5-nitrocytosines (**2**, Y = NR_2), 4-ethoxy-1-methyl-2-oxo-5-nitropyrimidine (**2h**), 2-oxo-5-nitropyrimidines (**3**), 4-oxo-5-nitropyrimidine (**4**), 2-amino-4-oxo-5-nitropyrimidine (**5**), and 2-oxo-5-nitropyridines (**6**). With compounds **1–3** and **6**, which are not alkylated at N-1, only salt formation between these acidic nitro compounds and the reagent is observed. Therefore ammonium chloride (in slight molar excess relative to the sodium azide) was added to these reaction

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant CA 08748).

(2) For recent reviews on the chemistry of *v*-triazolo[4,5-*d*]pyrimidines, see (a) J. Gut, *Advan. Heterocycl. Chem.*, **1**, 238 (1963); (b) R. K. Robins in "Heterocyclic Compounds," Vol. 8, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1967, p 434.

(3) For leading references on the antimicrobial and antitumor activity by 8-azapurines, see (a) R. E. Handschumacher and A. D. Welch in "The Nucleic Acids," Vol. 3, E. Chargaff and J. N. Davidson, Ed., Academic Press, New York, N. Y., 1960, p 453; (b) H. G. Mandel, *Pharmacol. Rev.*, **11**, 743 (1959); (c) A. Albert and K. Tratt, *J. Chem. Soc., C*, 344 (1968).

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(8) H. U. Blank and J. J. Fox, *J. Amer. Chem. Soc.*, **90**, 7175 (1968).

TABLE I

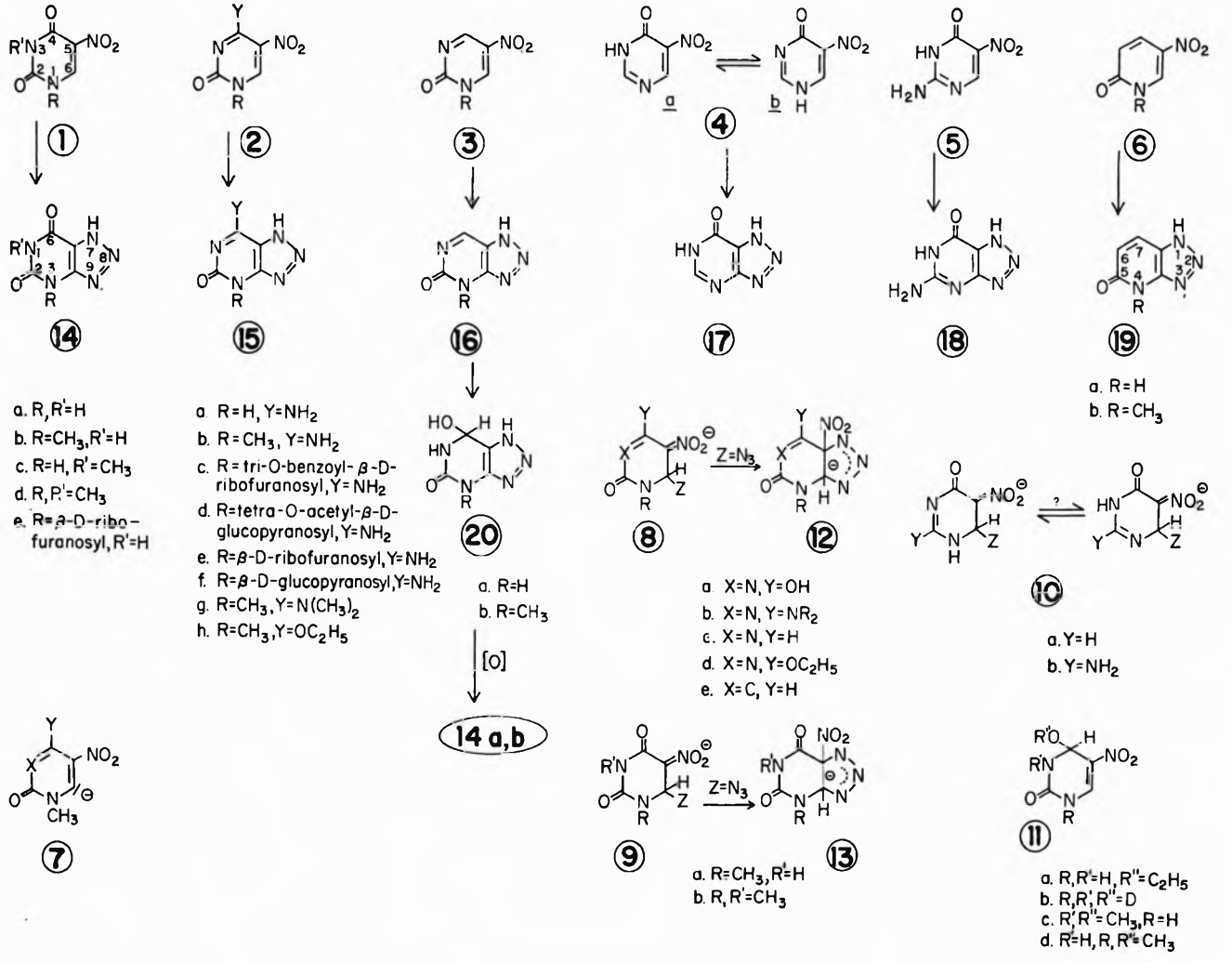
Starting material	Reaction to v-triazolo compounds: Equiv NaN_3 (solvent)	Temp, °C	Time, hr	Yield, %	Products of reaction with NaN_3[a]	Mp, °C (solvent of recrystn)	Uv (in H_2O): pK_a[b]	λ_{max}, mμ	ϵ_{max}	pH	Ionic species[c]
5-Nitrouracil (1a)	4 (DMF)	70	144	86	8-Azaxanthine[d] (14a)	>320 (H_2O)	4.66	263	6,450	2	0
							9.79	265	8,510	7	−
								(235)	(2,360)	13	2−
								285	6,450		
1-Methyl-5-nitrouracil (1b)	1.1 (EtOH)	78	16	86	3-Methyl-8-azaxanthine[d] (14b)	316 dec (50% EtOH) [lit. 313 (H_2O)]	4.42	270	5,370	2	0
							11.37	268	7,080	7	−
								245	8,710	14	2−
								271	10,715		
3-Methyl-5-nitrouracil (1c)	2.6 (DMF)	90	72	44	1-Methyl-8-azaxanthine[d] (14c)	261 (H_2O) [lit. 262 (H_2O)]	4.67	(230)	(4,175)	2	0
							9.85	263	6,310		
								(230)	(3,715)	7	−
								265	8,130		
								(235)	(4,890)	13	2−
								285	6,025		
1,3-Dimethyl-5-nitrouracil (1d)	1.2 (EtOH)	78	14	95	1,3-Dimethyl-8-azaxanthine[d] (14d)	258–260 (H_2O) [lit. 260 (H_2O)]	4.47	(230)	(3,980)	2	0
	1.3 (DMF)	24	16	83				271	6,310		
	1.3 (CH_3CN)	82	72	94				(230)	(4,170)	7	−
	1.4 (HMPT)	60	0.7	85				269	8,510		
5-Nitrouridine[e] (1e)	1.3 (DMF)	24	16	81	3-β-D-Ribofuranosyl-8-azaxanthine (14e) ($C_9H_{11}N_5O_6 \cdot H_2O$)	164–166 dec (H_2O)	4.13	263	7,510	0.3	0
							10.31	264	9,820	6	−
								242.5	10,230	12	2−
								268	11,170		
5-Nitrocytosine (2a)	2 (DMF)	90	72	50	6-Amino-2-oxo-8-azapurine[f] (15a)	>320 (6 *N* HCl) (lit. no mp)		277	2,330	2	
								250	6,310	6.7	
								277	9,035		
								250	7,450	8.6	
								277	9,375		
1-Methyl-5-nitrocytosine (2b)	2.5 (DMF)	90	3.5	77	6-Amino-3-methyl-2-oxo-8-azapurine (15b) ($C_6H_6N_6O$)	>360 (H_2O)	2.67	(235)	(4,635)	0	+
							5.93	285	7,260		
								(250)	(3,820)	4	0
								284	9,310		
								250	9,150	12	−
								281	10,030		
1-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5-nitrocytosine[g] (2c)	2 (DMF)	75	3	62	6-Amino-3-(tri-*O*-benzoyl-β-D-ribofuranosyl)-2-oxo-8-azapurine (15c) ($C_{36}H_{24}N_6O_8$)	219–221 dec (EtOH)					
1-(Tetra-*o*-acetyl-β-D-glucopyranosyl)-5-nitrocytosine[g] (2d)	4.5 (DMF)	70	4	75	6-Amino-3-(tetra-*O*-acetyl-β-D-glucopyranosyl)-2-oxo-8-azapurine ((15d) ($C_{18}H_{22}N_6O_{10}$)	230 dec (EtOH)					
5-Nitrocytidine[g] (2e)	2 (DMF)	85	7.5	78	6-Amino-3-β-D-ribofuranosyl-2-oxo-8-azapurine (15e) [$C_9H_{12}N_6O_6 \cdot {}^1/_2H_2O$]	>230 dec (H_2O)	2.65	278	8,210	0	+
							5.26	~340	330		
								(250)	(5,030)	4	0
								282	9,870		
								248	10,760	8	−
								279	10,270		
1-β-D-Glucopyranosyl-5-nitrocytosine[g] (2f)	By deacylation of 2d			66	6-Amino-3-β-D-glucopyranosyl-2-oxo-8-azapurine (15f) ($C_{10}H_{14}N_6O_6 \cdot 2H_2O$)	>230 dec (H_2O)					
4-Dimethylamino-1-methyl-5-nitro-2-oxopyrimidine[h] (2g)	3.0 (DMF)	75	3.5	87	6-Dimethylamino-3-methyl-2-oxo-8-azapurine (15g) ($C_7H_{10}N_6O$)	343–344 (H_2O)	2.71	289	9,650	0	+
							5.71	(225)	(8,760)		
								288	12,120	3.8	0
								258	12,760	7	−
								284	13,560		
4-Ethoxy-1-methyl-5-nitro-2-oxopyrimidine[h] (2h)	1.1 (DMF)	85–95	6	68	6-Ethoxy-3-methyl-2-oxo-8-azapurine (15h) ($C_7H_8N_6O_2$)	219–220 (H_2O)		268	8,025	7[i]	
1-Methyl-5-nitro-2-oxopyrimidine[j] (3b)	1.7 (DMF)	70–75	22	>50[k]	3-Methyl-2-oxo-8-azapurine (16b) ($C_6H_6N_6O$) *and* 6-hydroxy-3-methyl-2-oxo-1,6-dihydro-8-azapurine (20b) ($C_6H_7N_6O_2$)	311 dec (H_2O)	−1.22	262	3,790	12 *N* HCl	+
	1.2 [HMPT–CH_3CN (1:5)]	Reflux	48	25			5.57[l]	319	6,000		
								245	7,070	2	0
								290	520		
								(270)	(4,740)	7.5	−
								310	9,110		
5-Nitro-4-oxopyrimidine[m] (4)	2.2 (HMPT)	125–140	26	1.7	8-Azahypoxanthine[n] (17)	>305 dec [lit. 308 (exptl)]	5.16	253	8,710	2	0
							10.78	259.5	9,120	8	−
								270	10,230	13	2−
2-Amino-5-nitro-4-oxopyrimidine (5)	2.4 (HMPT)	130–150	20	<1	8-Azaguanine[f] (18)		−1.04	247	11,220	3.8	0
							6.54	266	6,760		
								214	21,890	8.8	−
								244	5,760		
								278	6,030		
5-Nitro-2-oxopyridine (6a)	2 (DMF)	100	60	12	5-Oxo-v-triazolo[4,5-*b*]pyridine[o] (19a)	280 dec (H_2O) (lit. 280–282 dec)	5.90	235	3,140	0	0
							11.08	(291)	(11,190)		
								305	11,430		
								(262)	(2,200)	7	−
								315	13,850		
								260	3,110	14	2−
								312	10,600		
								~363	755		

TABLE I (*Continued*)

Starting material	Reaction to *v*-triazolo compounds: Equiv NaN_3 (solvent)	Temp, C°	Time, hr	Yield, %	Products of reaction with NaN_3[a]	Mp, °C (solvent of recrystn)	pK_a[b]	Uv (in H_2O) λ_{max}, mμ	ϵ_{max}	pH	Ionic species[c]
1-Methyl-5-nitro-2-oxopyridine (6b)	1.2 (DMF)	120 then 80	2 24	69	4-Methyl-5-oxo-*v*-triazolo[4,5-*b*]pyridine (19b)	276–278 dec (H_2O)	5.90	245 305 262.5	3,565 10,960 3,050	0 10	0 –
	2 (DMSO)	80	96	47	($C_6H_6N_4O$)			314	14,090		

[a] All new compounds reported herein with formulas gave satisfactory C, H, and N analyses. [b] Values for new compounds were obtained at 23.5 ± 0.5° and are accurate to ±0.05 pH unit except for **19a** and **19b**, for which the spread averaged ±0.1 pH unit. [c] Cationic species (+), neutral (0), anionic (−), dianionic (2−). [d] Alternate synthesis reported: G. Nubel and W. Pfleiderer, *Chem. Ber.*, **98**, 1060 (1965). p*K* values and uv data taken from this reference. [e] I. Wempen, I. L. Doerr, L. Kaplan, and J. J. Fox, *J. Amer. Chem. Soc.*, **82**, 1624 (1960); K. A. Watanabe and J. J. Fox, *J. Heterocycl. Chem.*, **6**, 109 (1969). [f] Alternate synthesis: L. F. Cavalieri, A. Bendich, J. F. Tinker, and G. B. Brown, *J. Amer. Chem. Soc.*, **70**, 3875 (1948). Uv data for **15a** taken from this reference. Uv data for **18** taken from ref 9. [g] J. J. Fox and D. van Praag, *J. Org. Chem.*, **26**, 526 (1961). [h] I. Wempen, D. van Praag, and J. J. Fox, unpublished results. [i] At acidic and basic pH values decomposition occurs, probably by conversion into 3-methyl-8-azaxanthine (**14b**). [j] L. M. Stempel, G. B. Brown, and J. J. Fox, Abstracts, 145th National Meeting of the American Chemical Society, New York, N. Y., Sept 1963, p 14–O. [k] Calculated on the basis of isolated 3-methyl-8-azaxanthine (**14b**) (*cf.* text for the oxidation of **20b** to **14b** by means of iodide). [l] Equilibrium constant; see text. Ionic species data: cation refers to **16b**, neutral species to **20b**, anion to **16b**. [m] See I. Wempen, H. U. Blank, and J. J. Fox, *J. Heterocycl. Chem.*, **6**, 593 (1969). [n] See ref 4 for alternate synthesis. Uv data from ref 3c. [o] H. Graboyes and A. R. Day, *J. Amer. Chem. Soc.*, **79**, 6421 (1957).

SCHEME I



mixtures to favor the neutral, undissociated 5-nitroheterocycles in the lactam form. Under these conditions reaction with azide does take place. No addition reaction with azide occurred with 1,3,6-trimethyl-5-nitrouracil, 2,4-diethoxy-5-nitropyrimidine, 2-ethoxy-5-nitropyrimidine, or 2-ethoxy-3-nitropyridine. Instead, sodium azide acted as a base with traces of water which may have been present in the solvent (DMF) to catalyze the slow hydrolysis of the latter two ethoxy derivatives to the corresponding oxonitroheterocycles.

Good to excellent yields of the 8-azapurine derivatives were obtained in the reaction of azide ion with 5-nitrouracils (**1**), 5-nitrocytosines (**2**), 2-oxopyrimidines (**3**), and even 5-nitro-2-oxopyridines (**6**), the latter of which should be less activated owing to the absence of one ring nitrogen. On the other hand, 5-nitro-4-oxopyrimidine (**4**) yielded only a small amount of

TABLE II

REACTIVITIES OF CERTAIN 5-NITRO-2-OXOPYRIMIDINES AND -PYRIDINES WITH NaN_3[a]

Reaction	Reaction temp, °C	Product formed, % (accuracy ± 4%)	Time, hr	Remarks
1d ⟶ 14d	Room	25	1.6	No decomposition or side reaction observed
	Room	53.5	19.7	
	Room	78	95.3	
	Room	>95	360.0	
3b ⟶ 16b	Room	None	15.0	A constant amount of adduct (*ca.* 10%) is observed in the mixture (see text)
	37	6	1.5	*Ca.* 13% adduct
	37	46	68.6	No adduct; some decomposition
6b ⟶ 19b	60	None	2.0	No decomposition or side reaction detectable
	100	None	0.5	
	120–122	29	1.7	
	120–122	40	4.0	
	120–122	58	9.6	
	120–122	67	18.0	

[a] The reactions were monitored by nmr spectroscopy in DMSO-d_6 (0.3 m). Each reaction solution contained 0.11 mmol of reactants. The relative insolubility of sodium azide in DMSO precluded the use of an excess of this reagent.

8-azahypoxanthine, and from compound **5** only a trace amount of 8-azaguanine was detected. Moreover, the N-1 alkylated derivatives of **1**–**3** and **6** usually afforded better yields of the corresponding 8-azapurines or *v*-triazolopyridines than did those without an alkyl substituent at N-1.

The formation of 8-azaguanine (**18**) from 5-nitrocytosine (**5**) was demonstrated by paper chromatography in four different solvent systems using for a comparison a commercial sample of **18**. Only traces of **18** could be detected in the very complex reaction mixture. No attempt was made to isolate **18** from this reaction mixture.

3-Methyl-2-oxo-8-azapurine (**16b**) formed a covalent hydrate (**20b**) across the 1,6 double bond by addition of water. Albert[9] had shown that 2-oxo-8-azapurine itself also forms the same type of hydrate. Attempts to crystallize pure **20b** from a mixture of **16b** and **20b** under varying conditions of pH were unsuccessful. The structure of **16b** was proved by uv and nmr spectroscopy[8] and by measurement of the equilibrium constant (5.57 ± 0.05) for the anion of **16b** ⇌ adduct **20b**. This value is in fair agreement with that determined by Albert[9] for **16a**. Conclusive proof of the structure **16b** ⇌ **20b** was obtained by oxidation of this mixture with iodine at pH 8 to the known 3-methyl-8-azaxanthine (**14b**).

The reactions with azide ion described herein were run in a variety of solvents, such as ethanol, acetonitrile, DMF, DMSO, and hexamethylphosphorotriamide (HMPT), as shown in Table I, along with other reaction conditions. The reactions were monitored by paper chromatography and by uv spectroscopy. From these data, as well as from practical considerations, DMF is the most convenient solvent.

A semiquantitative nmr study was done to compare the reactivities of 1,3-dimethyl-5-nitrouracil (**1d**) and 1-methyl-5-nitro-2-oxopyrimidine and -pyridine (**3b** and **6b**) with azide ion to their corresponding *v*-triazoles (**14d**, **16b**, and **19b**), as shown in Table II. Only for the reaction of **3b** to **16b** was an intermediate detected by a signal at δ 5.83. The structure of this intermediate will be discussed below. In the case of **1d** and **6b**, the nmr spectrum showed only the signals for the end products (**14d** and **19b**). These signals appeared at the same rate at which those for starting materials disappeared. The reaction was followed by observing the decrease of the H-6 signal. In the cases of **3b** and **6b** one observes also alteration in chemical shifts and a lowering in multiplicity as H-4 of **3b** and H-3 and H-4 of **6b** are converted into H-6 of **16b** and H-6 and H-7 of **19b**.

Intermediacy of Adducts.—During the reaction of **3b** to **16b** a compound which differed from starting material or end product in having a proton signal at δ 5.83 (*cf.* Table II) was detected by nmr spectroscopy. This signal is best explained by compound **8c** (Z = N_3), which is the sodium azide adduct of **3b**. That **8c** is the correct structure for this intermediate is based first on the existence of the analogous adducts of type **8** and **9** (Z = OH, OD, OEt),[10] as discussed below, and secondly on the fact that the H-6 signals of these stable adducts are all in the same region of δ 5.69–5.92 (see Table III). Evidence that adducts of type **8** and **9** (Z = OH, OD, OEt) are easily formed in solution and are sometimes isolable in crystalline form is as follows:

(A) Compound **9b** (Z = OC_2H_5) had been isolated as a stable sodium salt by Pfleiderer and Mosthof,[12] and this is probably one of the first examples of a crystalline Meisenheimer-type[13] adduct in the heterocyclic series.[14] In addition, evidence for the existence of **9b** (Z = OH) as a stable compound in alkaline solution is derived from the following fact. A "pK_a

(9) A. Albert, *J. Chem. Soc., B*, 427 (1966).

(10) In addition to hydroxide, deuteroxide, or ethoxide ion, other nucleophilic agents also attack at position 6 of some of these 5-nitroheterocycles. For example, treatment of 1,3-dimethyl-5-nitrouracil (**1d**) with some amines furnished compounds **9b** (Z = NH_2, $HNCH_2C_6H_5$, $HNNH_2$) as shown by nmr and uv spectroscopy.[11] These amine adducts are very labile, and hydrolyze easily with traces of water back to the starting material.

(11) H. U. Blank and J. J. Fox, unpublished results.

(12) W. Pfleiderer and H. Mosthof, *Chem. Ber.*, **90**, 728 (1957).

(13) For information about Meisenheimer adducts and related compounds, see R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966).

(14) Recently, it was shown that 2- and 4-methoxy-3,5-dinitropyridines and 2- and 4-methoxy-5-nitropyrimidines also form Meisenheimer-type compounds both at methoxyl- and hydrogen-bearing ring positions.[15]

(15) G. Illuminati and F. Stegel, *Tetrahedron Lett.*, 4169 (1968).

Table III

Reactions with NaOR[a]

Starting material	Conditions[b]	$t_{1/2}$ for H-6 → D-6	Adduct[c] in mixture (%)	Nmr signals of adducts[d] (starting materials), δ ppm
1b	A		**9a**, Z = OD (10)	H-6, 5.80 (9.24) CH_3, 2.90 (3.41)
1d	A	~3 days	**9b**, Z = OD (75)	H-6, 5.82 (9.28) CH_3, 3.00, 2.94 (3.48, 3.21)
	C		**9b**, Z = OEt (100)	H-6, 5.86 (9.28) CH_3, 2.99 (3.48, 3.21)
1e	B		Type **9a** Z = OD (20)	H-6, 5.86 (9.58)
2b	B	~60 min	**8b**, Z = OD (55)	H-6, 5.69 (9.25) CH_3, 2.90 (3.43)
2g	B	~60 min	**8b**, Z = OD (50)	H-6, 5.92 (9.01)
2h	B	>90% exchange in 25 min	**8d**, Z = OD (75)	H-6, 5.73 (9.32) CH_3, 2.87 (3.49)
3b	B	Slow dec	**8c**, Z = OD (>98)	H-4, 8.24 (9.17) H-6, 5.79 (9.49) CH_3, 2.93 (3.59) $J_{4,6}$ = 1.3 (3.5) Hz
	D		**11d**[b] (35)	H-6, 8.52 (9.49) H-4, 5.63, 5.57 (9.17) $J_{4,6}$ = 1.3 (3.5) Hz
6b	B	~3 min	**8e**, Z = OD (>95)	H-3, 5.13 (6.49) H-4, 7.34 (8.16) H-6, 5.89 (9.17) CH_3, 2.92 (3.57) $J_{3,4}$ = 9.5 (10) Hz $J_{4,6}$ <2 (3.2) Hz

[a] Qualitative data are given for the H–D exchange at position C-6 of some of these compounds and for the formation of some Meisenheimer-type adducts together with nmr data for these adducts. [b] Conditions were as follows. (A, B) The 5-nitroheterocycle (15 mg) was dissolved in DMSO-d_6 (0.5 ml). Two drops of 10% NaOD (A) or 20% NaOD (B) were then added to this solution. The data in columns 3–5 were obtained from the nmr spectrum of the resulting mixture of starting material and adduct. (C) The solid sodium ethylate adduct of **1d** (15 mg) was dissolved in DMSO-d_6 (0.5 ml). (D) Recrystallization of **3b** from methanol furnished a mixture of **3b** and a covalent methanol adduct to which structure **11d** is ascribed by analogy to the ethanol adduct **11a**. Footnote *m*, Table I. Another possible structure could be **11c**. The spectrum was taken in DMSO-d_6. [c] The percentage of Meisenheimer-type adduct given is calculated mainly from the intensity of the methyl signals of adduct and nonadduct and including material which may already have deuterium at position C-6 (*cf.* Scheme II). [d] The δ values given refer to TMS as internal standard. The δ values given in parentheses refer to the respective starting materials. Coupling constants (J) are expressed in hertz. In all cases nmr spectroscopy was done by adding 2 drops of 10% or 20% NaOD to a solution of **1–3** or **6** in DMSO-d_6.

value" (9.01 ± 0.04) was found[16] for 1,3-dimethyl-5-nitrouracil (**1d**) which is really an equilibrium constant for the reversible addition of water to the 5,6 double bond of **1d** in alkaline solution, resulting directly in **9b** (Z = OH).[16] The structure of compound **9b** (Z = OEt and Z = OD) has been proved unambiguously by nmr spectroscopy in DMSO-d_6. The value for H-6 in **1d** of δ 9.28 drops to δ 5.86 in **9b** (Z = OEt) and δ 5.82 in **9b** (Z = OD).

(B) Recently, a related type of adduct has been described, namely, the ethanol and the D_2O adducts of 2-oxo-5-nitropyrimidine (**3a**), formulated as **11a** and **11b**.[17]

(C) Nmr spectroscopy directly proves the formation of **9a** (Z = OD) (or **8a**),[18] **8b** [R = CH_3, Z = OD, Y = NH_2 or $N(CH_3)_2$], **8c** (R = CH_3, Z = OD), **8d** (R = CH_3, Z = OD), and **8e** (R = CH_3, Z = OD) starting from the appropriate compounds **1**, **2**, **3**, and **6**, respectively. The initial spectrum of these compounds in DMSO-d_6 changed drastically by addition of base, leading to a mixture of starting material together with varying proportions of the corresponding base adducts **8** or **9**. The observed chemical shifts for H-6 of the neutral nitropyrimidines and -pyridines and of their base adducts (**8** or **9**) are given in Table III together with a rough estimate of the relative composition of the mixtures.[19]

(D) The formation of **8b** (R = CH_3, Y = NH_2, Z = OH) and **8b** (R = CH_3, Y = $N(CH_3)_2$, Z = OH) is also proved and can be quantitatively measured by "pK" determination: 3-methyl-5-nitrocytosine (**2b**) and 5-nitrocytidine (**2e**) give, in the alkaline region, spectral shifts which were attributed to an acidic dissociation.[20,21] Brown[20] estimated this "acidic pK_a value" of 1-methyl-5-nitrocytosine (**2b**) to be 10.57 ± 0.03 and attributed this pK_a to dissociation of the 4-amino group. However, 1-methyl-4-dimethylamino-5-nitro-2-oxopyrimidine (**2g**) also had a "pK_a" value of 9.04 ± 0.05,[22] which is of the same magnitude as that of 1,3-dimethyl-5-nitrouracil. These data, together with the nmr evidence previously discussed, make it clear that, in aqueous base, nucleophilic attack at C-6 generally occurs with compounds **2** to furnish

(16) W. Pfleiderer and H. Braun, personal communication, from University of Konstanz, Germany.

(17) I. Wempen, H. U. Blank, and J. J. Fox, *J. Heterocycl. Chem.*, **6**, 593 (1969).

(18) Compounds **8a** and **9a** are different tautomeric forms of the same compound, probably **9a** being slightly favored.

(19) In some cases these mixtures slowly decomposed with time.

(20) D. J. Brown, *J. Appl. Chem.*, **9**, 203 (1959).

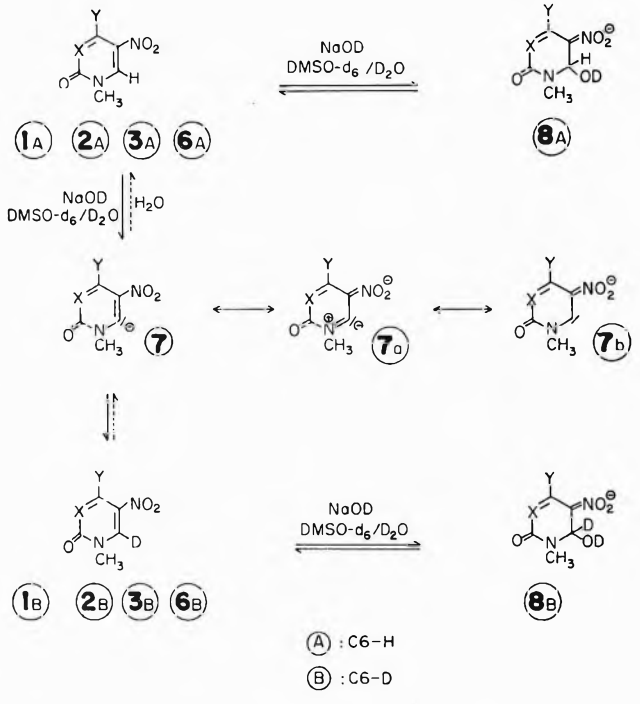
(21) J. J. Fox and D. van Praag, *J. Org. Chem.*, **26**, 526 (1961).

(22) J. J. Fox, I. Wempen, and D. van Praag, unpublished results.

anions **8b** (Z = OH). As described previously in the case of 1,3-dimethyl-5-nitrouracil (**1d**), the "pK_a" values for **2b**, **2e**, and **2g** represent the equilibrium constant for the reversible addition of water across the 5,6 double bond, leading to "acinitro" anions of type **8b** (Z = OH).

H–D Exchange at Position C-6.—Concomitant with the attack of the deuteroxide ion at position 6 of compounds **1–3** and **6** in DMSO-d_6 leading to **8** and **9**, a competitive reaction is observed (Scheme II): all

SCHEME II



these compounds more or less readily exchange the proton at C-6. This H–D exchange could occur starting from adducts **8A** or from **1A–3A**, and **6A**, respectively. Both types of compounds are present in the exchanging medium. The acidity of H-6 in the adducts of type **8** and **9** should be considerably less than that for H-6 of the respective starting materials **1A–3A** and **6A** for two reasons: first, the adducts are negatively charged; and secondly, the C-6–H bonds of the adduct have lower s character than the C-6–H bonds of the neutral starting materials. For these reasons we suggest the mechanism outlined in Scheme II, with **1A–3A** and **6A** being the reactive species involved in the H–D exchange reaction. (For **9b** a similar scheme can be written.) This mechanism postulates carbanions **7** as intermediates. Scheme II also offers a plausible explanation for the fact that H–D exchange is greatly depressed in certain cases such as **1d** and **3d** (*cf.* Table III). Thus strong mesomeric effects favor a high rate of formation and a high stability of the addition compounds **8** and **9**, thereby suppressing the H–D exchange reactions in certain cases. A similar explanation is given by Buncel, *et al.*,[23] to rationalize the fact that the base-catalyzed H–D exchange in 1,3,5-trinitrobenzene is more difficult than in 1,3-dinitrobenzene. A carbanion mechanism is also preferred by other workers in the case of base-catalyzed H–D exchange reactions. Thus the base-catalyzed H–D exchange of nitro aromatics[23,24] and of some heterocycles like pyridine N-oxides, N-methyl-2- and -4-pyridones, N-methylpyrimidones, and pyridinium salts,[25] which exchange most rapidly at the positions adjacent to the activating substituents or to the ring nitrogen, is believed to proceed by a carbanion mechanism.

In general, the reactions of **1–3** and **6** with base seem to be the result of two types of activation: for the direct attack at C-6, furnishing the Meisenheimer-type adducts, *mesomeric effects* of the substituents in *ortho* and *para* positions are most important for the rate of formation and for the stability of these adducts. In the case of H–D exchange, where attack is on hydrogen, mesomeric effects become much less important than *inductive effects*.[26] The activating inductive effect on C-6–H by N-1 and 5-NO_2 should be roughly in the same order of magnitude for all these compounds, whereas the activating mesomeric effect at C-6 shows greater variation.

Discussion

The experimental facts presented strongly support our postulated reaction mechanism[8] for the conversion of the 5-nitropyrimidines **1–3** and 5-nitropyridines **6** to *v*-triazolo compounds. Thus the first and most important step is the nucleophilic attack by azide ion on position 6 of these compounds, which would lead initially to intermediates **8** and **9**. These would then cyclize easily to the unstable intermediates **12** and **13**, respectively. Finally, these unstable intermediates then eliminate HNO_2, irreversibly, leading to the anions of the *v*-triazolo[4,5-*d*]pyrimidines **14–16** and to the *v*-triazolo[4,5-*b*]pyridines **19**. For the reaction of **4** and **5** with sodium azide, which afforded **17** and **18**, the conclusion is drawn by analogy that compounds **10a** and **10b**, respectively, are intermediates. This ionic mechanism is based first on analogies between the reactions of **1–3** and **6** with azide ion and with hydroxide, deuteroxide, and ethoxide: only compounds which easily form the stable Meisenheimer-type adducts **8** and **9** (Z = OH, OD, OEt) give good yields of 8-azapurines in the azide reaction. Second, the observed intermediate with the C–H signal at δ 5.83 should have structure **8c** as described above and not the alternative structure **12c**. Finally, certain trinitrobenzene derivatives react with azide ion to form stable addition complexes[27] analogous to Meisenheimer-type compounds.

An alternative mechanism would be a concerted reaction. This possibility is considered unlikely. In addition to the facts discussed above concerning the electrophilic reactivity of position 6 of these nitroheterocycles, the reactivity of azide ion itself points toward a nucleophilic reaction of azide *ion* in the first step of this reaction. To our best knowledge, no

(23) E. Buncel, A. R. Norris, and K. E. Russell, *Quart. Rev.* (London), **22**, 123 (1968).

(24) E. Buncel and A. W. Zabel, *J. Amer. Chem. Soc.*, **89**, 3082 (1967).

(25) (a) R. A. Abramovitch, G. M. Singer, and A. R. Vinutha, *Chem. Commun.*, 55 (1967); (b) J. A. Zoltweicz, G. M. Kauffman, and C. L. Smith, *J. Amer. Chem. Soc.*, **90**, 5939 (1968); (c) P. Beak and J. Bonham, *ibid.*, **87**, 3365 (1965); P. Beak and E. Monroe, *J. Org. Chem.*, **34**, 589 (1969).

(26) A. Streitwieser, Jr., and J. H. Hammons, *Progr. Phys. Org. Chem.*, **3**, 41 (1965), and leading references therein.

(27) P. Caveng and H. Zollinger, *Helv. Chim. Acta*, **50**, 861 (1967).

concerted reactions of this strong nucleophile, azide *ion*, are known.[28]

Another reaction leading to *v*-triazolo derivatives is worthy of mention. Meek and Fowler[29] showed that reaction of sodium azide with 1,2-di-*p*-toluenesulfonylethylene yielded 4(5)-tosyl-*v*-triazole. Their reaction proceeds first by *substitution* of tosyl by azide followed by *cyclization* and tautomerism to a *v*-triazole, whereas in our case the first step is a nucleophilic *addition* followed by a *cyclization*, etc. Their reaction therefore is quite different. It should also be noted that Rembarz, *et al.*,[30] and Callaghan, *et al.*,[31] have observed the elimination of nitrous acid from certain *v*-triazolines to form *v*-triazoles.

Brief mention should be made of the scope and limitations of the reaction of 5-nitroheterocycles with azide ion. Since most of the starting materials used in this study are commercially available or can be prepared easily,[32] this method should be more economical and facile for the syntheses of some known *v*-triazolo derivatives. Moreover, by this procedure some interesting new compounds have been prepared (see Table I), especially compounds **14e** and **15e**, which are new nucleoside analogs. These latter compounds may be viewed either as 5,6-disubstituted pyrimidine nucleosides or as 3-glycosyl-8-azapurines.

From experimental observations, it appears that in both the 5-nitropyrimidine and -pyridine series an oxo[33] substituent in the 2 or 4 positions must be present in the starting material for reaction with azide ion. Such a substituent functions as an additional activating group and prevents cyclic delocalization of the π-electron system in these compounds. The 5,6 double bond in the reactive compounds therefore can be characterized as being localized and highly activated by both a nitro and an oxo group, and also by the fact that in all cases except **5**, the mesomeric system, which causes that activation, ends at position 6. In the excepted compound **5**, in which the proton probably resides on N-3 and not on N-1, the mesomeric system extends to C-2. In the case of 5-nitro-4-oxopyrimidine (**4**), both tautomeric forms, **4a** and **4b**,[34] should be present in the reaction mixture, with **4b** probably being the more reactive species in the reaction with azide ion. Experimentally the importance of the final above-mentioned point became apparent. All compounds with a 2-oxo substituent furnished 8-azapurines in good yields, whereas 2-amino-, 2-ethoxy-, or 2-unsubstituted 5-nitropyrimidines or -pyridines gave only poor yields or did not react to form 8-azapurines at all. On the other hand, 4-ethoxy-1-methyl-2-oxo-5-nitropyrimidine (**2h**) reacted with relative ease with sodium azide to afford the 8-azapurine derivative (**15h**). This latter example demonstrates that in this case attack of azide ion at position 6 is favored over substitution at C-4. Theoretically, an alternative reaction might have been a reversible nucleophilic attack at position 4 of **2h** with subsequent substitution of the ethoxide group by azido; however, this substitution reaction was not observed experimentally.

The structures of all known compounds synthesized herein were established by comparison of their ultraviolet spectral characteristics or other physical data with reported values (see Table I). The 3-ribosyl derivative of 8-azaxanthine (**14e**) was established by the similarity of its uv spectrum as a function of pH with that for 3-methyl-8-azaxanthine (**1b**).[36] For compounds **15b** and **15g**, the uv data of Cavalieri, *et al.*,[37] on 8-azaisoguanine (**15a**) was used for comparison. In addition, the structures were confirmed by pK_a data (spectrophotometrically determined) and by nmr analyses. Some of these data are included in Table I.

Experimental Section

Melting points were determined on a Thomas–Hoover apparatus (capillary method) and are corrected. The nmr spectra were determined on a Varian A-60 spectrometer using DMSO-d_6 as solvent and tetramethylsilane as internal reference. The uv spectra were determined on a Cary Model 15 spectrometer; the apparent pK_a values were determined spectrophotometrically using buffers and techniques previously described.[38] Paper chromatography was performed on Schleicher and Schuell paper No. 597 in the following systems: (A) 4% sodium citrate solution (descending); (B) 3% ammonium chloride solution (descending); (C) acetonitrile–water–concentrated ammonium hydroxide (7:2:1, ascending); (D) *t*-butyl alcohol–methyl ethyl ketone–50% formic acid (40:30:30, ascending). The compounds were visualized on the developed chromatograms under uv light. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and by Galbraith Laboratories, Inc., Knoxville, Tenn.

General Procedure.—The nitroheterocycle (0.001 mol) and finely powdered sodium azide (0.0015–0.003 mol) were suspended in 10–15 ml of DMF. (In the case of starting compounds which were unsubstituted at N-1, ammonium chloride, in slight molar excess over the sodium azide, was added.) The mixture was stirred and heated where necessary. The progress of the reaction was monitored spectrophotometrically by adjusting the pH of an aliquot to *ca.* 12 and observing the disappearance of the uv maximum in the 330–370-mμ region and the rise of a new maximum in the 270–320-mμ region. After the reaction was complete, the DMF was removed by evaporation *in vacuo*. The dry residue was dissolved in hot water and acidified to pH 3–4 with HCl or acetic acid. In many cases, the precipitated product was chromatographically pure. Recrystallization or fractional crystallization from H_2O or ethanol was necessitated with impure products. The purity of all products was established by paper chromatography in four systems. In Table I data are presented regarding reaction temperatures and times, solvents used, yields obtained, and solvents of recrystallization together with physical values for compounds shown in Scheme I.

Registry No.—Adduct **8b** of **2b** (Z = OD), 12407-92-0; adduct **8c** of **3b** (Z = OD), 12407-95-3; adduct **8d** of **2h** (Z = OD), 12407-91-9; adduct **8e** of **6b** (Z =

(28) Concerted reaction mechanisms have been demonstrated for *neutral* azides, RN$_3$. See R. Huisgen, *Angew. Chem. Intern. Ed. Engl.*, **2**, 565, 633 (1963), for a review.

(29) J. S. Meek and J. S. Fowler, *J. Amer. Chem. Soc.*, **89**, 1967 (1967).

(30) G. Rembarz, B. Kirchhoff, and G. Dongowski, *J. Prakt. Chem.*, **33**, 199 (1966).

(31) P. D. Callaghan and M. S. Gibson, *Chem. Commun.*, 918 (1967).

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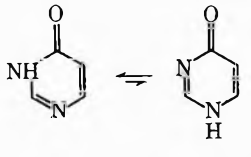
(33) Though thiono analogs of the oxopyrimidines discussed herein have not been studied, it is possible that they, too, would serve in this reaction.

(34) For pyrimidone-4 the equilibrium is roughly known: log $K_{o,p}$ = 0.18 calculated by the pK method and 0.40 as determined from uv data.[35]



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OD), 12407-89-5; adduct **9a** of **1b** (Z = OD), 12407-88-4; adduct **9a** of **1e** (Z = OD), 12407-94-2; adduct **9b** of **1d** (Z = OD), 12407-90-8; adduct **9b** of **1d** (Z = OEt), 12407-93-1; **11d**, 23430-66-2; **14a**, 1468-26-4; **14b**, 2083-04-7; **14c**, 2083-05-8; **14d**, 2278-15-1; **14e**, 22855-06-7; **15a**, 4730-46-5; **15b**, 23430-72-0; **15c**, 23110-95-4; **15d**, 22855-07-8; **15e**, 22855-08-9; **15f**, 22855-09-0; **15g**, 23465-14-7; **15h**, 23430-73-1; **16b**, 22699-23-6; **17**, 2683-90-1; **18**, 134-58-7; **19a**, 23431-04-1; **19b**, 22699-22-5; **20b**, 22699-24-7.

Pyridazines. XXXIII. Valence Isomerizations of Some Tetrazolo[1,5-*b*]pyridazines

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Received October 14, 1969

Several examples of valence isomerizations of fused tetrazolo rings of different tetrazolo[1,5-*b*]pyridazines and related systems into azido functions are presented. Valence isomerization could be induced by forming a new fused five- or six-membered hetero ring or by N oxidation.

Recently, we were able to show that fusion of an azolo ring, involving a pyridazine ring nitrogen at the bridgehead of the bicyclic system, caused spontaneous valence isomerization of tetrazolo[1,5-*b*]pyridazines into the corresponding azidopyridazines.[1-3]

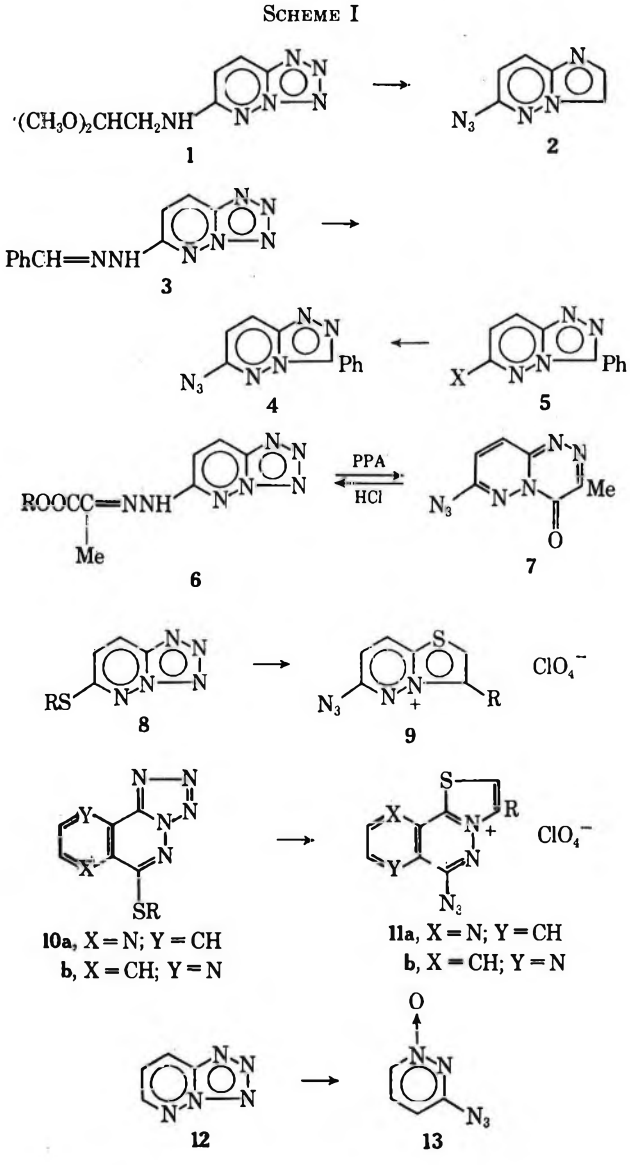
In order to test the generality of such valence isomerizations in the tetrazolopyridazine series, further experiments have been performed which include the formation of a fused azole or azine ring, a sulfur-containing five-membered ring, or an introduction of a N-oxide function.

Since earlier attempts[1] toward simultaneous formation of a fused imidazole ring were not successful, another approach to such conversion has been attempted. It was now possible to convert 6-dimethoxyethylaminotetrazolo[1,5-*b*]pyridazine (**1**) with polyphosphoric acid into the corresponding 6-azidoimidazo[1,2-*b*]pyridazine (**2**) (see Scheme I) and thus induce a complete elimination of the fused tetrazolo ring as is evident from infrared and nmr spectra. The presence of the tetrazolo isomer in a solution of deuteriochloroform could not be detected.

Similarly, the formation of a fused *s*-triazolo ring could be now extended by employing procedures designed previously for syntheses of simple *s*-triazolo[4,3-*b*]pyridazines[4] or *s*-triazolo[4,3-*a*]-1,3,5-triazines.[5] In this manner, the hydrazone **3** could be transformed into the bicyclic compound **4** by employing either the lead tetraacetate technique or by means of bromine. Here again, valence isomerization was discernible from spectral data and, in addition, from chemical transformations of compounds **5** (R = $NHNH_2$) with nitrous acid or (**5**, R = Cl) by means of sodium azide. As anticipated, in both cases no ring closure to a fused tetrazolo heterocycle occurred and only an azide group was formed (**4**).

A fused six-membered ring could be generated in the reaction of **6** (R = Et) with polyphosphoric acid, and once more the tetrazolo ring was isomerized to the azido group. The obtained bicyclic compound **7**, a representative of the newly discovered pyridazino[6,1-*c*]*as*-triazine system,[6] is susceptible to acid hydrolysis and as soon as the fused *as*-triazine ring was opened this resulted in immediate generation of the fused tetrazolo ring (**6**, R = H) from the azido group present in the starting compound.

SCHEME I



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(2) B. Stanovnik and M. Tišler, *Tetrahedron*, **25**, 3313 (1969).

(3) B. Stanovnik, M. Tišler, and P. Škufca, *J. Org. Chem.*, **33**, 2910 (1968).

(4) A. Pollak and M. Tišler, *Tetrahedron*, **22**, 2073 (1966).

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As an extension of the above reactions, compounds with a fused thiazolium ring were prepared in order to investigate further valence isomerization. Thiazolo[3,2-*b*]pyridazin-4-ium perchlorates **9** were formed from the corresponding sulfides of the type **8** and in their infrared spectra strong azide absorption bands were discernible. In contrast to earlier observations[7] no intermediate 3-hydroxy derivatives could be isolated when working in an organic solvent in the absence of a base. This can be ascribed to somewhat more rigorous reaction conditions which have to be employed in order to convert the sulfides into the bicyclic thiazolium salts. In order to establish the stability of this ring system, 6-azido-3-phenylthiazolo[3,2-*b*]pyridazin-4-ium perchlorate (**9**, R = Ph) has been submitted to various reactions. The compound was found to be stable in boiling water or boiling 20% hydrochloric acid after 2 hr.

Application of this reaction sequence to the isomeric substituted thiopyridotetrazolo[5,1-*b*]pyridazines **10a** and **10b** revealed that the anticipated valence isomerization proceeded in the same manner, and salts of both fused thiazolium systems **11a** and **11b** showed as solids strong azide absorption bands in the region 2137–2165 cm^{-1}, characteristic for the presence of azido groups.

Finally, direct N oxidation of tetrazolo[1,5-*b*]pyridazine (**12**) with concentrated hydrogen peroxide in polyphosphoric acid led to simultaneous N oxidation and ring opening and thus 3-azidopyridazine 1-oxide (**13**) could be detected and isolated in low yield.

It seems that the driving force for the described valence isomerizations of tetrazolopyridazines is due primarily to the electron-withdrawing influence of a π-excessive fused azolo ring (or N-oxide function). In this manner the fused tetrazolo ring becomes destabilized and the electron-donating azido group is formed.

Experimental Section

Melting points were taken on a Kofler micro hot stage and are corrected. Infrared spectra were recorded on a Perkin-Elmer 137 Infracord as mulls in Nujol or as KBr disks, and nmr spectra were recorded on a JEOL JNM-C-60HL spectrometer using tetramethylsilane as internal standard.

6-(1′,1′-Dimethoxyethylamino)tetrazolo[1,5-*b*]pyridazine (1).—After 6-chlorotetrazolo[1,5-*b*]pyridazine (1.55 g) was treated with aminoacetaldehyde dimethyl acetal (1.05 g) the mixture evolved heat and was warmed up to 80°. It was then heated on a water bath for 15 min and cooled; the precipitate was filtered off (1.80 g, 80%) and crystallized from ethanol, mp 129°.

Anal. Calcd for $C_8H_{12}N_6O_2$: C, 42.85; H, 5.39; N, 37.48. Found: C, 43.08; H, 5.45; N, 37.55.

6-Azidoimidazo[1,2-*b*]pyridazine (2).—The above acetal (**1**, 2.25 g) and polyphosphoric acid (20 g) were heated slowly up to 110° (about 1 hr) and this temperature was maintained then for 15 min. To the cooled reaction mixture crushed ice (30 g) was added and the mixture neutralized with solid sodium bicarbonate. The separated product was crystallized from a mixture of benzene and petroleum ether (1:3) and had mp 108° (yield 0.72 g, 45%). The compound was found to be identical with the specimen obtained from 6-hydrazinoimidazo[1,2-*b*]pyridazine after treatment with nitrous acid:[8] ir (KBr) 2132 cm^{-1} (N_3); nmr ($CDCl_3$) δ 2.41 (d, H_2), 2.29 (d, H_3), 3.51 (d, H_7), 2.27 (d, H_8), $J_{2,3} = 0.75$, $J_{7,8} = 9.15$ cps.

6-Benzylidenehydrazinotetrazolo[1,5-*b*]pyridazine (3).—This compound was prepared from 6-hydrazinotetrazolo[1,5-*b*]-pyridazine[1,9,10] and benzaldehyde in the usual way; mp 315–317° with partial decomposition over 310° (from N,N-dimethylformamide and ethanol, 3:1).

Anal. Calcd for $C_{11}H_9N_7$: C, 55.22; H, 3.79; N, 40.99. Found: C, 54.88; H, 4.02; N, 41.34.

6-Azido-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine (4). A.—To a suspension of the above hydrazone (**3**, 1.2 g) in glacial acetic acid (25 ml), anhydrous sodium acetate (1.64 g) and a solution of bromine in glacial acetic acid (0.8 g in 2 ml) were added. The reaction mixture was heated up to 100°, left for 5 min at this temperature, and cooled. It was then poured on crushed ice (70 g); the separated product was filtered off and washed with iced water (69% yield). Crystallization was performed from ethanol: mp 168°; ir (KBr) 2141 cm^{-1} (N_3).

Anal. Calcd for $C_{11}H_7N_7$: C, 55.69; H, 2.97; N, 41.34. Found: C, 55.46; H, 3.29; N, 41.53.

The compound is identical with the product obtained either from a similar cyclization of the hydrazone with lead tetraacetate (B) or from treatment of 6-hydrazino compound with nitrous acid (C) or from 6-chloro compound after reaction with sodium azide (C).

B.—The hydrazone **3** (1.2 g) was suspended in glacial acetic acid (20 ml), lead tetraacetate (2.21 g) was added, and the mixture was heated to 75°. After 5 min at this temperature the reaction mixture was cooled and poured onto ice (50 g). The product, after crystallization from ethanol, was found to be identical with compounds described under A or C by comparison of mixture melting points and infrared spectra, mp 168°.

C.—The azido compound was equally well prepared by nitrozation of 6-hydrazino-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine (83% yield) or from 6-chloro-3-phenyl-*s*-triazolo[4,3-*b*]pyridazine by treatment with sodium azide in ethanol (67% yield). Both products were identical with compounds prepared as described in A or B.

6-(α-Carbethoxyethylidenehydrazino)tetrazolo[1,5-*b*]pyridazine (6, R = Et).—6-Hydrazinotetrazolo[1,5-*b*]pyridazine (1.51 g) was suspended in ethanol (2 ml), the mixture was heated to boiling, and thereafter acetic acid (0.5 ml) and ethyl pyruvate (1.16 g) were added. The reaction mixture was heated under reflux for 5 min and cooled; the product was filtered off and washed with ethanol. After crystallization from ethanol and N,N-dimethylformamide (2:1) the pure compound melted at 245–247°; ir (KBr) 3425 cm^{-1} (NH) and 1727 cm^{-1} (CO).

Anal. Calcd for $C_9H_{11}N_7O_2$: C, 43.37; H, 4.45; N, 39.34. Found: C, 43.58; H, 4.44; N, 39.84.

In an analogous way, but using methyl pyruvate, the corresponding **6-(α-carbomethoxyethylidenehydrazino) analog** was prepared, mp 252–254°.

7-Azido-3-methylpyridazino[6,1-c]-*as*-triazin-4-one (7).—Compound **6** (R = Et) (2.49 g) was thoroughly mixed with polyphosphoric acid (25 g) and the mixture was slowly heated on an oil bath to 150° (about 1 hr) and then heated at this temperature for a further 20 min. The reaction mixture was cooled on ice, treated with crushed ice (40 g), and neutralized with solid sodium bicarbonate. The separated product was filtered off and washed with ice–water (yield 0.81 g, 39%). Upon crystallization from ethyl acetate and petroleum ether (1:3) the compound had mp 147–148°: ir (KBr) 2151 cm^{-1} (N_3), 1715 cm^{-1} (CO); nmr spectrum ($CDCl_3$) τ 3.15 (d, H_8), 2.26 (d, H_9), 7.40 (s, 3-CH_3); $J_{8,9} = 9.5$ cps.

Anal. Calcd for $C_7H_5N_7O$: C, 41.40; H, 2.48; N, 48.27. Found: C, 41.21; H, 2.66; N, 48.42.

An identical product is obtained also from the 6-(α-carbomethoxyethylidenehydrazino) derivative.

6-(α-Carboxyethylidenehydrazino)tetrazolo[1,5-*b*]pyridazine (6, R = H). A.—The bicyclic compound **7** (100 mg) was suspended in hydrochloric acid (1 ml of 20%) and the mixture was heated to boiling for 2 min. After cooling the separated product was filtered off and found to be identical with the compound as obtained under B (yield 93%). Crystallization was accomplished from 2 *N* hydrochloric acid: mp 251–252°; ir (KBr) 1681 cm^{-1} (CO).

Anal. Calcd for $C_7H_7N_7O_2$: C, 38.01; H, 3.19; N, 44.32. Found: C, 37.90; H, 3.32; N, 44.48.

B.—A suspension of 6-hydrazinotetrazolo[1,5-*b*]pyridazine (1.51 g) in ethanol (20 ml) was heated to boiling and thereafter glacial acetic acid (0.5 ml) and pyruvic acid (0.88 g) were added. The mixture was heated under reflux for 5 min and cooled; the

(7) B. Stanovnik, M. Tišler, and A. Vrbanič, *J. Org. Chem.*, **34**, 996 (1969).
(8) B. Stanovnik and M. Tisler, *Tetrahedron*, **23**, 387 (1967).
(9) N. Takahayashi, *J. Pharm. Soc.*, **76**, 765 (1956); *Chem. Abstr.*, **51**, 1192 (1957).
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product was filtered off and washed with ethanol (yield 86%). Crystallization was performed from 2 *N* hydrochloric acid, mp 251–252°. The compound was identical with the sample as prepared under A.

6-Mercaptotetrazolo[1,5-*b*]pyridazine (8, R = H).—6-Chlorotetrazolo[1,5-*b*]pyridazine (1.55 g) was added to a solution of 0.03 mol of potassium hydrogen sulfide in ethanol (30 ml). The mixture was heated in a pressure vessel at 120° for 3 hr. The solvent was then evaporated and the residue dissolved in water, some charcoal was added, and after filtration the filtrate was acidified with concentrated hydrochloric acid. The separated product (70% yield) was for analysis dissolved in a solution of sodium carbonate, charcoaled, filtered, and acidified with concentrated hydrochloric acid, and washed with ice–water. The pure compound had mp 135–137°; ir (KBr) 2500 cm^{-1} (SH).

Anal. Calcd for $C_4H_3N_5S$: C, 31.38; H, 1.98; N, 45.75; S, 20.90. Found: C, 31.30; H, 2.15; N, 45.68; S, 20.75.

The 6-methylthio derivative (8, R = Me) was prepared in the usual way in 67% yield; mp 169–170°.

Anal. Calcd for $C_5H_5N_5S$: C, 35.93; H, 3.02; N, 41.91; S, 19.15. Found: C, 35.86; H, 3.34; N, 42.04; S, 19.33.

The 6-phenylthio derivative (8, R = Ph) was obtained from the reaction with sodium thiophenolate in 60% yield, mp 128.5–129.5° (from ethanol).

Anal. Calcd for $C_{10}H_7N_5S$: C, 52.40; H, 3.08; N, 30.56; S, 13.96. Found: C, 52.10; H, 3.46; N, 30.80; S, 14.00.

6-Phenacylthiotetrazolo[1,5-*b*]pyridazine (8, R = $PhCOCH_2$).—A mixture of the mercapto compound (8, R = H; 0.765 g), ethanol (10 ml), and phenacyl bromide (1.0 g) was shaken at room temperature for 30 min and the product was then filtered off. Upon crystallization from a mixture of N,N-dimethylformamide and ethanol (1:4) the compound had mp 170–172° (yield 84%); ir (KBr) 1667 cm^{-1} (CO).

Anal. Calcd for $C_{12}H_9N_5OS$: C, 53.14; H, 3.34; N, 25.82; S, 11.80. Found: C, 53.09; H, 3.57; N, 25.55; S, 11.81.

In an analogous way **6-acetonylthiotetrazolo[1,5-*b*]pyridazine (8, R = CH_3COCH_2)** was obtained in 78% yield; mp 124–125° (from ethanol and ethyl acetate, 1:1).

Anal. Calcd for $C_7H_7N_5OS$: C, 40.19; H, 3.37; N, 33.48; S, 15.30. Found: C, 40.33; H, 3.58; N, 33.54; S, 15.45.

6-Azido-3-phenylthiazolo[3,2-*b*]pyridazin-4-ium Perchlorate (9, R = Ph).—The phenacylthio compound (8, R = $PhCOCH_2$) (1.35 g) was dissolved in 8 ml of concentrated sulfuric acid and the mixture was heated on a water bath for 3 hr. Upon cooling, the mixture was poured into diethyl ether (150 ml), the ethereal layer was decanted, and the residual oil was dissolved in water (20 ml). The insoluble part was filtered off and the filtrate was treated with perchloric acid (2 ml of 70%). The separated perchlorate salt was filtered off, washed with water, and thereafter crystallized from ethanol (yield 51%). The compound is hygroscopic: mp 170–172°; ir (KBr) 2169 cm^{-1} (N_3).

Anal. Calcd for $C_{12}H_8ClN_5O_4S$: C, 40.74; H, 2.28; N, 19.80. Found: C, 40.60; H, 2.47; N, 20.06.

By using the above procedure the **3-methyl analog (9, R = Me)** could be obtained in 26% yield, mp 140–141° (from ethanol); the compound is hygroscopic.

Anal. Calcd for $C_7H_6ClN_5O_4S$: C, 28.82; H, 2.08; N, 24.01; S, 10.99. Found: C, 28.72; H, 2.38; N, 23.86; S, 11.25.

6-Mercaptopyrido[3,2-*d*]tetrazolo[5,1-*b*]pyridazine (10a, R = H).—To an ethanolic solution of potassium hydrogen sulfide, prepared from 1.7 g of potassium hydroxide in 30 ml of ethanol and then saturated with hydrogen sulfide, the 6-chloro compound[11] (10a, R = Cl) (2.04 g) was added and the reaction mixture was heated in an autoclave at 120° for 3 hr. The separated product was filtered off and dissolved in 0.5 *N* potassium hydroxide, the solution was filtered, and the filtrate was acidified with concentrated hydrochloric acid. For analysis a sample was repeatedly purified by dissolution in potassium hydroxide and subsequent acidification, mp 260° dec.

Anal. Calcd for $C_7H_4N_6S$: C, 41.18; H, 1.98; N, 41.17; S, 15.67. Found: C, 41.02; H, 2.23; N, 41.02; S, 15.89.

6-Mercaptopyrido[2,3-*d*]tetrazolo[5,1-*b*]pyridazine (10b, R = H).—This compound was obtained by the same procedure as described above for the isomeric **10a** (R = H): mp 205° dec; ir (KBr) 2268 cm^{-1} (SH).

Anal. Calcd for $C_7H_4N_6S$: C, 41.18; H, 1.98; S, 15.67. Found: C, 41.36; H, 2.08; S, 15.44.

6-Methylthiopyrido[3,2-*d*]tetrazolo[5,1-*b*]pyridazine (10a, R = Me).—A solution of compound **10a** (R = H; 51 mg) in aqueous sodium hydroxide (2.5 ml of 0.1 *N*) was treated with methyl iodide (50 mg) and the mixture was shaken in a sealed flask at room temperature during 30 min. The crude product was separated, washed with water, and dried. Upon crystallization from water and ethanol (1:1) the compound had mp 246–247°.

Anal. Calcd for $C_8H_6N_6S$: C, 44.04; H, 2.77; N, 38.52; S, 14.67. Found: C, 44.46; H, 2.97; N, 38.60; S, 14.57.

The isomeric 6-methylthiopyrido[2,3-*d*]tetrazolo[5,1-*b*]pyridazine (10b, R = Me) was prepared in essentially the same way (yield 77%), mp 283–285°.

Anal. Calcd for $C_8H_6N_6S$: C, 44.04; H, 2.77; N, 38.52; S, 14.67. Found: C, 44.27; H, 2.91; N, 38.43; S, 14.48.

6-Acetonylthiopyrido[3,2-*d*]tetrazolo[5,1-*b*]pyridazine (10a, R = CH_3COCH_2).—The potassium salt of **10a** (R = K) (1.21 g), prepared by addition of equimolar quantity of 0.1 *N* potassium hydroxide, was treated with ethanol (12 ml) and bromoacetone (0.7 g). The mixture was shaken at room temperature during 1 hr; the product was filtered off, washed with ice–water, and crystallized from N,N-dimethylformamide and ethanol (3:1): mp 210°; yield 60%; ir (KBr) 1715 cm^{-1} (CO).

Anal. Calcd for $C_{10}H_8N_6OS$: C, 46.16; H, 3.10; N, 32.30; S, 12.30. Found: C, 46.38; H, 3.30; N, 32.64; S, 12.45.

Similarly **6-acetonylthiopyrido[2,3-*d*]tetrazolo[5,1-*b*]pyridazine (10b, R = CH_3COCH_2)** was obtained in 49% yield: mp 227° (from ethanol); ir (KBr) 1721 cm^{-1} (CO).

Anal. Calcd for $C_{10}H_8N_6OS$: C, 46.16; H, 3.10; N, 32.30; S, 12.30. Found: C, 46.23; H, 3.09; N, 32.04; S, 11.92.

6-Phenacylthiopyrido[3,2-*d*]tetrazolo[5,1-*b*]pyridazine (10a, R = $PhCOCH_2$).—A mixture of **10a** (R = H; 0.51 g), ethanol (8 ml), and phenacyl bromide (0.5 g) was shaken at room temperature during 1 hr; the product was separated by filtration, washed with ethanol, and crystallized from a mixture of N,N-dimethylformamide and ethanol (2:1) (yield 80%): mp 244°; ir (KBr) 1675 cm^{-1} (CO).

Anal. Calcd for $C_{15}H_{10}N_6OS$: C, 55.90; H, 3.13; N, 26.08; S, 9.93. Found: C, 55.74; H, 3.43; N, 25.92; S, 10.32.

The isomeric 6-phenacythiopyrido[2,3-*d*]tetrazolo[5,1-*b*]pyridazine (10b, R = $PhCOCH_2$) was prepared in an analogous way in 64% yield: mp 231–232° (from ethanol and N,N-dimethylformamide, 2:1); ir (KBr) 1675 cm^{-1} (CO).

Anal. Calcd for $C_{15}H_{10}N_6OS$: C, 55.90; H, 3.13; N, 26.08; S, 9.93. Found: C, 55.61; H, 3.44; N, 26.01; S, 9.93.

6-Azido-3-methylpyrido[2,3-*d*]thiazolo[3,2-*b*]pyridazin-4-ium Perchlorate (11a, R = Me).—The acetonyl compound (**10a**, R = CH_3COCH_2; 1.0 g) was heated in concentrated sulfuric acid (10 g) on a water bath for 2 hr. The cooled reaction mixture was poured slowly into ice-cold ether (100 ml). The ethereal layer was decanted, the residual oil was dissolved in water (25 ml), and the perchlorate salt was precipitated with dropwise addition of 70% perchloric acid. The salt was filtered off and washed with water and hot ethanol (yield 20%): mp 236°; ir (KBr) 2137 cm^{-1} (N_3).

Anal. Calcd for $C_{10}H_7ClN_6O_4S$: C, 35.05; H, 2.06; N, 24.52; S, 9.36. Found: C, 35.26; H, 2.38; N, 24.27; S, 9.55.

Following the above procedure the following compounds were prepared.

6-Azido-3-phenylpyrido[2,3-*d*]thiazolo[3,2-*b*]pyridazin-4-ium perchlorate (11a, R = Ph) was obtained in 51% yield: mp 135°; ir (KBr) 2165 cm^{-1} (N_3).

Anal. Calcd for $C_{15}H_9ClN_6O_4S$: C, 44.51; H, 2.24; N, 20.76. Found: C, 44.28; H, 2.61; N, 20.94.

6-Azido-3-methylpyrido[3,2-*d*]thiazolo[3,2-*b*]pyridazin-4-ium perchlorate (11b, R = Me) had mp 195°, ir (KBr) 2155 cm^{-1} (N_3).

Anal. Calcd for $C_{10}H_7ClN_6O_4S$: C, 35.05; H, 2.06; S, 9.36. Found: C, 35.47; H, 2.33; S, 9.26.

6-Azido-3-phenylpyrido[3,2-*d*]thiazolo[3,2-*b*]pyridazin-4-ium perchlorate (11b, R = Ph) melted at 203–204° dec; ir (KBr) 2137 cm^{-1} (N_3).

Anal. Calcd for $C_{15}H_9ClN_6O_4S$: C, 44.51; H, 2.24; N, 20.76. Found: C, 44.67; H, 2.48; N, 20.79.

3-Azidopyridazine 1-Oxide (13).—A suspension of tetrazolo[1,5-*b*]pyridazine (12, 1.21 g) in polyphosphoric acid (10 ml) was treated under stirring dropwise with 1 ml of 85% hydrogen peroxide and the mixture was left to stand at room temperature

(11) B. Stanovnik, A. Krbavčič, and M. Tišler, *J. Org. Chem.* **32**, 1139 (1967).

in the dark for 4 days. During this period the evolution of gases ceased and a clear solution was obtained. The reaction mixture was diluted with water (50 ml) and neutralized with solid sodium bicarbonate. In addition, 30 ml of water was added and the whole extracted with six portions of 50 ml of chloroform. The combined extracts were dried over anhydrous sodium sulfate and then evaporated to dryness to obtain 0.83 g of a residue.

By thin layer chromatography on silica gel, using commercially available plates (DC-Fertigplatten Kieselgel F 254, Merck) and developing them with ethyl acetate, it could be shown that the obtained product was a mixture of the starting compound (R_f 0.59) and 3-azidopyridazine 1-oxide (R_f 0.45) (detection in uv light).

A solution of 300 mg of the crude product in 3 ml of chloroform was separated on a chromatoplate with the above-mentioned absorbent, and the part containing the azide was separated and the compound eluted with chloroform. Upon evaporation of the solvent 12 mg of the residue which consisted of practically pure 3-azidopyridazine 1-oxide[10] was obtaind (yield 2.4%); mp 151–152° and mixture melting point with an authentic specimen obtained from nitrosation of 3-hydrazinopyridazine 1-oxide[12] was undepressed. Moreover, ir spectra of both products were identical [2179 and 2146 cm^{-1} (N_3) and 1263 cm^{-1} (N–O)].

Registry No.—**1**, 23439-79-4; **3**, 23406-38-4; **4**, 23406-39-5; **6**, R = H, 23406-40-8; **6**, R = Et, 23406-41-9; **7**, 23406-42-0; **8**, R = H, 23439-80-7; **8**, R = Me, 23406-43-1; **8**, R = Ph, 23406-44-2; **8**, R = Ph-$COCH_2$, 23406-45-3; **8**, R = CH_3COCH_2, 23406-46-4; **9**, R = Me, 23439-81-8; **9**, R = Ph, 23406-47-5; **10a**, R = H, 23406-48-6; **10a**, R = Me, 23406-49-7; **10a**, R = $PhCOCH_2$, 23439-82-9; **10a**, R = CH_3COCH_2, 23439-83-0; **10b**, R = H, 23439-84-1; **10b**, R = Me, 23406-50-0; **10b**, R = $PhCOCH_2$, 23439-85-2; **10b**, R = CH_3COCH_2, 23410-93-7; **11a**, R = Me, 23410-94-8; **11a**, R = Ph, 23410-95-9; **11b**, R = Me, 23410-96-0; **11b**, R = Ph, 23439-86-3.

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The Kinetics of Deuteration of Imidazole[1]

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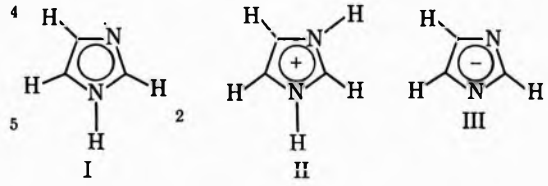
Received August 14, 1969

Rates of deuteration of imidazole in heavy aqueous solution were measured at various pD values at 65 and 70° for the 2 position and at 180 and 190° for the 4(5) position. Parallel rate-determining proton abstractions from the conjugate acid of imidazole by OD^- and by D_2O leading to an ylide intermediate accounted for the observed pD–rate profile for 2-position deuteration. These paths, together with proton abstraction from the imidazole molecule by OD^-, accounted for the 4(5)-position profile. The relative reactivities of hydrogen exchange sites in imidazole and other heterocycles were interpreted in terms of CNDO/2 ylide or anion stabilities.

In recent years, considerable attention has been focussed upon the relative electrophilic reactivities of various ring sites in aromatic heterocyclic compounds.[2,3] These electrophilic reactivities depend both upon the nature of the substrate and the nature of the electrophile. The case of imidazole (I) is of particular interest because the 4(5) position is said to be more reactive in iodination than the 2 position,[4] while the reverse is true for deuteration.[5] In order that different positions of a given substrate be compared for the same or different electrophilic reagents, it is important that the detailed kinetics of substitution for each site and each reaction be known. For example, imidazole may exist in the conjugate acid II or conjugate base III forms in addition to that of the molecule I. Kinetic



I II III

data could indicate which of these forms undergoes attack. The kinetics of iodination of imidazole has been studied in depth,[4,6,7] whereas that for the deuteration of imidazole has not been presented in comparable detail.[5,8,9] Thus, Harris and Randall[5] reported the kinetics of protonation of the 2 position of 1-methylimidazole, Olofson, Thompson, and Michelman[10] the rate of deuteration of the 2 positions of 1,3-dimethylimidazolium and other dialkylazolium cations, and Haake, Bauscher, and Miller[11] the rate of deuteration of 1,3,4-trimethylimidazolium cation. However, no kinetic studies of hydrogen exchange in the 4 and 5 positions of imidazole have been reported, and no detailed mechanistic analyses presented for either the 2 or the 4 and 5 positions. Accordingly, the purpose of this investigation was to study the kinetics of deuteration of the 2 and the equivalent 4 and 5 positions in imidazole, to propose mechanisms compatible with these rate laws and interpret the observed deuteration reactivities according to mechanistic and theoretical arguments.

Experimental Section

Materials.—Imidazole was recrystallized three times from benzene, mp 90.0°. Deuterium chloride (38% in D_2O), sodium deuterioxide (40% in D_2O), and heavy water (99.5%), obtained from Merck Sharp and Dohme of Canada Ltd., Volk Radiochemical, and International Chemical and Nuclear Corporation, were used without further purification. Reagent grade sodium chloride was also used without further purification.

Kinetic Runs.—All kinetic runs were made in heavy water solution. DCl or NaOD were added to adjust the pD of the solution from 0 to 14. The ionic strength of the solution was set

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(3) J. H. Ridd, "Physical Methods in Heterocyclic Chemistry," Vol. I, A. R. Katritsky, Ed., Academic Press, New York, N. Y., 1963, p 109.

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(10) R. A. Olofson, W. R. Thompson, and J. S. Michelman, *J. Amer. Chem. Soc.*, **86**, 1865 (1964).

(11) P. Haake, L. P. Bauscher, and W. B. Miller, *ibid.*, **91**, 1113 (1969).

at 1.00 M by measured addition of heavy aqueous NaCl. Eight 1.0-ml aliquots were prepared for each run; each aliquot was sealed in a 3.0-ml thick-wall borosilicate glass tube. Seven of the tubes were then plunged into an oil bath set at an appropriate elevated temperature, then removed at intervals and quenched in cold water. Samples taken from the tubes were analyzed with the Varian A-60A nuclear magnetic resonance spectrometer. Proton peak areas were determined by the cut and weigh method; the same proton peak area observed in a sample from the eighth (unheated) aliquot was used as a reference. Pseudo-first-order rate constants were obtained from plots of log (per cent area) *vs.* time.

Kinetic runs were made at 65.0 and 70.0° for deuteration of the 2 position and at 180 and 190° for the 4(5) position. The uncertainty in the lower temperatures was ±0.1° and that at the higher temperatures ±1.0°. Rate constants were reproducible to within ±10%.

pD values outside the buffer region were measured with the Beckman Zeromatic pH meter, corrected by the formula of Glaskoe and Long [pD = pH (meter reading) + 0.40].[12] Within the region of self-buffering (5 < pD < 10) pD values were calculated from the equilibrium relation

$$pK_a = pD - \log \frac{[Im]}{[Im^+]} = 7.62 \pm 0.02$$

where [Im] and [Im$^+$] are the concentrations of imidazole and its conjugate acid, respectively. The pK_a value is the average of two measurements at 25° made on heavy water solutions with buffer ratio of unity and ionic strength of 1.0 M.

TABLE I

PSEUDO-FIRST-ORDER RATE CONSTANTS FOR THE DEUTERATION OF IMIDAZOLE

	$k_1 \times 10^4$ (sec^{-1})			
	Position 2		Position 4(5)	
pD[a]	65°	70°	180°	190°
0.26	0.30, 0.20			
2.88	0.17		0.288	
6.92	1.06			
7.32	1.35		0.620	
7.62	1.57	2.11	0.779, 0.740	1.31, 1.36
7.71		2.15	0.787	1.35
7.83	1.66	2.35	0.856	
7.89			0.900	1.50
7.99	1.78	2.47	0.907	1.52
8.10	1.82		0.945	1.71, 1.61
8.22		2.56		1.85, 1.89
8.40	1.93	2.58	1.01, 1.05	1.98
8.47	2.06	2.63	1.11, 1.26, 1.24	2.11
8.90	2.10	2.64	1.29, 1.37	2.20, 2.16
10.56[b]	2.47	2.87	1.44	2.46
12.10			1.68	
13.65	2.43		28.0	
13.80			40.5	

[a] Room-temperature values. [b] $k_1 = 1.75 \times 10^{-4}$ sec^{-1} at 60.0°.

Results and Discussion

Uncertainties in Concentrations of Reactants.—The largest uncertainty in the kinetic data was that arising from changes in the concentrations of reagents at the higher temperatures. Accurate calculation of these concentrations at 180 and 190° would require consideration of the thermal expansion of the sealed glass ampoules, knowledge of the partial molar volumes of all solutes and the solvent at the temperatures, and the extent of loss of the solute into the vapor phase. A rough calculation that utilized the ideal gas law and the vapor pressure and density of liquid water at 180° indicated a 15% increase in the volume of liquid water attending the increase in temperature from 25 to 180°. The change in volume would introduce corresponding changes in the concentrations of reagents. Accurate calculation of changes in concentration was not feasible. Since the ionic strength was adjusted to a constant value for all reacting solutions, it is reasonable to assume that these changes would be determinate in principle if not in practice. Accordingly, all concentrations used in analyzing reaction orders were room-temperature values. The kinetic runs were pseudo first order in imidazole, where the imidazole concentration was observed in thermally quenched samples at room temperature. Hence, the uncertainty in reagent concentration could affect only the order in the deuterium ion concentration, arising from possible lateral shifts in the concentration coordinate at elevated temperatures.

pD Dependence.—Pseudo-first-order rate constants were determined for the 2 and 4(5) positions at two temperatures each for a range of room temperature pD values. The results are given in Table I. The pD profiles of the pseudo-first-order rate constants for the 2 position at 65° and the 4(5) position at 180° are shown in Figures 1 and 2, respectively. The relative rate constants exhibited in those profiles are based upon pseudo-first-order rate constants at pD = 10.56, that is, for heavy aqueous imidazole with no added DCl nor NaOD. The 2 position profile is similar in form to that observed by Harris and Randall for the protonation of 1-methylimidazole-2d,[5] except that a nonvanishing rate of deuteration was observed for imidazole even at high acidities, while no protonation of 1-methylimidazole-2d was reported at high acidities (pH ~0–1). The 4(5) position profile of imidazole closely resembles that of the 2 position for pD values ranging from 0 to ~10, but does not exhibit the flattening observed for the 2 position of imidazole (and for the 2 position of 1-methylimidazole) for pD > 10; the relative rate constants for pD values of 13.65 and 13.80 are too large to be included in Figure 2.

The Arrhenius activation energy at pD = 10.56 (room-temperature value) is 11.1 ± 3.0 kcal for the 2 position and 22.3 ± 3.0 kcal for the 4(5) position. The corresponding pseudo-unimolecular collision factors are $3.2 \times 10^3 \pm 2.6 \times 10^3$ sec^{-1} and $1.9 \times 10^7 \pm 0.7 \times 10^7$ sec^{-1}, respectively. It appears therefore that the far greater exchange reactivity of the 2 position relative to the 4(5) position is attributable to activation energy, not to the preexponential factor.

Mechanism.—A suitable mechanism for the deuteration of imidazole would be one that accounted quantitatively for the pD–rate profiles exhibited in Figures 1 and 2, and also conformed to other available evidence. In addition to the profiles, we know that 1-methylimidazole-2d undergoes protonation (2 position) readily at room temperature,[5] whereas the deuteration of the 2 position of imidazole requires a higher temperature. This result would seem to eliminate the conjugate base of imidazole III as the active nucleophile. Olofson, Thompson, and Michelman[10] reported the facile deuteration of 1,3-dimethylimidazolium iodide at 31°, indicating the conjugate acid form of imidazole II as a likely substrate in the hydrogen exchange; these authors postulated that the cationic substrate undergoes base-catalyzed abstraction of a ring proton to form the ylide

(12) P. K. Glaskoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960).

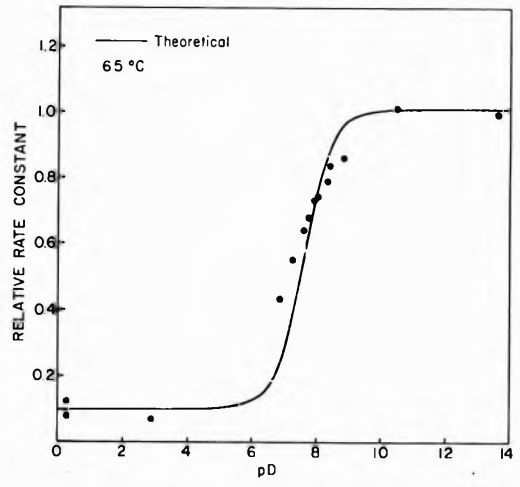


Figure 1.—The pD profile for deuteration of the 2 position in imidazole at 65° and at unit ionic strength.

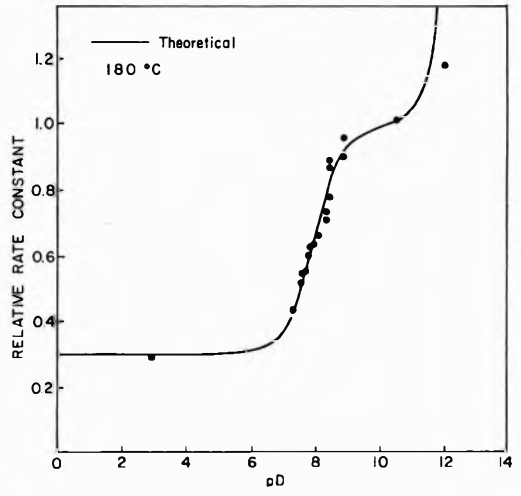
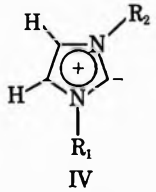


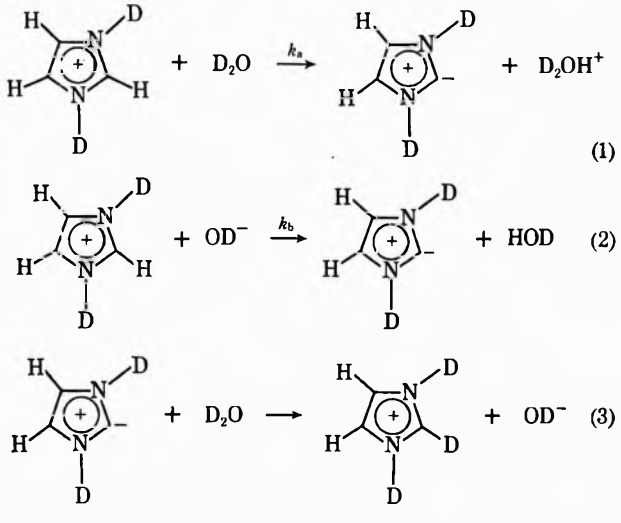
Figure 2.—The pD profile for deuteration of the 4(5) position in imidazole at 180° and at unit ionic strength.

IV in the rate-determining step. Similarly, Harris and Randall[5] proposed the same mechanism for the protonation of 1-methylimidazole-2*d*.



IV

The deuteration of the 2 position of imidazole can be interpreted in terms of two rate-determining steps leading to the ylide intermediate.



The pD profile for the 2 position can be derived for the entire pD range by considering the region of self-buffering. Here the observed pseudo-first-order rate constant k_2^{obsd} is −(slope) of ln [Im⁰] *vs.* *t*, where [Im⁰] = [Im] + [Im⁺]. In this pD region, both the molecule Im and the conjugate acid Im⁺ coexist in greater than trace concentrations, but cannot be distinguished in the reacting solution because of the rapid equilibrium between them. Steps 1 and 2 give

$$\text{rate} = \{k_a[D_2O] + k_b[OD^-]\}[Im^+]$$

Since

$$[Im^+] = [Im^0][D^+]/(K_a + [D^+])$$

the pseudo-first-order rate constant for 2-position deuteration reduces to

$$k_2^{obsd} = (k_a[D_2O][D^+] + k_bK_w)/(K_a + [D^+]) \quad (4)$$

where

$$K_a = [Im][D^+]/[Im^+]$$

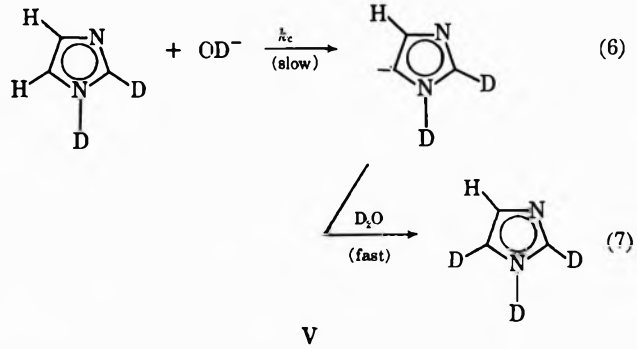
$$K_w = [D^+][OD^-]$$

At low pD, $[D^+] \gg K_a$, and $\lim_{[D^+]\to\infty} k_2^{obsd} = k_a[D_2O]$, while at high pD, $[D^+] \ll K_a$, so that

$$\lim_{[D^+]\to 0} k_2^{obsd} = k_bK_w/K_a \quad (5)$$

Clearly, the limiting relations account for the flattened pD profile in the low and the high pD regions. In Figure 1, the theoretical curve (eq 4) was fitted with $k_a \cdot [D_2O]/2.47 \times 10^{-4} = 0.10$, $k_bK_w/K_a\,(2.47 \times 10^{-4}) = 1.0$, and $K_a = 10^{-7.6}$.

To understand the pD profile of the 4(5) position, steps 1 and 2 [with proton abstraction from the 4(5) position] plus a third path (eq 6) that exhibits direct dependence upon [D⁺] is needed. Therefore, we propose the following additional mechanism operative at high pD values. The acid and self-buffering regions



V

can be adequately described by steps 1 and 2 to pD ~ 8, while the region pD > 8 requires inclusion of 6. At high pD

$$k_{4(5)}^{obsd} = k_bK_w/K_a + k_c[OD^-] = k_bK_w/K_a + k_cK_w/[D^+] \quad (8)$$

The theoretical curve in Figure 2 was fitted with $k_a \cdot [D_2O]/1.44 \times 10^{-4} = 0.30$, $k_bK_w/K_a\,(1.44 \times 10^{-4}) =$

0.98, $k_c/1.44 \times 10^{-4} = 32$, and $K_a = 1.02 \times 10^{-8}$. The theoretical curve and the observed relative rate constants agree satisfactorily.[13] Theoretical valves of the rate constants for pD = 13.65 and pD = 13.80 using the parameters given above are 24.5×10^{-4} sec^{-1} and 47.5×10^{-4} sec^{-1}, respectively (*cf.* Table I); in view of the short half-lives of the reactions in strong alkali, the agreement between theory and experiment is acceptable.

Other mechanistic paths for 4(5) deuteration operative at high pD values could be proposed, in particular those involving σ intermediate formation. For example, the conjugate base of imidazole could react with D_2O to form a σ intermediate followed by proton removal to yield products. Alternatively, the imidazole molecule I could react rapidly with D_2O to form the intermediate, which could then undergo slow deuteroxide-catalyzed proton removal. Although the present kinetic data do not rule out these possibilities, they seem less likely than path 6 by analogy with the observed kinetics of deuteration of the 4 position in pyrazole,[15] the 1,2 isomer of imidazole. The derived rate equation for 4-position deuteration in pyrazole corresponded to *acid*-catalyzed σ intermediate formation, with pD dependence opposite that observed in 4(5)deuteration of imidazole.

Relative Hydrogen Exchange Reactivities.—To obtain quantitative exchange reactivities of different substrates, the exchange kinetics must be run under comparable reaction conditions. For example, it is not feasible to compare the 2-position reactivity of imidazole determined in D_2O with a position in another substrate determined in CH_3OD. In other cases, too little kinetic information may be supplied (*e.g.*, such as reactant concentrations and ionic strength) to warrant reactivity comparisons. The number of meaningful reactivity comparisons is therefore small, despite the large body of literature on hydrogen exchange kinetics. Accordingly, we propose to limit the discussion of relative exchange to imidazole and related substrates[11,14,16] studied under comparable conditions.

Haake, *et al.*,[11] reported second-order rate constants for deuteroxide-catalyzed deprotonation of the 2 position in five-member cationic systems at 33°, corresponding to our k_b rate constant (path 2). At 65°, eq 5 may be rearranged to give $k_b = k_2^{obsd}K_a/K_w$. Correcting the pseudo-first-order rate constant k_2^{obsd} to 33° using the Arrhenius activation energy of 11.1 ± 3.0 kcal, then using $pK_a = 7.62$[17] and $pK_w = 14.54$,[18] we obtain $k_b = 360 \pm 120$ sec^{-1} M^{-1} (33°). Similarly, Olofson, *et al.*,[14] calculated[19] the second-order rate constant for deuteration of the 2 position in thiazolium cation to be 1×10^6 sec^{-1} M^{-1} at 31°. These second-order rate constants can be inserted into the Haake, *et al.*,[11] cation reactivity order: 3,4-dimethyloxazolium(2)[11]: thiazolium(2)[14]:3,4 - dimethylthiazolium(2)[11]:imidazolium(2):1,3,4-trimethylimidazolium(2)[11] = 2.9×10^5: 7.7×10^3:2.8×10^3:2.8:1. The agreement between imidazolium(2) and 1,3,4-trimethylimidazolium(2) and between thiazolium(2) and 3,4-dimethylimidazolium(2) is good,[20] which supports the proposed mechanism (path 2).

Zoltewicz, *et al.*,[16] studied the deuteration of 1-methylpyridinium chloride at 165° in phosphate buffered heavy water. At pD = 6.46 (30°), the pseudo-first-order constant for the 2(6) position was reported to be 7.83×10^{-4} sec^{-1}. Using this pD value and $pK_w = 14.54$,[18] we estimate the second-order constant to be 10^5 sec^{-1} M^{-1} at 165°. The 3(5) and 4 positions were indicated by the authors to be less reactive than 2(6) by factors of 10^3 and 3.4×10^3, respectively. Equation 5, the activation energy 22.3 ± 3.0 kcal, and the pseudo-first-order constant for 4(5) deuteration of imidazole (180°) may be used to estimate the second-order constant k_b for imidazolium(4,5) at 165°; here $k_b \sim 2.5$ sec^{-1} M^{-1}. The uncertainties in the estimated second-order constants are quite large. However, since room-temperature values in pK_a, pK_w, and pD were used for *all* estimates, their relative magnitudes are likely to be correctly ordered. Accordingly, we propose the following additional reactivity order: imidazolium(2) ≫ 1-methylpyridinium(2,6)[16] ≫ 1-methylpyridinium-(3,5)[16] > 1-methylpyridinium(4)[16] > imidazolium(4,5).

Recently, relative deuteration reactivity was discussed in terms of both the ground state properties of the substrate and ylide intermediate stability.[11] ^{13}C–H coupling constants were considered indices of the potential acidities of corresponding C–H bonds in the substrate ground state; thus the ^{13}C–H coupling constant would suggest the relative ease of proton removal in the transition state, other factors being equal. The ylide intermediate represents an exaggerated model of the transition state.[10,11,15] It has been shown that large differences in hydrogen exchange reactivity may be found in cases where the ^{13}C–H coupling constants are essentially identical in magnitude[11]; in such cases, the difference in reactivity was attributed to factors specifically affecting ylide (and hence transition state) stability. Therefore, it is of interest to ascertain to what extent calculated ylide and anion stabilities can be used to interpret observed relative exchange reactivities directly. One might expect potential acidity differences to be implicit in the stabilities of the intermediates, if the stabilization energy is proportional to the free energy of activation. The success of a correlation between intermediate stability and reactivity depends upon the following factors: (1) the degree of the similarity between intermediate and transition state, (2) the relative importance of the preexponential factor and energy of activation in the reaction being considered, and (3) the accuracy of the method of calculation. We have used the CNDO/2 method[21] for estimating cation to ylide deprotonation[22] and molecule to anion V deprotonation energies. We neglected the entropy change attending intermediate formation; this neglect is consistent with the apparently dominant

(13) Recently, the pD profile for 2-position deuteration of thiazole was reported to be qualitatively similar to 4(5) deuteration in imidazole. Rate laws 4 and 8 were derived independently by the authors.[14]

(14) R. A. Coburn, J. M. Landesberg, D. S. Kemp, and R. A. Olofson, *Tetrahedron*, in press.

(15) E. C. Wu and J. D. Vaughan, *J. Org. Chem.*, **35**, 1146 (1970).

(16) J. A. Zoltewicz, G. M. Kauffman, and C. L. Smith, *J. Amer. Chem. Soc.*, **90**, 5939 (1968).

(17) pK_a was not corrected from 25 to 33° in this estimate.

(18) A. K. Covington, R. A. Robinson, and R. G. Bates, *J. Phys. Chem.*, **70**, 3820 (1966).

(19) Using eq 5 independently conceived by the authors.[14]

(20) See reference 14, where thiazolium(2) is compared with 3-ethylthiazolium(2) with similarly good agreement.

(21) J. A. Pople and G. A. Segal, *J. Chem. Phys.*, **44**, 3289 (1966).

(22) Schroeder and Tolles showed that CNDO/2 cation to ylide deprotonation energies correlate well with observed hydrogen exchange reactivities of diazolium and tetrazolium salts, private communication, 1968.

effect of the activation energy noted above for the deuteration of the 2 and 4(5) positions in imidazole. Since geometries are not known for the cations, ylides, anions, and most of the molecules, we assumed the five-member heterocycles to be pentagons 1.38 Å on a side,[23] six-member heterocycles to be hexagons 1.397 Å per side, and C–H and N–H distances to be 1.08 and 1.00 Å,[24] respectively. In the CNDO/2 approximation, the deprotonation energy is defined

$$\Delta E_T = E_T(\text{intermediate}) - E_T(\text{substrate})$$

where E_T is the valence electronic energy plus the core repulsion energy. The results of the calculation are given in Table II. Here, calculations were not made for sulfur containing compounds, because the program used did not provide for d orbitals, an essential requirement for substrates and intermediates that contain third period elements.[25] A number of conclusions may be drawn from the results of Table II. First, the effect of methyl substituents is of interest. A methyl group in the 4 position leads to a small destabilization in the ylide (2) intermediate, whereas one in the 1 position causes a slightly larger destabilization. Clearly, the 1,3,4-trimethylimidazolium ylide (2) would be further destabilized. This destabilization is probably a consequence of methyl-group electron release, which would render the ring atoms less electronegative and therefore *decrease* the inductive stabilization of the ylide intermediate. Since the ^{13}C–2H coupling constant for the 2 position is not sensitive to methyl substituents on the imidazolium nucleus,[11] the observed smaller exchange reactivity of the 1,3,4-trimethylimidazole relative to imidazole is consistent with methyl-group destabilization of the ylide. Further, the apparently smaller reactivity of 3,4-dimethylthiazolium relative to thiazolium supports this conclusion. Second, ΔE_T values correctly indicate that the 2 position in imidazole is more reactive than the 4(5) position, and that the 2(6) position in 1-methylpyridinium[26] is more reactive than the 3(5) and (4) positions. Note that 1-methylpyridinium is approximated by pyridinium, since methyl substituents have comparatively small effect upon ylide stabilities. Third, ΔE_T values correctly indicate the conjugate acid form of imidazole to be much more reactive than the molecule in all positions. The same result is indicated for the 2 position in oxazole. Fourth, the relative exchange reactivities for different cationic substrates is roughly predicted to be oxazolium(2) > imidazolium(2) > pyridinium(2,6) > imidazolium(4,5) > pyridinium(4) > pyridinium(3,5). The general trend is correctly indicated except for imidazolium(4,5), which is the least reactive of the substrate positions listed. Replacement of N–H by O evidently leads to enhanced inductive stabilization of the ylide. Though calculations were not made on sulfur-containing substrates, it is readily surmised from CNDO/2 input electronegativities $[(I + A)/2)]$[21] that thiazolium(2) would appear less reactive than imidazolium(2) if d orbitals are excluded; it is clear therefore that d orbitals must be included to account for the unusually stable ylide intermediates of thiazolium substrates, in agreement with prior discussions elsewhere.[10,11] In summary, it appears that CNDO/2 ylide and anion stabilities can be useful indices of exchange reactivities in heterocycles, especially in those cases where reactivity differences are large.

TABLE II

CNDO/2 YLIDE AND ANION STABILITIES[a,b]

Substrate	Intermediate[c]	ΔE_T (au)
Imidazolium	Ylide (2)	0.631
	Ylide (4,5)	0.693
Imidazole	Anion (2)	0.951
	Anion (4)	0.989
	Anion (5)	0.969
4-Methylimidazolium	Ylide (2)	0.639
1-Methylimidazolium	Ylide (2)	0.642
4-Methyloxazolium	Ylide (2)	0.604
Oxazole	Anion (2)	0.929
Pyridinium	Ylide (2,6)	0.667
	Ylide (3,5)	0.706
	Ylide (4)	0.703

[a] Calculations carried out on the CDC 6400 computer, using a program obtained from the Quantum Chemistry Program Exchange (QCPE 91). [b] A small value for ΔE_T implies relatively high stability for the intermediate. [c] For example, ylide (*n*) refers to an ylide intermediate formed from the cation designated in the left column; *n* refers to the position of proton abstraction.

(23) See reference 18 for a discussion of the problem of unknown molecular geometries.

(24) "Tables of Interatomic Distances and Configurations in Molecules and Ions," The Chemical Society, London, 1968.

(25) D. P. Santry and G. A. Segal, *J. Chem. Phys.*, **47**, 158 (1967).

(26) Recent extended Hückel theory (EHT) calculations[27] of ylide and anion stabilities indicated the 3(5) position to be more reactive than the 2(6) position, contrary to experiment. However, the EHT calculations correctly predicted the 4(5) position of pyridazine to be the most reactive in that molecule and the 5 position the most reactive in pyrimidine. The CNDO/2 calculations gave the correct reactivity orders in pyridinium and pyridazine,[28] but incorrectly indicated the 2 position to be the most reactive in pyrimidine.[28]

(27) W. Adam, A. Grimison, and R. Hoffmann, *J. Amer. Chem. Soc.*, **91**, 2590 (1969).

(28) J. D. Vaughan, unpublished results, 1969.

Registry No.—Imidazole, 288-32-4.

The Kinetics of Deuteration of Pyrazole[1a]

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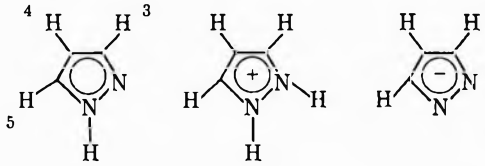
The kinetics of deuteration of the 4 position and the 3(5) position in pyrazole was studied in sealed tubes at 200° and higher temperatures. The mechanism proposed for 4-position deuteration involved general acid catalyzed formation of σ intermediates from the molecular and conjugate-base forms of pyrazole. The rate of deuteration of the 3(5) position exhibited neither buffer catalysis nor pD dependence. This behavior is consistent with formation of an ylide intermediate from attack of the conjugate acid of pyrazole by OD^- ions.

Pyrazole exhibits both weakly basic and very weakly acidic properties in aqueous solution ($pK_b = 11.53$ and $pK_a \cong 14$).[2] Therefore, the molecule I, the conjugate acid II, and the conjugate base III may be subject to electrophilic attack in aqueous media. Thus, the conjugate acid undergoes nitration in the 4 position in stongly acidic media,[3] whereas iodination in media



I II III

ranging from pH 6.0 to 8.0 appears to involve the conjugate base in the 4 position.[4,5] Prior to the research reported in this paper, there has been no report of kinetic studies of the deuteration of unsubstituted pyrazole. However, Olofson, Thompson, and Michelman[6] observed that the 3(5) position but not the 4 position in 1,2-dimethylpyrazolium cation undergoes hydrogen exchange at 31°. Accordingly, it is of interest to study the kinetics of deuteration of pyrazole in heavy aqueous solution to ascertain the relative reactivities of the 4 and equivalent 3 and 5 positions, to determine the rate laws for deuteration of these positions, to propose mechanisms compatible with these rate laws, and to interpret the reactivities of ring positions theoretically and mechanistically.

Experimental Section

Materials.—Pyrazole from Aldrich Chemical Co. was recrystallized three times from cyclohexane, mp 68.5°. D_2O (99.5%), DCl (38% in D_2O), ND_4OD (26% in D_2O), and pyridine-d_5 obtained from Merck Sharp and Dohme of Canada Ltd., were used without further purification. Reagent grade NaCl was also used without further purification.

Kinetic Runs.—The details of the kinetic procedure are given in the preceding paper of this series.[7] The ionic strength was adjusted to 1.00 *M* by NaCl in all runs. Runs were made with ammonia-d_3, ammonium-d_4 buffer, pyridine-d_5, pyridinium-d_6 buffer, and with no added buffer. Deuterations were carried out in heavy water solutions in sealed heavy-wall borosilicate glass ampoules at temperatures ranging from 200 to 250°. Temperatures were reproducible to within ±1° and rate constants to within ±10%. Uncertainties in concentrations of reagents arising from thermal changes in volume are discussed in the proceding paper.[7]

pD values were measured at room temperature with the Beckman Zeromatic pH meter, corrected by the formula of Glaskoe and Long (pD = pH (meter reading) + 0.4).[8]

Results and Discussion

Rate constants for the deuteration of the 4 position and the equivalent 3 and 5 positions are recorded in Tables I and II, respectively. These rate constants are pseudo first order in pyrazole, since D_2O was in

TABLE I

PSEUDO-FIRST-ORDER RATE CONSTANTS FOR THE DEUTERATION OF THE 4 POSITION IN PYRAZOLE

Base concentration[a]	Buffer ratio[b,c]	pD[c]	Temp, °C	$k_4^{obsd} \times 10^4$ sec^{-1}
	ND_3, ND_4^+ Buffer			
1.92	3.75	10.56	200	7.68
0.96				4.43
0.48				2.45
0.24				1.78
0.12				1.35
1.99	8.50	10.92	200	4.68
0.70	1.375	10.13	200	3.53
	Pyridine-d_5, Pyridinium-d_6 Buffer			
0.70	1.34	6.15	200	21.9
0.35				17.8
0.17				15.8
0.09				14.6
0.67	2.08	6.34	200	16.2
0.34				13.1
0.17				12.3
0.085				11.8
0.78	6.03	6.80	200	8.16
0.39				6.15
0.20				5.47
0.10				5.00
0.068	12.7	7.13	200	5.23
0.034				3.98
0.017				3.10
0.0085				2.78
	No Added Buffer			
0.0		7.50	200	0.82
			215	1.61
			230	3.12
			238	4.13
			245	6.48
			245	6.53

[a] Mole/liter. [b] [base]/[acid]. [c] Room-temperature value.

(1) (a) Department of Chemistry, Contribution No. 7-69, supported in part by Atomic Energy Commission Grant AT(11-1)-1620. (b) Addressee for reprints.

(2) A. Albert, "Physical Methods in Heterocyclic Chemistry," Vol. I, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963.

(3) M. W. Austin, J. R. Blackborow, J. H. Ridd, and B. V. Smith, *J. Chem. Soc.*, 1051 (1965).

(4) J. D. Vaughan, D. G. Lambert, and V. L. Vaughan, *J. Amer. Chem. Soc.*, **86**, 2857 (1964).

(5) J. D. Vaughan, G. L. Jewett, and V. L. Vaughan, *ibid.*, **89**, 6218 (1967).

(6) R. A. Olofson, W. R. Thompson, and J. S. Michelman, *ibid.*, **86**, 1856 (1964).

(7) J. D. Vaughan, Z. Mughrabi, and E. C. Wu, *J. Org. Chem.*, **35**, 1141 (1970).

(8) P. K. Glaskoe and F. A. Long, *J. Phys. Chem.*, **64**, 188 (1960).

TABLE II
PSEUDO-FIRST-ORDER RATE CONSTANTS FOR THE DEUTERATION OF THE 3(5) POSITION IN PYRAZOLE

Base concentration[a]	Buffer ratio[b,c]	pD[c]	Temp, °C	$k_{3(5)}^{obsd} \times 10^5$ sec^{-1}
		ND_3, ND_4^+ Buffer		
1.92	3.75	10.56	230	3.95
1.92				3.27
0.96				4.03
1.35	3.44	10.53	230	4.17
0.79	1.1	10.03	230	2.95
		Pyridine-d_5, Pyridinium-d_6 Buffer		
1.90	3.69	6.60	230	2.28
0.95				2.08
0.47				2.27
0.24				2.28
0.70	1.34	6.15	230	2.08
0.35				2.58
0.17				2.88
0.088				2.88
0.044				2.85
0.022				2.58
		No Adder Buffer		
0.00		7.50	220	1.65
			230	3.05
			240	8.55
			250	14.5

[a-c] See footnotes to Table I.

great excess. The rate data for the 4 position conforms to general acid catalyzed deuteration (eq 1–4).

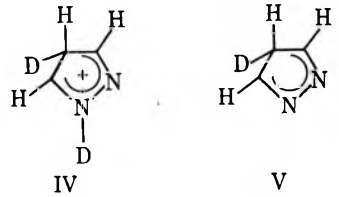
$$SH + D_3O^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Q^+ + D_2O \xrightarrow{k_3} SD + HD_2O^+ \quad (1)$$

$$SH + BD^+ \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} Q^+ + B \xrightarrow{k_4} SD + BH^+ \quad (2)$$

$$SH^- + D_3O^+ \underset{k_{-1'}}{\overset{k_1'}{\rightleftharpoons}} Q + D_2O \xrightarrow{k_3'} SD^- + HD_2O^+ \quad (3)$$

$$SH^- + BD^+ \underset{k_{-2'}}{\overset{k_2'}{\rightleftharpoons}} Q + B \xrightarrow{k_4'} SD^- + BH^+ \quad (4)$$

Here SH refers to pyrazole (I), SD to pyrazole-4*d*, SH^- and SD^- to the conjugate bases of SH and SD, respectively, BD^+ and BH^+ to general acids, and Q^+ and Q to Wheland intermediates IV and V, respectively.



IV

V

This mechanism is similar to that proposed by Kresge and Chiang[9] for acid-catalyzed hydrogen exchange in 1,3,5-trimethoxylbenzene, complicated by the presence of added buffer and by the appearance of two rather than one substrate. The kinetic analysis that follows is an extension of that reported by Kresge and Chiang. We assume that

$$k_1 < k_{-1} \sim k_3$$
$$k_2 < k_{-2} \sim k_4$$
$$k_1' < k_{-1}' \sim k_3'$$
$$k_2' < k_{-2}' \sim k_4'$$

(9) A. J. Kresge and Y. Chiang, *J. Amer. Chem. Soc.*, **89**, 4411 (1967).

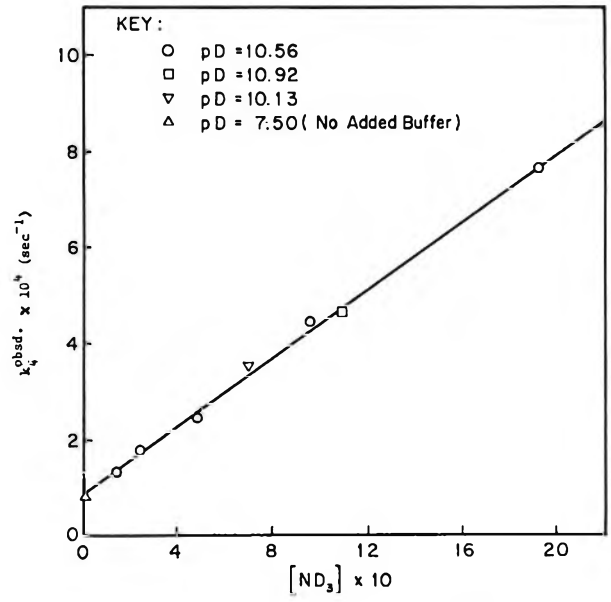


Figure 1.—Rate of deuteration of the 4 position of pyrazole at 200° in ammonia buffer.

where the pairs on the right of the inequality (*e.g.*, k_{-1}, k_3, etc.) differ only because of the primary isotope effect. Therefore

$$\text{rate (4 position)} = k_1[SH][D_3O^+] - k_{-1}[Q^+][D_2O] + k_2[SH][BD^+] - k_{-2}[Q^+][B] + k_1'[SH^-][D_3O^+] - k_{-1}'[Q][D_2O] + k_2[SH^-][BD^+] - k_{-2}[Q][B]$$

Using the steady-state approximation to eliminate $[Q^+]$ and [Q], together with the relations

$$K_a = [SH^-][D_3O^+]/[SH]$$
$$K_b = [BD^+]K_w/[B][D_3O^+]$$

to eliminate $[SH^-]$ and $[BD^+]$, we derive the pseudo-first-order rate constant for 4-position deuteration to be

$$k_4^{obsd} = \{k_1X[D_3O^+] + k_1'K_aX'\} + \{(k_2K_bX/K_w)[D_3O^+] + (k_2'K_aK_bX'/K_w)\}[B] \quad (5)$$

where

$$X = \frac{k_3[D_2O] + k_4[B]}{(k_{-1} + k_3)[D_2O] + (k_{-2} + k_4)[B]}$$

$$X' = \frac{k_3'[D_2O] + k_4'[B]}{(k_{-1}' + k_3')[D_2O] + (k_{-2}' + k_{-4}')[B]}$$

and $K_w = [D_3O^+][OD^-]$. If no buffer is present and if the reacting medium is strongly acidic, then $[SH] \gg [SH^-]$, $[BD^+] = [B] = 0$, and eq 5 reduces to the Kresge and Chiange rate equation[9]

$$k_4^{obsd} = \left(\frac{k_1}{1 + k_{-1}/k_3}\right)[D_3O^+] \quad (6)$$

In the general case (eq 5), X and X' each are functions of B, so that k_4^{obsd} contains terms in the second degree. However, Figures 1 and 2 exhibit first-order dependence upon [B] for the ammonia-d_3 and pyridine-d_5 buffers, respectively. This behavior is consistent with eq 5 provided that X and X′ are constant, irrespective of [B]; the conditions for constancy of X and X' are that

$$\frac{k_3}{k_{-1} + k_3} = \frac{k_4}{k_{-2} + k_4} \quad (7)$$

$$\frac{k_3'}{k_{-1}' + k_3'} = \frac{k_4'}{k_{-2}' + k_4'} \quad (8)$$

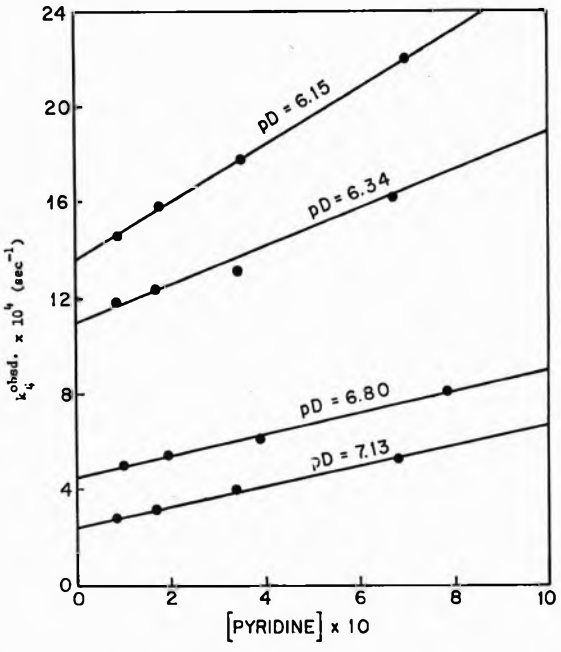


Figure 2.—Rate of deuteration of the 4 position of pyrazole at 200° in pyridine buffer.

Because paths 1 and 2 are quite similar in nature, as are paths 3 and 4, respectively, we conclude that the conditions expressed by eq 7 and 8 are realized, and that X and X' are indeed constant. In the ammonia buffer case, pD is large and $[D_3O^+]$ vanishingly small; therefore, eq 5 predicts that k_4^{obsd} will be independent of pD, as observed in Figure 1. In the pyridine buffer case, where the solutions range from neutral to weakly acidic, $[D_3O^+]$ is 10^3 to 10^4 times larger than in ammonia buffer, so that one might expect the $[D_3O^+]$ terms in eq 5 to become significant. Therefore, in pyridine buffer, eq 5 predicts a family of linear plots of k_4^{obsd} *vs.* [pyridine] for given pD values, as seen in Figure 2. According to eq 5, the intercepts (k^0) and slopes (k^s) observed in Figures 1 and 2 should depend linearly upon $[D_3O^+]$; this behavior is exhibited in Figure 3. In earlier work, electrophilic attack of a free molecule and its conjugate base was proposed by Katritzky and coworkers[10] to account for the deuteration of phenol (2,4,6 positions).

The results of Figures 1 and 3 may be used to estimate the relative electrophilic reactivities of the pyrazole molecule and its conjugate base. In Figure 1, the intercept $k^0 = 0.8 \times 10^{-4}$ sec^{-1} $= k_1'K_aX'$; in Figure 3, $k^0 = 5 \times 10^{-4}$ sec^{-1} at $[D_3O^+] = 2 \times 10^{-7}$. Therefore, since $k^0 = k_1X[D_3O^+] + k_1'K_aX'$ and if we let $K_a = 10^{-14}$ for pyrazole,[2] we find that $k_1X \sim 2 \times 10^3$ sec^{-1} M^{-1} and that $k_1'X' \sim 8 \times 10^9$ sec^{-1} M^{-1}. Accordingly, we estimate that the conjugate base is about 4×10^6 more reactive than the molecule with respect to the D_3O^+ electrophile; the rates of deuteration of the anion and molecule are calculated to be about equal at pD = 7.4 (room-temperature value).[11] By comparative iodinations of pyrazole and 1-methylpyrazole, the reactivity (relative to I_2 or IOH_2^+) of the conjugate base of pyrazole was estimated to be between 10^9 and 10^{13} greater than that of the molecule.[5]

(10) G. P. Bean, *et al.*, *J. Chem. Soc.*, *B*, 1222 (1967).

(11) Compare phenol, where the phenoxide anion is estimated to be 2×10^7 more reactive than the phenol molecule, and the rates of deuteration of the two substrates to be equal at pD = 3.4.[10]

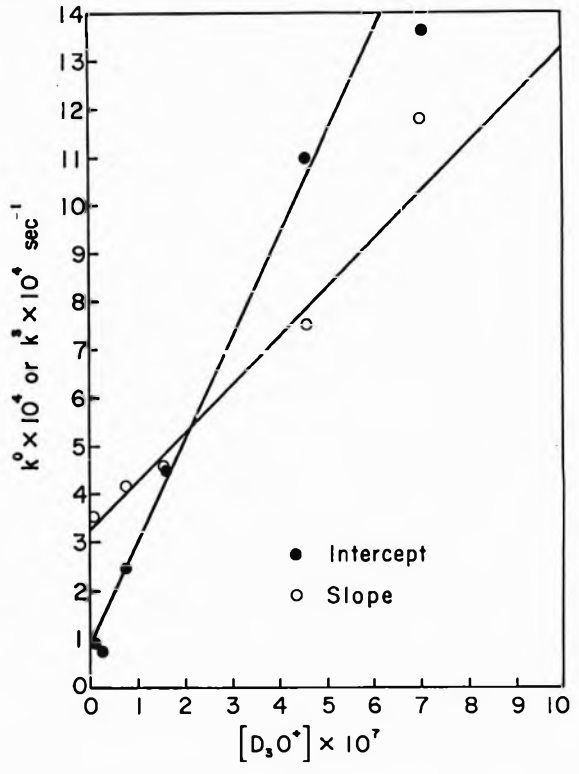
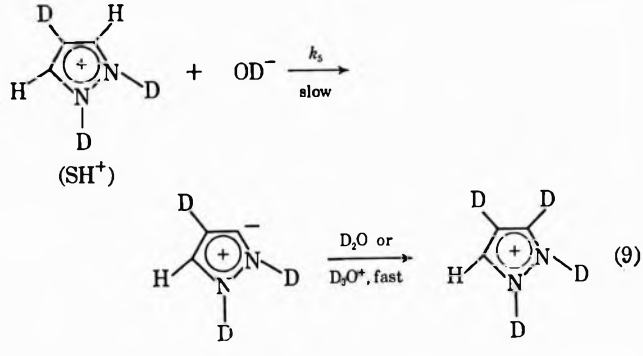


Figure 3.—Dependence of buffer-catalyzed (slopes) and uncatalyzed (intercepts) deuteration of the 4 position in pyrazole at 200°.

Numerous other examples of Wheland-intermediate mechanisms have been proposed for hydrogen exchange in aromatic substrates, chiefly in six-member-ring systems.[12]

The deuteration of the 3(5) position of pyrazole at 230° is sensibly independent of both buffer and pD from pD = 6.15 to pD = 10.56 (Table II). This behavior conforms to deuterioxide-catalyzed ylide formation.



(9)

Here rate [3(5) position] $= k_5[SH^+][OD^-]$; noting that $K_a' = [SH][D_3O^+]/[SH^+]$, we derive

$$k_{3(5)}^{obsd} = \frac{k_5K_w}{K_a'} \qquad (10)$$

which agrees with experiment. Similar independence of the rate of deuteration upon $[OD^-]$ attributable to the ylide-intermediate mechanism has been reported.[7,13,14] An alternative path for 3(5) deuteration independent of pD could involve attack of the conjugate base III by D_3O^+ to form a Wheland intermediate.

(12) For example, see G. P. Bean, C. D. Johnson, A. R. Katritzky, B. J. Ridgewell, and A. M. White, *J. Chem. Soc.*, *B*, 1219 (1967).

(13) J. A. Zoltewicz and J. D. Meyer, *Tetrahedron Lett.*, 421 (1968).

(14) T. M. Harris and J. C. Randall, *Chem. Ind.* (London), 1728 (1965).

However, the independence of the rate of ND_4^+ and pyridinium-d_5 casts doubt upon this alternative. Further, the numerous examples of other heteroatomic aromatic substrates[6,15-20] that appear to undergo hydrogen exchange in α positions through ylide intermediates support this mechanism for the 3(5) position in pyrazole. Of particular interest, 1,2-dimethylpyrazolium cation undergoes deuteration in the 3(5) position at 31° in alkaline solution.[6] Here, the much smaller rate of deuteration of the 3(5) position in pyrazole in terms of the ylide path is a consequence of the very weak base strength of pyrazole.[2]

The experimental activation energy for the 4 position is 21.8 ± 1.6 kcal and that for the 3(5) position is 38.8 ± 6.4 kcal. Corresponding pseudo-unimolecular collision factors are 7.6 ± 10^5 sec^{-1} and 2.1 × 10^{12} sec^{-1}, respectively. The activation energy for the 3(5) position is unexpectedly large;[21] the smaller exchange reactivity for the 3(5) position compared to the 4 position is due to the great difference in activation energies of these positions, partially offset by the larger preexponential factor of the 3(5) position.

It is evident that two types of exchange mechanism are operative in aromatic heterocyclic systems. The first type involves base-catalyzed proton removal from the exchange site of the substrate. The second type involves acid-catalyzed Wheland intermediate formation. In general, in neutral, weakly acidic, or weakly alkaline solutions, positions next to nitrogen, oxygen, or sulfur heteroatoms undergo exchange by the first type,[6,7,15-20] whereas positions with carbon neighbors may react through the first[22] or the second type.[10,12,23] The relative reactivities of the conjugate acid, conjugate base, and molecule forms of the substrates differ, depending upon which type mechanism is operative. Thus, for the proton abstraction mechanism, the conjugate acid is most reactive, the molecule next,[7,19] and the conjugate base apparently unreactive. Here protonation of the heteroatom leads to rate enhancement in two ways: first, by increased inductive stabilization of transition states leading to ylide or anion intermediates[6,7,20] and second, by the increased entropy of activation attending reactions between ions of opposite charge. For the Wheland intermediate mechanism, the conjugate base is most reactive, the molecule next, and the conjugate acid least. In the latter case, deprotonation of the heteroatom appears to stabilize transition states leading to the Wheland intermediate, and also to cause the entropy of activation to increase for positively charged electrophiles.

Registry No.—Pyrazole, 288-13-1.

(15) H. S. Staub, *Tetrahedron Lett.*, 845 (1964).
(16) P. Beak and J. Bonham, *J. Amer. Chem. Soc.*, **87**, 3365 (1965).
(17) P. Haake and W. B. Miller, *ibid.*, **85**, 4044 (1963).
(18) R. Breslow, *Ann. N. Y. Acad. Sci.*, **98**, 445 (1962).
(19) R. A. Olofson, J. M. Landesberg, K. N. Houk, and J. S. Michelman, *J. Amer. Chem. Soc.*, **88**, 4265 (1966).
(20) P. Haake, L. S. Bauscher, and W. B. Miller, *ibid.*, **91**, 1113 (1969).
(21) For example, the activation energy for exchange in the 4(5) position in imidazole is about 22 kcal.[7]
(22) J. A. Zoltewicz, G. Grahe, and C. L. Smith, *J. Amer. Chem. Soc.*, **91**, 5501 (1969).
(23) The β position in 4-aminopyridines exhibits mechanism type 1 in alkaline solution and type 2 in acid solution. See ref 13.

The Azodiformate Adduct of Indene and the Stereochemistry of Some 1,2-Disubstituted Indans[1]

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Received June 26, 1968

It has been shown by chemical degradations that the structure of the adduct of indene and diethyl azodiformate is correctly formulated as an oxadiazine. The stereochemical structure assigned to a 2-amino-1-indanol by interpretation of nmr data has been shown to be erroneous. The generalizations proposed to deduce the stereochemistry of 1,2-disubstituted indan on the basis of nmr spectra have been shown to be an oversimplification.

A recent study on Diels–Alder reactions of indene[3] presented physical data on whose basis the long-known adduct of indene and diethyl azodiformate[4] was formulated as diazetidine **1**. Chemical evidence now, however, shows this substance to be represented properly by the oxadiazine structure.[5] In this connection it is noteworthy that reaction of indene with sterically restricted phthalazine-1,4-dione leads to 1,2 addition and hence to the formation of an authentic diazetidine **2**,[6] while reactions of azodiformates with other olefins have been shown recently to yield both 1,2 and 1,4 adducts.[7]

Structure **1** became untenable when a hydrazino alcohol was obtained upon its reduction by lithium aluminum hydride. Proof of the nature of the reduction product and formulation of its structure as **4** emerged from the following observations. Its nmr spectrum showed the presence of two replaceable hydrogens and two N-methyl groups. Acetylation gave an O,N-diacetyl derivative. Hydrogenation of **4** over platinum oxide in acetic acid gave an amino alcohol

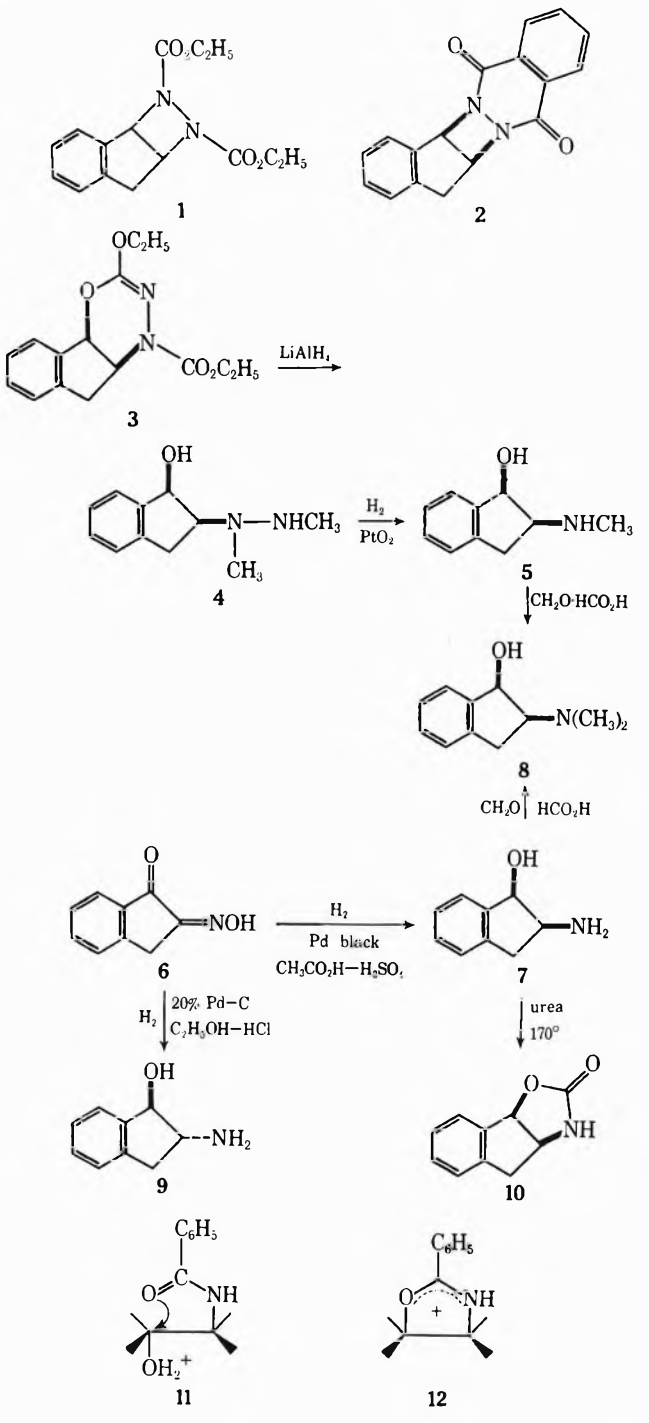
(1) Delay in publication of this paper was the responsibility of the editor. Since acceptance of this paper for publication the correct structures for **1** and **7** have been proposed by others: (a) H. M. R. Hoffmann, *Angew. Chem. Int. Ed. Engl.*, **8**, 556 (1969); (b) H. Rimek, T. Yupraphat, and F. Zymalkowski, *Justus Liebigs Ann. Chem.*, **725**, 116 (1969); (c) H. Rimek, T. Yupraphat, and F. Zymalkowski, *ibid.*, **726**, 25 (1969).
(2) (a) CIBA Pharmaceutical Co.; (b) Indiana University.
(3) C. F. Huebner, P. L. Strachan, E. M. Donoghue, N. Cahoon, L. Dorfman, R. Margerison, and E. Wenkert, *J. Org. Chem.*, **32**, 1126 (1967).
(4) O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **450**, 237 (1926).
(5) Dr. E. Koerner von Gustorf also concluded that this new structure is the correct one (private communication). He has since then completed his evidence for this structure: E. K. von Gustorf, D. White, B. Kim, D. Hess and J. Leitich, *J. Org. Chem.*, **35**, (155 197). His earlier paper, E. K. von Gustorf and B. Kim, *Angew. Chem.*, **76**, 592 (1964), proposing the diazetidine structure, was neither abstracted nor indexed by *Chemical Abstracts*.
(6) O. L. Chapman and S. J. Dominianni, *J. Org. Chem.*, **31**, 3862 (1966).
(7) J. J. Tufariello, T. F. Mich, and P. S. Miller, *Tetrahedron Lett.*, 2293 (1966); G. Ahlgren and B. Akermark, *Acta Chem. Scand.*, **21**, 2910 (1967).

$C_{10}H_{13}NO$ (**5**), with loss of methylamine. The positions of the alcohol and amino groups were shown by formaldehyde–formic acid methylation of **5** to a dimethylamino alcohol **8** identical with that obtained by similar methylation of the known 2-amino-1-indanol (**7**) (mp 107–108°) prepared by the method of Rosen and Green,[8] hydrogenation of 2-oximino-1-indanone (**6**) in acetic acid–sulfuric acid over palladium black. To rule out any acid-catalyzed rearrangement of the amino alcohols **5** and **7**, especially at the benzyl alcohol position,[9] both compounds were methylated under basic conditions with methyl iodide, and an identical quaternary ammonium salt was obtained. Thus, the gross structure of the indene adduct is indicated by **3**, with only the stereochemistry of the ring fusion to be defined. Since no stereochemical change would be expected to occur during the reaction sequence **3** → **8**, the stereochemistry of the 2-amino-1-indanol **7** is that of the ring fusion in the adduct **3**. The *trans* structure has been assigned to **7** by Rosen, *et al.*,[10] on the basis of its nmr spectrum, now requiring **3** also to be *trans*. Since this appeared most improbable, the stereochemical assignment of **7** was reexamined and means of establishing the stereochemistry by methods other than nmr spectroscopy were sought.

In previous work we had obtained the isomeric 2-amino-1-indanol **9** (mp 104–105°) as the major product from the hydrogenation of 2-oximino-1-indanone (**6**) in ethanol containing hydrochloric acid over palladium on carbon, even though hydrogenation of **6** under the not too dissimilar conditions of acetic acid containing sulfuric acid over palladium black gave the other isomer **7** as the major product (see Scheme I). The reason for this divergence in results under the described empirically determined hydrogenation conditions is not apparent. Having on hand both the isomeric amino alcohols **7** and **9**, stereochemical assignments could be made more rigorously. The infrared spectrum of **7** in methylene chloride at successive dilutions showed band shifts associated with intramolecular hydrogen bonding. A broad hydroxyl stretching band at 3590 cm^{-1} with an inflection at 3650 cm^{-1} due to the unbonded form is seen. There was no material change in the shape of the curve on successive dilutions. The spectrum of **9** showed the bonded hydroxyl band at 3580 cm^{-1} and a distinct band due to the unassociated hydroxyl at 3680 cm^{-1}. Successive dilutions increased the intensity of the latter at the expense of the 3580-cm^{-1} band. These measurements indicated **7** to be the *cis* and **9** the *trans* amino alcohol. This difference in infrared spectra could be seen more clearly on the dimethylamino alcohols **8** and **13**. The broad bonded hydroxyl stretching band at 3375 cm^{-1} seen in the spectrum of **8** was not changed by dilution, while the corresponding band of **13** at 3380 cm^{-1} virtually disappeared on dilution and the sharp band at 3580 cm^{-1} due to unbonded hydroxyl grew in intensity.

Chemical evidence indicating the *cis* stereochemistry of **7** is also available. Close[11] has shown that

SCHEME I



pseudoephedrine, in which the hydroxyl and amino groups in their preferred conformations are closer to each other than in ephedrine,[12] gives an oxazolone on reaction with urea. By contrast, ephedrine gives an imidazolone. We found **7** to give the oxazolone **10** in good yield on reaction with urea. Under the same reaction conditions **9** gave an intractable resinous material.

Acid-catalyzed N → O acyl migrations are well known in systems in which the interacting groups are close. N-Benzoylpseudoephedrine rearranges very readily to the O-benzoate under conditions which leave the ephedrine derivative unchanged.[13] However, applying

(8) W. E. Rosen and M. J. Green, *J. Org. Chem.*, **28**, 2797 (1963).

(9) It is known that the ephedrine ⇌ pseudoephedrine equilibration with a similarly situated benzyl hydroxyl is acid catalyzed by 25% hydrochloric acid; see H. Emde, *Helv. Chim. Acta*, **12**, 377 (1929).

(10) W. E. Rosen, L. Dorfman, and M. P. Linfield, *J. Org. Chem.*, **29**, 1723 (1964).

(11) W. J. Close, *ibid.*, **15**, 1131 (1950).

(12) J. B. Hyne, *Can. J. Chem.*, **39**, 2536 (1961).

(13) G. Fodor, V. Bruckner, J. Kiss, and G. Óhegyi, *J. Org. Chem.*, **14**, 337 (1949).

this technique to the differentiation of **7** and **9** was of no value. The N-benzoates of **7** and **9** both rearranged under acid catalysis to a single O-benzoate and at about equal rates. Acyl migration of the *trans* benzoate (**11**) must readily occur *via* the intermediate **12** with inversion at C-1 to give the *cis* O-benzoate.

During the course of the present work a publication reinforcing our data appeared.[14] Thrift found that reductive acetylation of **6** followed by sodium borohydride reduction of the ketone gave an acetamidoindanol which on acid hydrolysis gave one aminoindanol and on basic hydrolysis another. It was reasoned that the acid-catalyzed hydrolysis proceeding *via* an intermediate of the type of **12** would yield the inverted or *cis* compound. However, it is also possible that the acetamidoindanol could have the *cis* configuration and acid hydrolysis would give the *trans* amino alcohol, since it is known[9] that acid may invert the benzyl alcohol. The N-acyl group is not necessary for inversion to occur.[15]

Despite several descriptions of the two 2-amino-1-indanols[16] their distinction by the melting points of the isomeric bases and hydrochlorides is not possible: melting point of **7**, 107–108°; hydrochloride, 206°; O-N-diacetate, 118–120°; melting point of **9**, 102–104°; hydrochloride, 229–230°; O-N-diacetate, 210–212°. They can be distinguished, however, by the melting points of the diacetyl derivatives. Judged solely on the basis of melting points, previous reports[16] probably dealt with mixtures.

The methylamino alcohol **5** is identical (mixture melting points and infrared spectra) with one of unspecified stereochemistry described by Heinzelmann, *et al.*[17] It had been prepared by substitution of *trans*-1,2-dibromoindane first at the 1 position by a benzyloxy and then at the 2 position by a benzylmethylamino group, followed by removal of the benzyl groups. The configuration of the amino alcohol resulting from these two consecutive nucelophilic substitution reactions could not be predicted with certainty, although it is recognized that the bromo group is a stronger participating neighboring group than is alkoxy.[18] Since the structure of this amino alcohol **5** is now shown to be *cis*, it is evident that the first substitution reaction proceeded with retention and the second with inversion.

Two incidental observations of chemical behavior of the aminoindanols remain to be described. When either *cis*-2-dimethylamino-1-indanol (**8**) or the *trans* isomer **13** was dissolved in trifluoroacetic acid, complete esterification had occurred within the time required for a nmr spectral determination (2 min). The esters **14** and **15** were shown to be present by the downfield shift of the C-1 proton in their nmr spectra and by the ester carbonyl bands in the infrared spectra.

(14) R. I. Thrift, *J. Chem. Soc.*, 288 (1967).

(15) The configurational assignments of the amino indanols parallel those of the amino tetralols [F. Zymalkowski and H. J. Rimek, *Arch. Pharm.* (Weinheim), **294**, 581 (1961)]. The stereochemistry of the latter was confirmed recently by interpretation of their nmr spectra [R. Violland, R. Gaige, and H. Pacheco, *Bull. Soc. Chim. Fr.*, 2105 (1967)].

(16) *Cf.* N. Levin, B. E. Graham, and H. G. Kolloff, *J. Org. Chem.*, **9**, 380 (1944); T. Kametani, H. Sugahara, and S. Asagi, *Chem. Pharm. Bull.* (Tokyo), **14**, 1409 (1966).

(17) R. V. Heinzelmann, B. O. Aspergren, and J. H. Hunter, *J. Org. Chem.*, **14**, 906 (1949). We thank Dr. Heinzelmann for a sample with which to make this comparison.

(18) C. A. Bunton, "Nucleophilic Substitution at a Saturated Carbon," Elsevier Publishing Co., New York, N. Y., 1963, p 53.

In order to confirm that the unusually large C_1 proton shift caused by the dissolution of **8** and **13** in trifluoroacetic acid was indeed due to a combination of esterification and protonation and not purely a protonation effect, a number of comparisons were made. Though the spectra were not taken in trifluoroacetic acid, it could be seen that the downfield effect of protonation of the C-2 nitrogen from compounds **5**, **7**, **8**, **9**, and **13** in deuterium oxide was in the order of 52–67 cps (Table I), the smaller value being the N-methyl compounds. Compounds **14** and **15**, the trifluoroacetic esters, exhibit a downfield shift of 102 and 99 cps, respectively. The additional shift of 50 cps over that seen by N-protonation alone is due to esterification. It should be noted that O-acetylation of compound **8** shifts the C-1 proton 78 cps downfield. Making the salt (spectrum in sulfuric acid-d_2: deuterium oxide) produced an additional effect of 30 cps or a total of 108 cps.

Since a unique ester is formed from each alcohol, esterification must have been taken place without inversion. If it had occurred *via* a benzyl carbonium ion, the same ester or mixture of esters should have been present from either **8** or **13**. During attempts to isolate the pure trifluoroacetate esters by basification of the amine salt mixture obtained by removal of either excess trifluoroacetic acid or anhydride, such rapid hydrolysis occurred that only a mixture of predominantly alcohol plus a minor amount of ester could be obtained. Ester could be recognized by the infrared spectra but could not be separated in a pure state from the mixture. The fact that the starting alcohol was obtained is additional evidence that esterification occurred without inversion.

When a trifluoroacetic acid solution of **8** or **13** was allowed to stand, equilibration of the esters was observed and within 3 days the same 55–45% mixture of esters, with the *trans* isomer predominating, was obtained. Refluxing of **8** in 2 *N* hydrochloric acid causes equilibration of the alcohols. Because the extremely rapid esterification at 25° of **8** and **13** by trifluoroacetic acid was somewhat unexpected, it was considered of interest to briefly examine the esterification of simpler benzyl alcohols. 1-Indanol immediately forms an insoluble polymer in trifluoroacetic acid. Benzyl alcohol is esterified considerably slower in trifluoroacetic acid under the same conditions as used for **8** and **13** with a half-life at 42° of about 12 min. Addition of one molar equivalent of triethylamine caused no change in this rate of esterification. Finally, it might be noted that by ring opening of **3** mild acid hydrolysis yields the amino alcohol derivative **16**. Since there is no reason to believe that hydrolysis has taken place with inversion, **16** most probably belongs to the *cis* series.

Since the *cis*-2-aminoindanol (**7**) had been assigned erroneously, the *trans* configuration by Rosen, *et al.*,[10] a reevaluation of the nmr data on 1,2-disubstituted indanes became necessary. The previous authors noted that a small series of simple 1,2-disubstituted indanes could be divided into two groups on the basis of the complexity of the nmr signals of the C-3 methylene protons. These protons in the *cis* compounds were seen as a doublet and in the *trans* compounds as an octet. Since **7** showed a multiplicity of bands which

TABLE I

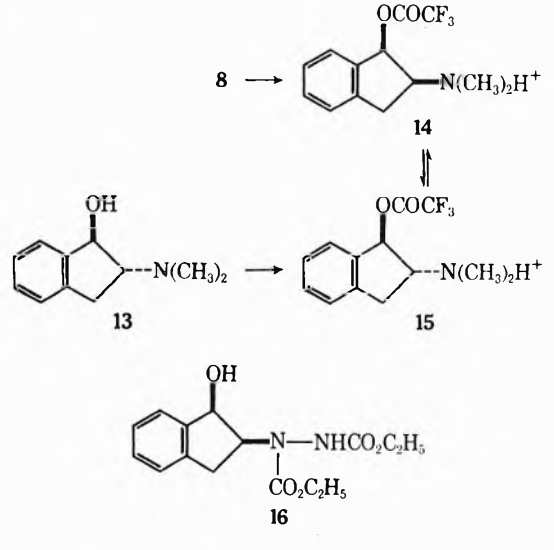
NUCLEAR MAGNETIC RESONANCE DATA OF *cis*- AND *trans*-1,2-DISUBSTITUTED INDANS[a]

Compd	Substituent C1	Substituent C2		H_{3a}		H_{3b}	H_2	H_1	Other hydrogens	
7	OH	NH_2	*cis*[b]		172[c] m		215 q	285 d (5.4)	OH, NH_2	153
	OH	$NH_2 \cdot HCl$	*cis*[d]		220[c] m		270 q	346 d (5.8)		
9	OH	NH_2	*trans*[b]	147 q		~186 m	~203 m	281 d (6.1)	OH, NH_2	173
	OH	$NH_2 \cdot HCl$	*trans*[d]	206 q		240 q	~260 m	348 d (5.2)		
5	OH	$NHCH_3$	*cis*[b]		174[e] m		~193 m	289 d (5.5)	CH_3	145
	OH	$NHCH_3 \cdot HCl$	*cis*[d]		218[c] m		254 m	341 d (5.4)	CH_3	198
8	OH	$N(CH_3)_2$	*cis*[b]		~173[e] m		~173 m	290 d (5.0)	CH_3	140
									OH	241
	OH	$N^+(CH_3)_2H$	*cis*[d]		~222 m		~252 m	342 d (4.9)	CH_3	206, 211
13	OH	$N(CH_3)_2$	*trans*[b]		~167[c] m		~167 m	302[g] t[j]	CH_3	135
									OH	331
	OH	$N^+(CH_3)_2H$	*trans*[f]		~238 m		~238 m	354 d (6.0)	CH_3	202, 208
	OH	$N^+(CH_3)_3I^-$	*cis*[d]				~263 m	354 d (5.0)	CH_3	229
	$OCOCH_3$	$N(CH_3)_2$	*cis*[b]		~182 m		~182 m	368 d (4.9)	CH_3	141
									$COCH_3$	122
	$OCOCH_3$	$N^+(CH_3)_2H$	*cis*[f]		~227 d		~260 m	398 d (5.0)	CH_3	207, 209
									$COCH_3$	148
14	$OCOCF_3$	$N^+(CH_3)_2H$	*cis*[g]		209[c] m		252 m	392 d (4.7)	CH_3	196
15	$OCOCF_3$	$N^+(CH_3)_2H$	*trans*[g]		~210[i]		260 m	401 d (4.3)	CH_3	185
17	$OCOCH_3$	$NHCOCH_3$	*cis*[b]		184[c] m		290 m	365 d (6.1)	CH_3	120, 122
20	$OCOCH_3$	$NHCOCH_3$	*trans*[b]	162 q		210 q	273 m	369 d (6.0)	CH_3	117, 126
18	OH	$NHCOC_6H_5$	*cis*[h]		186[c] m		278 m	300 d (6.0)		
19	OH	$NHCOC_6H_5$	*trans*[h]	166 q		194 q	264 m	311 d (7.0)		
16	OH	$N(COOC_2H_5)(NHCOOC_2H_5)$	*cis*[d]		180[c] m		284 m	315 q[j] (8.5)	CH_3 t	77 (6.8)
									CH_2 q	253
	OH	NHCHO	*trans*[h]	164 q		193 q	250 m	296 d (6)	CHO	488
21	$OCOC_6H_5$	$NH_2 \cdot HCl$	*cis*[d]		~221[c] m		~274 m	401 d (5.5)		
4	OH	$N(CH_3)(NHCH_3)$	*cis*[b]		~180[e] m		~180 m	300 d (4.4)	CH_3	152, 154
3			*cis*[b]		193[c] m		301 m	327 d (4.5)	CH_3	79 t (7.0)
										83 t (7.0)
									CH_2	260 q
										264 q
10			*cis*[h]		183[c] m		274 m	354 d (7.5)		

[a] The spectra were obtained with a Varian A-60 spectrometer. All data reported in cycles per second (cps) from tetramethylsilane as internal standard. d = doublet, t = triplet, q = quartet, m = multiplet, and values in parentheses are coupling constant in cps obtained by first-order analysis. The symbol ~ indicates the values are approximate due to overlapping bands from other protons. [b] Chloroform-*d*. [c] See text for interpretation. [d] Deuterium oxide. [e] The observed triplet is most likely a quartet. H_1 is coupled (4.3) to H_2 and each band split (3.5) by the H_3 proton which forms a figure W with the C_1 [S. Sternhell, *Rev. Pure Appl. Chem.*, 14, 15 (1964)]. [f] Sulfuric acid-d_2. [g] Trifluoroacetic acid. [h] Dimethyl sulfoxide-d_6. [i] Assignment of the respective protons was difficult; however, they have the general appearance of an octet with a spread of at least 50 cps. [j] Coupling of H_1 with OH is removed by addition of D_2O.

appeared to be an octet, it was assigned the *trans* stereochemistry. We have listed (Table I) the spectral data for a number of *cis* and *trans* compounds whose stereochemistry now has been established unequivocally.

Three types of spectra can be observed for our series of 1,2-disubstituted indanes. Provided an electronegative group is present at C-2 producing an appreciable chemical shift difference between the protons at C-2 and C-3, the *trans* series always gives AMX-type spectra. *cis* compounds have ABX spectra in which the differences in chemical shift between the C-3 methylene protons vary, but are always smaller than those of the related *trans* compound. These ABX spectra may vary. For example, the *cis* amino alcohol **7** shows four strong bands of irregular intensity in a central cluster with very weak wings. The diacetate **17** exhibits three bands. An irregular doublet is seen for **16** and **17**. The oxadiazene **3** exhibits seven bands. In general, the AB bands overlap. Since AMX and ABX spectra merge as the difference in chemical shift between the C-3 protons decreases, it is advisable to examine the spectra of both the *cis* and *trans* compound when using nmr data in assigning



stereochemical configuration. A third type of spectrum, the ABC type in which the difference in chemical shift between C-2 and C-3 is small, is of no help in determining stereochemistry. The methylated amino alcohols **4**, **8**, and **13** fall into this class.

The vicinal coupling constants of the C-1 and C-2 protons cannot be used to determine stereochemistry. If the five-membered ring were planar, *cis* compounds with a vicinal angle of 0° should have a larger coupling constant than *trans* compounds. However, the five-membered ring in 1,2-dihydroxyindane is known to be puckered,[19] and the extent of puckering will be dependent on the type of substitution at C-1 and C-2. Thus, even if the Karplus values were to hold rigidly, coupling constants would not unerringly give correct stereochemistry since the degree of distortion from planarity is not known beforehand. For example, $J_{1,2}$ is larger for the *trans* amino alcohol **9** than for the *cis* **7**, while the reverse is true for their respective hydrochlorides. Similarly, the *trans* N-benzoate **19** has a larger $J_{1,2}$ than does the *cis* stereoisomer **18**. A similar situation has been encountered in some 2,3-disubstituted dihydrobenzofurans.[20]

Experimental Section[21]

2-(1,2-Dimethylhydrazino)-1-indanol (4).—A solution of 5.1 g of the oxadiazine **3** in 175 ml of anhydrous ether was added dropwise with stirring to a suspension of 3 g of lithium aluminum hydride in 20 ml of ether. The reaction mixture was refluxed for 2 hr then decomposed by the cautious addition of 15 ml of ethyl acetate, followed by 3 ml of water, 6 ml of 12% sodium hydroxide solution, and finally 9 ml of water. The inorganic solids were filtered and the filtrate extracted with 5% hydrochloric acid. The aqueous layer was made basic with ammonium hydroxide and the organic material extracted into ether. The ether was dried ($MgSO_4$) and evaporated. The solid residue was triturated with petroleum ether (bp 30–60°), giving 1.4 g of product **4**, mp 70–73°.

Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.82; H, 8.34; N, 14.39.

2-(2-Acetyl-1,2-dimethylhydrazino)-1-indanyl Acetate.—A solution of 250 mg of **4** in 0.25 ml of pyridine and 0.25 ml of acetic anhydride was allowed to stand at room temperature for 1 week, then poured into ice–water and shaken for 15 min. The reaction mixture was made basic with ammonium hydroxide and the organic material extracted into chloroform. The chloroform solution was washed with water, dried ($MgSO_4$), and evaporated *in vacuo*. The residue, which slowly solidified was recrystallized from benzene–petroleum ether (bp 30–60°), mp 84–86°.

Anal. Calcd for $C_{15}H_{20}N_2O_3$: C, 65.19; H, 7.30; N, 10.14. Found: C, 65.51; H, 7.43; N, 10.38.

Reductions of 4 to *cis*-2-Methylamino-1-indanol (5).—A solution of 0.6 g of **4** in 10 ml of 90% acetic acid was reduced over 40 mg of platinum oxide at atmospheric pressure. After the uptake of one molar equivalent of hydrogen, the catalyst was filtered off and the solvent evaporated *in vacuo*. The residue after treatment with excess 50% potassium hydroxide was extracted with ethyl acetate. Evaporation of the solvent left a crystalline residue (mp 70–72°) which by analysis appeared to be essentially **5**.

Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 72.61; H, 8.16; N, 8.75.

The picrate melted at 170–171° after recrystallization from ethanol.

Anal. Calcd for $C_{10}H_{13}NO \cdot C_6H_3N_3O_7$: C, 48.98; H, 4.11; N, 14.28. Found: C, 48.71; H, 4.18; N, 13.98.

Braun[22] reported a trace amount of a methylamino indanol formed at the end of a reaction sequence beginning with 1-bromo-2-indanol melting at 77–79° and a picrate melting at 171° which is undoubtedly **5**. The hydrochloride of **8** prepared with ethanolic hydrogen chloride and recrystallized from ethanol–ether melted at 168–170°. A sample of **5** obtained from Dr. Heinzelmann[17] melted at 160–162° (mixture melting point with our sample 161–163°). Infrared absorption spectra of the two samples were identical.

Anal. Calcd for $C_{10}H_{13}NO \cdot HCl$: C, 60.12; H, 7.07; N, 7.01. Found: C, 60.31; H, 6.89; N, 7.36.

***cis*-2-Dimethylamino-1-indanol (8) from 5 and *cis*-2-Amino-1-indanol (7).**—A solution of 0.6 g of **5** was refluxed in 8 ml of propanol with 0.7 ml of 36% formaldehyde solution and 0.55 ml of formic acid for 6 hr. After evaporation *in vacuo* the residue was treated with excess 50% potassium hydroxide and extracted with ethyl acetate. Evaporation of the solvent and recrystallization of the residue from methanol yielded 0.4 g of **8**, mp 124–126°.

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.99. Found: C, 74.30; H, 8.46; N, 7.80.

The hydrochloride (recrystallized from ethanol–ethyl acetate) melted at 175–176°.

Anal. Calcd for $C_{11}H_{15}NO \cdot HCl$: C, 61.81; H, 7.52; N, 6.56. Found: C, 61.81; H, 7.79; N, 6.47.

Similar methylation of **7**[8] gave a sample of the dimethyl derivative **8** which by mixture melting point, nmr, and infrared spectra proved to be identical with the sample of **8** derived by the monomethylation of **5** described above.

***cis*-2-Dimethylamino-1-indanol Methiodide from 5 and 7.**—A mixture of 0.15 g of **5**, 0.18 ml of methyl iodide, and 0.7 g of potassium carbonate in 5 ml of acetonitrile was refluxed for 6 hr. The inorganic salts were filtered off hot, and cooling the filtrate yielded 0.20 g of the methiodide of **8**, melting point after recrystallization from ethanol 227–230° dec.

Anal. Calcd for $C_{12}H_{18}INO$: C, 45.14; H, 5.68; N, 4.39. Found: C, 45.16; H, 5.77; N, 4.42.

Similar methylation of **7** or treatment of the dimethyl derivative **8** with methyl iodide gave methiodides shown to be identical by mixture melting point and infrared spectra with the sample described above.

***trans*-2-Amino-1-indanol (9) Hydrochloride and Base.**—A solution of 3.7 g of 2-hydroxyimino-1-indanone (**6**) and 13.5 ml of 6.1 *N* ethanolic hydrogen chloride in 230 ml of ethanol in the presence of 600 mg of 20% palladium on carbon was hydrogenated at 40 psi pressure. The absorption of hydrogen ceased after 30 min, during which time approximately 3 mol of hydrogen was absorbed. The catalyst was filtered and the filtrate evaporated *in vacuo*. The solid residue was washed well with ether and recrystallized three times from ethanol–ether, mp 222–224°.

Anal. Calcd for $C_9H_{11}NO \cdot HCl$: C, 58.12; H, 6.52; N, 7.54. Found: C, 58.28; H, 6.27; N, 7.32.

The corresponding base was prepared by dissolving the hydrochloride in a minimum amount of water, making it strongly basic with ammonium hydroxide, and extracting into ether. The ether solution was dried ($MgSO_4$) and concentrated and the solid residue recrystallized from benzene, mp 100–103°.

Anal. Calcd for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.42; H, 7.66; N, 9.11.

3,3a,4,8b-Tetrahydroindeno[2,1-*d*]oxazol-2-one (10).—A mixture of 0.15 g of **7** and 0.15 g of urea in 5 ml of ethanol was acidified with 6 *N* ethanolic hydrogen chloride, evaporated to dryness, and heated in an oil bath at 170° for 0.5 hr and at 200° for 1 hr. The residue was washed with water and recrystallized from ethanol yielding **10**, mp 205–206°.

Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.26; H, 5.07; N, 8.06.

Heating of **9** hydrochloride with urea at various temperatures yielded only starting material or an intractable tar.

***cis*-N-(1-Hydroxy-2-indanyl)benzamide (18).**—A mixture of 300 mg of the *cis* amino alcohol **7** and 337 mg of benzoyl chloride was react under the usual Schotten–Baumann conditions. The product was recrystallized from ethanol: mp 200–202°; yield, 250 mg; infrared 1630 cm^{-1} (amide I), 1560 cm^{-1} (amide II).

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.90; H, 6.13; N, 5.31.

***trans*-N-(1-Hydroxy-2-indanyl)benzamide (19).**—Similarly 500 mg of the *trans* amino alcohol **9** was benzoylated. After recrystallization from ethanol–benzene the product melted at 229–230° dec: yield 580 mg; infrared 1630 cm^{-1} (amide I), 1560 cm^{-1} (amide II).

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.79; H, 5.95; N, 5.60.

Rearrangement of 18 and 19 to Yield *cis*-2-Amino-1-indanol Benzoate Hydrochloride (21).—A solution of 250 mg of *cis*-N-(1-hydroxy-2-indanyl)benzamide in 10 ml of ethanol and 0.18 ml of

(19) F. V. Brutcher, Jr., and E. L. James, *Diss. Abstr.*, **24**, 1938 (1963).

(20) L. H. Zalkow and M. Ghosal, *Chem. Commun.*, 922 (1967).

(21) Nmr spectra were recorded on a Varian A-60 instrument using tetramethylsilane as an internal standard. Solvents are recorded in Table I. Infrared spectra were run as Nujol mulls on a Perkin-Elmer 521 spectrophotometer. Melting points were determined with a Thomas–Hoover apparatus.

(22) J. V. Braun and K. Weissbach, *Ber.*, **63**, 3052 (1930).

6.088 *N* ethanolic hydrogen chloride was refluxed on a steam bath for 15 min. The solvent was evaporated *in vacuo* and the residue was triturated with 10 ml of water and filtered. The filtrate was evaporated to dryness *in vacuo* and the solid residue was washed well with ether: yield of **21**, 70 mg; mp 122–123°; infrared 1715 cm^{-1} (ester C=O).

Anal. Calcd for $C_{16}H_{15}NO_2 \cdot HCl$: C, 66.31; H, 5.56; N, 4.83. Found: C, 66.31; H, 5.48; N, 4.65.

The water-insoluble precipitate, mp 185–186°, weighed 1 70 mg; infrared 1630 cm^{-1} (amide I), 1560 cm^{-1} (amide II).

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.90; H, 6.13; N, 5.31.

Treatment of 200 mg of *trans*-N-(1-hydroxy-2-indanyl)benzamide with 0.15 ml of 6.088 *N* ethanolic hydrogen chloride in an analogous manner yielded 160 mg of unchanged N-benzamide and 30 mg of **21** whose infrared and nmr spectra were identical with that of the *cis* compound described above.

***cis*-2-Acetamidoindanyl Acetate (17).**—A solution of 250 mg of the *cis* amino alcohol (**7**) in 1 ml of pyridine and 1 ml of acetic anhydride was allowed to stand at room temperature for 5 days, then poured into 5 ml of ice and 10 ml of water. The reaction mixture was stirred for 1 hr, keeping the temperature below 25°, then made basic with ammonium hydroxide. The organic material was extracted into ether, washed with water, dried ($MgSO_4$), and evaporated. The solid residue was recrystallized from benzene–petroleum ether (bp 30–60°), mp 118–120°, yield 140 mg.

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 67.11; H, 6.53; N, 5.87.

***trans*-2-Acetamidoindanyl Acetate (20).**—The *trans* amino alcohol **9** (250 mg) was treated as described above, mp 210–212°, yield 230 mg.

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 67.05; H, 6.46; N, 5.92.

***cis*-1-Amino-2-indanol (7) Hydrochloride.**—The salt prepared from a purified sample of **7**[8] with ethanolic hydrogen chloride and recrystallized from 2-propanol melted at 206° rather than the 181–182° reported.[8]

Anal. Calcd for $C_9H_{11}NO \cdot HCl$: C, 58.12; H, 6.52; N, 7.54. Found: C, 58.00; H, 6.33; N, 7.39.

***trans*-2-Dimethylamino-1-indanol (13).**—A solution of 1.75 g of the *trans* amino alcohol **9**, 2.1 ml of 36% formaldehyde solution, and 1.65 ml of formic acid in 25 ml of propanol was reacted as described above. The solid residue was recrystallized from ethyl acetate–ether, mp 105–107°.

Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.99. Found: C, 74.78; H, 8.65; N, 7.81.

***cis*- and *trans*-2-Dimethylamino-1-indanol Trifluoroacetates (14 and 15).**—Nmr spectra were run by dissolving 50 mg of **8** and **13** in 0.1 ml of trifluoroacetic acid and completing the spectra as quickly as possible. The whole operation was completed in 2 min. The probe temperature was 40°. The spectrum of **14** resulting from the solution of **8** and of **15** resulting from the solution of **13** were characterized by doublets at 392 and 401 cps, respectively, due to the protons at C-1. No detectable amount of the unesterified **8** or **13** were present. By 2 hr later, at room temperature, measureable amounts of the C-1 epimer were detectable in the spectra of both **14** and **15**. By 3 days later, both had reached the equilibrium value of 55–45% with **15** predominating. Infrared spectra were run on the noncrystalline powder obtained by quickly evaporating freshly made solutions of **8** and **13** in trifluoroacetic acid. The ester bands of **14** and **15** were seen at 1775 and 1770 cm^{-1}, respectively. When attempts were made to isolate the bases **14** and **15** obtained from the solutions of **8** or **13** in trifluoroacetic acid or anhydride by basification of the salts with ammonia or sodium hydroxide and rapid extraction into ether, mixtures containing largely alcohol (infrared) were obtained. Recrystallization was unsuccessful in separating in a pure state the minor amount of unsaponified ester.

Esterification of Benzyl Alcohol with Trifluoroacetic Acid.—Benzyl alcohol (150 mg) was added to 0.4 ml of trifluoroacetic acid at 42° in a nmr probe. It was placed in the spectrometer, with the probe kept at 42°, and integrated between 250 and 350 cps at 1-min intervals. Integration of the singlet due to the methylene protons of benzyl alcohol at 282 cps and that due to the corresponding protons of the esterified alcohol at 319 cps was used to measure the rate of esterification. At 2 min esterification was 10% complete and at 12 min half complete.

Epimerization of *cis*-2-Dimethylamino-1-indanol (8).—A solution of 0.6 g of **8** in 6.3 ml of 1.6 *N* hydrochloric acid (3 molar equivalents) was refluxed for 16 hr. Addition of potassium hydroxide pellets and extraction with ethyl acetate gave a crude base which by nmr spectral analysis of the C-1 proton region was shown to be 62% *cis* (**8**) and 38% *trans* alcohol (**13**). (See Table I for nmr data.) Repetition of the acid treatment for an additional 36 hr gave a 50–50% mixture of the two alcohols.

Ethyl 2-(1-Hydroxy-2-indanyl)bicarbamate (16).—A solution of 4 g of the oxadiazine **3** in 10 ml of ethanol and 10 ml of water containing 1.25 ml of 8 *N* ethanolic HCl was refluxed for 1 hr. A small amount of flocculent material was filtered off, then the solvent was evaporated *in vacuo*. The organic material was taken up in ether and the ether solution washed with water, 10% sodium bicarbonate, and water, dried ($MgSO_4$), and evaporated. The oily residue, which slowly solidified, was recrystallized from benzene–petroleum ether (bp 30–60°), mp 128–129°.

Anal. Calcd for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.49; H, 6.52; N, 8.95.

Registry No.—**3**, 23337-75-9; **4** (*cis*), 23337-76-0; **5** (*cis*), 23337-77-1; **5** (HCl) (*cis*), 23337-78-2; **5** (picrate) (*cis*), 23337-79-3; **7** (*cis*), 23337-80-6; **7** (HCl) (*cis*), 23337-81-7; **8** (*cis*), 23359-90-2; **8** (cation H^+) (*cis*), 23335-56-0; **8** (HCl) (*cis*), 23337-82-8; **8** (methiodide) (*cis*), 23337-83-9; **9** (*trans*), 23359-91-3; **9** (HCl) (*trans*), 23337-84-0; **10**, 23337-85-1; **13** (*trans*), 23337-86-2; **13** (cation H^+) (*trans*), 23335-57-1; **13** (acetate) (*cis*), 23353-58-4; **13** (acetate) (cation H^+) (*cis*), 23335-58-2; **14** (cation H^+) (*cis*), 23335-59-3; **15** (cation H^+) (*trans*), 23355-56-8; **16** (*cis*), 23353-59-5; **16** (formylamine) (*trans*), 23353-60-8; **17** (*cis*), 23353-61-9; **18** (*cis*), 23353-62-0; **19** (*trans*), 23359-92-4; **20** (*trans*), 23359-93-5; **21** (*cis*), 23359-94-6; **21** (HCl) (*cis*), 23359-95-7; 2-(2-acetyl-1,2-dimethylhydrazino)-1-indanyl acetate, 23359-96-8; indene, 95-13-6.

Acknowledgment.—We wish to thank Dr. G. de-Stevens for support. Analyses were carried out under the supervision of Mr. G. Robertson and nmr spectra by Miss Ruth Behnke.

Photochemical and Thermal 1,2- and 1,4-Cycloaddition Reactions of Azodicarbonyl Compounds with Monoolefins

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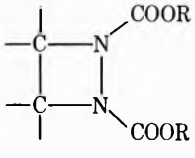
Received December 3, 1968

Dialkyl azodiformates form dihydrooxadiazines with indene, dihydro-1,4-dioxine, vinylene carbonate, *cis*- and *trans*-1,2-dimethoxyethylene, and vinyl acetate by 1,4 addition; 1,2 addition yielding diazetidines is observed with vinyl ethers. Diazetidines also result from the addition of 4-phenyl-Δ^1-1,2,4-triazoline-3,5-dione (PTD) to indene and dihydro-1,4-dioxine. Dihydrooxadiazines are formed in a concerted Diels–Alder reaction with *inverse electron demand*, the diazetidines *via* dipolar intermediates. The acceleration of azodiformate addition by illumination is due to the photochemical production of *cis* azodiformates, which show increased thermal reaction rates compared with the *trans* isomers.

The thermal reaction of azodicarbonyl compounds (*e.g.*, diethyl azodiformate) with monoolefins normally results in substitution, which may be combined with an obligatory shift of the double bond following a concerted[5-8] or free-radical path,[7c,9] or consists of a formal insertion into a =CH bond.[5,10]

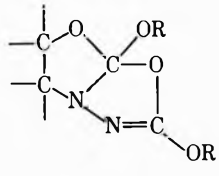
Of the variety of conceivable cycloaddition reactions the following four appear as the most plausible.

1,2 addition



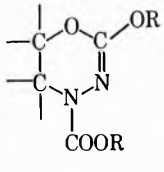
1

1,3 addition



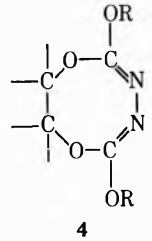
2

1,4 addition



3

1,6 addition



4

Only a few instances have been reported of 1,2-cycloaddition reactions[11-16] leading to diazetidines **1**, and of 1,4-cycloaddition reactions[16-18] with formation of dihydrooxadiazines **3**. 1,3 addition has been proposed for the reaction of $(CH_3)_3CCON{=}NCOC(CH_3)_3$ with diphenyl ketene.[19] To our knowledge no examples of 1,6 addition have been reported.

The mechanisms of these cycloaddition reactions have not yet been explored, and the factors governing the different paths are unknown. In this paper we wish (a) to present spectral and chemical evidence which allows one to distinguish between the different products, (b) to contribute to the understanding of the mechanisms of the 1,2- and 1,4-cycloaddition reactions, and (c) to discuss the photochemical acceleration of the two latter processes.

Results

Dihydrooxadiazines.—1,2-Disubstituted olefins without easily abstractable allylic hydrogen should undergo cycloaddition reactions with azodicarbonyl compounds. The two ring protons should have identical environments in **1** and **4**, but different ones in **2** and **3**, thus allowing a distinction by nmr.

Dihydro-1,4-dioxine, vinylene carbonate, and *trans*-1,2-dimethoxyethylene gave the 1:1 adducts **5–7** with dimethyl azodiformate (DMAD). The nmr data (Table I) show the two ring protons to be different; therefore **1** and **4** can be ruled out as structural possibilities.[20] The distinction between **2** and **3** should be possible by ir: two valence vibrations (C=O and C=N) are

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(3) Taken in part from the Ph.D. thesis D. V. White, Boston College, May 1969.

(4) Taken in part from the doctoral dissertation B. Kim, Göttingen University, 1966.

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(10) K. Alder and H. Niklas, *ibid.*, **585**, 97 (1954).

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(20) It could be argued that hindered rotation about the N–COOR bonds in **1** could possibly make the ring protons different. However, the nmr spectra of **5–7** remained unchanged at 70°, that is, far beyond the coalescence temperature for such processes.[21]

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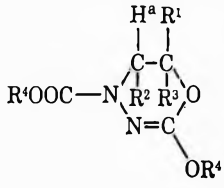
TABLE I

NMR DATA OF DIHYDROOXADIAZINES[a]



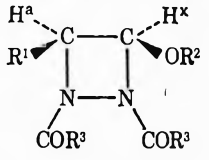
Compd	τ					Cps			Solvent
	H^a	R^1	R^2	R^3	R^4	J_{ax}	J_{bx}	J_{ab}	
5	4.51 (d)[b]	5.17 (d)[b]	6.9 (m)		6.44 (s); 6.48 (s)	1.9			C_6D_6
6	3.23 (d)[b]	3.68 (d)[b]			6.05 (s); 6.07 (s)	6.1			$CDCl_3$
7	4.45 (d)	6.97 (s)	6.73 (s)	5.10 (d)	6.42 (s)	1.4			C_6D_6
8	4.40 (d)	5.33 (d)	6.63 (s)[b]	6.72 (s)[b]	6.30 (s); 6.35 (s)	1.8			C_6D_6
9	6.55 (q)	7.90 (s)	6.0 (q)	3.51 (t)	5.82 (q); 8.70 (t)	2.5	2.5	13.5	CCl_4

Compd	Substituent			
5	H^x	OCH_2CH_2O		CH_3
6	H^x	OCO ‖ O		CH_3
7	OCH_3	OCH_3	H^x	CH_3
8	H^x	OCH_3	OCH_3	CH_3
9	—O—C—CH_3 ‖ O	H^b	H^x	C_2H_5

[a] The nmr spectra were recorded with a Varian A-60 A and HA-100; the letter abbreviations used follow: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, o = octet, m = multiplet, b = broad; tetramethylsilane was used as internal standard. [b] Reversed assignment possible.

TABLE II

NMR DATA OF DIAZETIDINES[a]



Compd	τ					Cps			Solvent
	H^a	H^x	R^1	R^2	R^3	J_{ab}	J_{ax}	J_{bx}	
10	5.57 (q)	4.77 (q)	5.99 (q)	6.51 (s)	6.17 (s); 6.19 (s)	9.5	6	4	$CDCl_3$
11	Under $R^2 + R^3$	4.80 (q)	Under $R^2 + R^3$	Obsc. (m); 8.78 (t)	5.82 (q); 8.74 (t)		6	4	CCl_4
12	5.55 (q)	4.67 (q)	5.95 (q)	~6.2 (m); 8.73 (t)	6.17 (s); 6.19 (s)	9.5	6	4	$CDCl_3$
12-D_1	5.55 (d)	4.62 (d)		~6.3 (m); 8.74 (t)	6.17 (s); 6.19 (s)		6		$CDCl_3$
13	4.78 (s)	= H^a	6.50 (s)	= R^1	6.44 (s)				C_6D_6
14	5.17 (s)	= H^a	6.26 (m)	= R^1	2.61 (m)				CD_3CN

Compd	Substituent		
10	H^b	CH_3	OCH_3
11	H^b	C_2H_5	OC_2H_5
12	H^b	C_2H_5	OCH_3
12-D_1	D	C_2H_5	OCH_3
13	OCH_3	CH_3	OCH_3

[a] See footnote *a*, Table I.

expected for **3**, one (C=N) for **2** in the 1600–1800-cm^{-1} region. However, all three adducts display three bands in this area, *e.g.*, **7** at 1678, 1714, and 1750 cm^{-1} (in CCl_4). While this observation appears incompatible with the structural type **2**, it easily can be reconciled with the dihydrooxadiazine structure **3**: two conformers with different overlap between the C=O π-orbital and the nitrogen nonbonding orbital result from hindered rotation about the N–COOR bond. This process has been demonstrated in a detailed nmr study published elsewhere,[22] and the ratio of the two conformers from nmr corresponds to the ratio of intensities of the 1714- and 1750-cm^{-1} bands in **7**. Therefore, these bands are assigned to the C=O vibrations and the 1678-cm^{-1} band to the C=N group.[23]

The dihydrooxadiazine **7** is formed in quantitative yield, but from *cis*-1,2-dimethoxy-ethylene and DMAD we obtained the dihydrooxadiazine **8** (Table I) and the diazetidine **13** (Table II) in a 4:1 ratio according to nmr. Vinyl acetate gave the dihydrooxadiazine **9** with diethyl azodiformate (DEAD); the structural assignment rests on the band at 1675 cm^{-1} (C=N).[24]

(22) E. Koerner von Gustorf, D. V. White, and J. Leitich, *Tetrahedron Lett.*, 3109 (1969).

(23) Cyclic C=N groups are known to cause strong absorption in the 1630–1680-cm^{-1} region: E. Fahr, K. Königsdorfer, and F. Scheckenbach, *Justus Liebigs Ann. Chem.*, **690**, 138 (1965); A. I. Meyers, *J. Org. Chem.*, **26**, 218 (1961).

(24) An earlier assignment[4,12] of a diazetidine structure to **9** is herewith revised.

TABLE III
NMR DATA OF INDENE ADDUCTS[a]

Compd	τ					Cps				
	H^a	H^b	H^x	H^y	R	J_{ab}	J_{ax}	J_{bx}	J_{xy}	Solvent
30a	6.9 (o)		5.17 (o)	4.78 (d)	5.82 (q) 5.88 (q) 8.72 (t) 8.77 (t)	16	9	7.5	5	CCl_4
30b	6.83 (o)		5.06 (o)	4.65 (d)	6.14 (s) 6.18 (s)	16	9	7.5	5	$CDCl_3$
21	6.78 (q)	6.08 (q)	4.61 (o)	4.07 (d)		18.8	6.6	1.1	5.6	$CDCl_3$
24	6.85 (q)	7.12 (d)	7.30 (t)	6.39 (d)		16.5	7	≦1.0	5.5	CD_3COCD_3

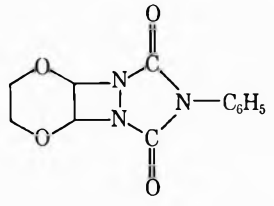
[a] See footnote *a*, Table I.

All dihydrooxadiazines failed to undergo catalytic hydrogenation at room temperature and normal pressure.

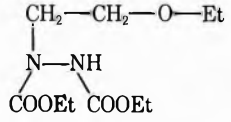
Diazetidines.—DMAD and DEAD form 1:1 adducts **10–12** with methyl and ethyl vinyl ether.[12,15] Compounds **10–12** (Table II) showed two bands at >1700 cm^{-1} in the 1600–1800-cm^{-1} region. The only structure compatible therewith is that of a diazetidine **1**. Compound **11** underwent ring opening to **15** on catalytic hydrogenation.

4-Phenyl-Δ^1-1,2,4-triazoline-3,5-dione[25] (PTD) is a *cis*-locked azodicarbonyl compound and a very electrophilic cyclophile: of the different modes of cycloaddition (**1–4**) only **1** is possible in this case.

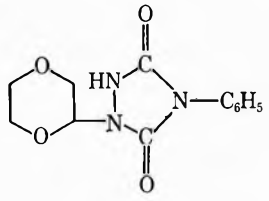
The diazetidine **14** (Table II) was obtained from PTD and dihydro-1,4-dioxine besides some polymeric material and showed identical ring protons as expected. Catalytic hydrogenation of **14** gave **16**.



14

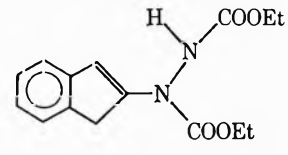


15

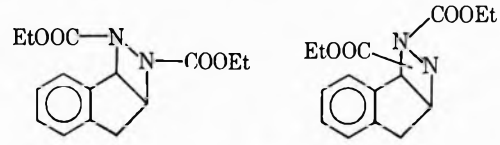


16

Azodiformate and PTD Adducts of Indene.—DEAD and indene form a 1:1 adduct at room temperature (80% yield after 1 month),[26] for which structures **17** and **18** have been suggested. Alder, *et al.*[10] showed a preference for **17**, since 2-indanone resulted from alkaline hydrolysis, and **29** was obtained by catalytic hydrogenation of the adduct. We recently ruled out **17** on the basis of spectral data and suggested[4,12] **18**; independently, Huebner, *et al.*,[27] reached the same conclusion.



17

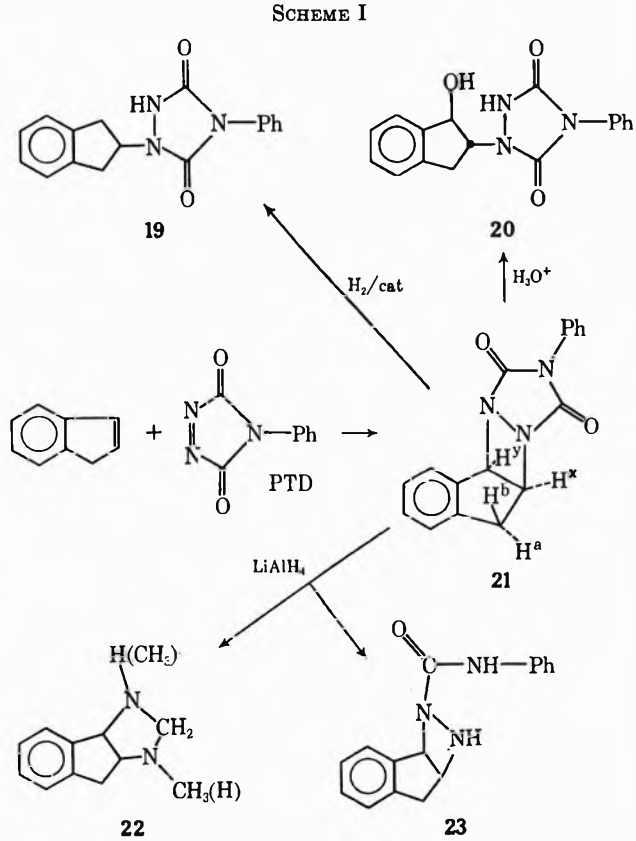


18

This structure has also to be revised on the basis of the following data. The reaction of indene with PTD gives the diazetidine **21**. The structure of **21** is based on its ir spectrum (>C=O at 1712 and 1782 cm^{-1} in KBr, no >NH), mass spectrum and nmr data (Table III); almost identical ABXY systems reveal the structural similarities of **21** (Scheme I) with the adduct (**25**) of indene and phthalazine-1,4-dione.[14]

The formation of **19** by ring cleavage in the benzylic

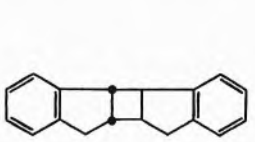
SCHEME I



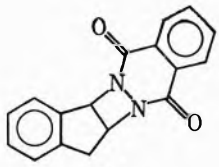
(25) J. Sauer and B. Schröder, *Chem. Ber.*, **100**, 678 (1967). We are grateful to Professor Sauer for detailed information about his procedure prior to publication, and for a generous sample of PTD. R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *J. Chem. Soc., C*, 1905 (1967).

(26) O. Diels and K. Alder, *Justus Liebigs Ann. Chem.*, **460**, 237 (1926).

(27) C. F. Huebner, *et al.*, *J. Org. Chem.*, **32**, 1126 (1967).



24

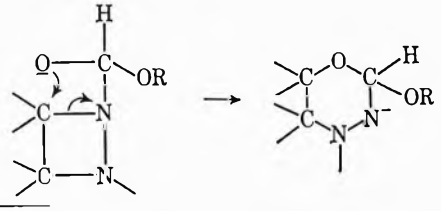


25

position on catalytic hydrogenation, and the proton-catalyzed attack of water leading to **20** are also in accord with **21**. A *trans* configuration has been assigned to **20** without further proof, since this should result from both SN2- or SN1-type attack of water on **21**.

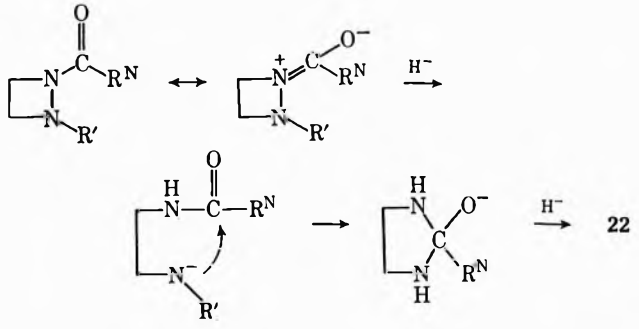
The reduction of **21** with $LiAlH_4$ yields N-methylaniline, aniline, N-N-dimethylaniline, indene, and large amounts of tarry materials. As further products only traces of the imidazole derivative **22** and of the diazetidine **23** could be isolated; their structures have been assigned tentatively on the basis of spectral evidence.[28] No alcoholic product was detected in the $LiAlH_4$ reduction of **21**.

A comparison of the reactions of **21** (Scheme I) with those of the adduct of indene and diethyl azodiformate (Scheme II) shows that hydrogenation[32] and hydrolysis lead to the analogous products **29** and **30**, whose structures are indicated by their spectra. However, with the formation of **28** in high yields with $LiAlH_4$ a basic difference between the two indene adducts becomes apparent. According to the results with **21** the OH in **28** does not stem from an attack by water on a diazacyclobutane system in the course of the work-up procedure. A formation of **28** *via* a rearrangement of **18** by AlH_4^- (eq 1) seems very unlikely.[34]

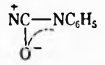


(1)

(28) The reduction of $NCONR_2 \rightarrow NCH_3$ in **22** parallels the behavior of carbamates[29] and diethyl tetrahydropyridazine-1.2-dicarboxylates[30] toward $LiAlH_4$; the mechanism of the rearrangement observed in the formation of **22** could be pictured as follows.



The carbonyl group in **23** is protected from further reduction, probably by formation of the resonance stabilized anion



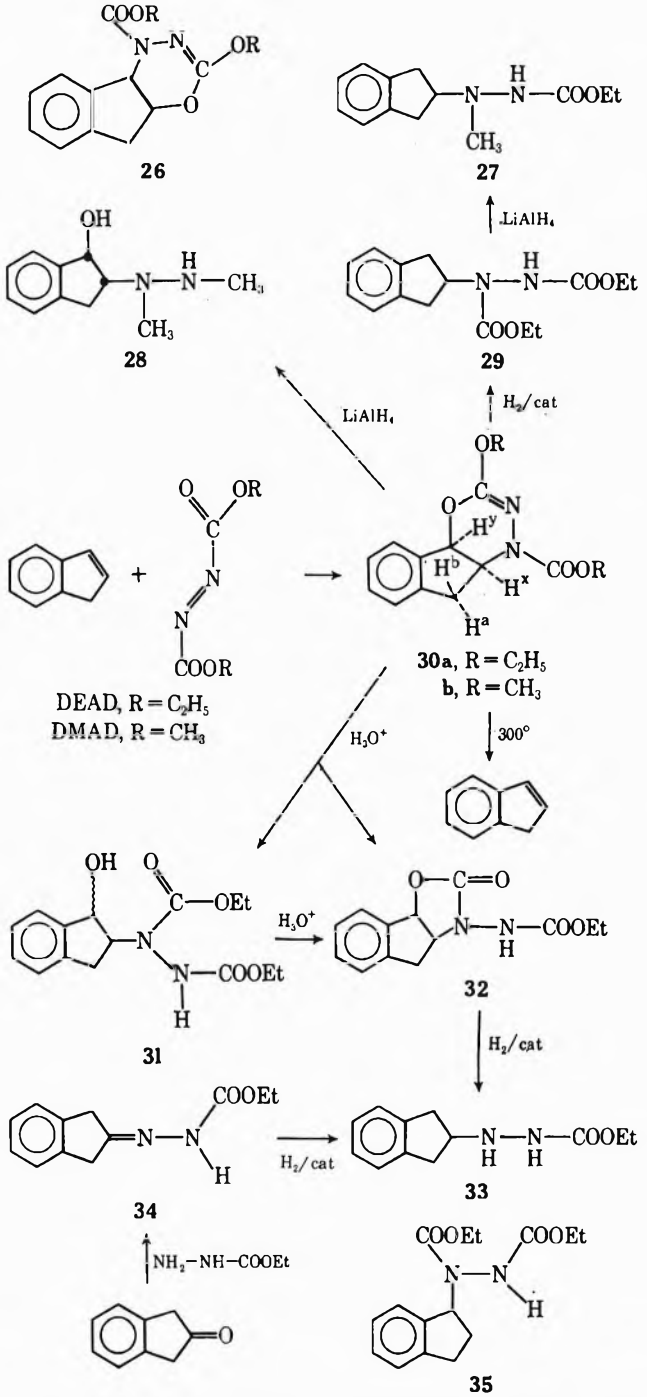
as postulated in a similar case.[31]

(29) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, p 636; B. Weiss, *J. Org. Chem.*, **30**, 2483 (1965).

(30) H. R. Snyder and J. G. Michels, *ibid.*, **28**, 1144 (1963).

(31) R. Huisgen, F. Jakob, W. Siegel, and A. Cadus, *Justus Liebigs Ann. Chem.*, **590**, 1 (1954).

SCHEME II[a]



[a] All reactions shown in this scheme have been carried out with **30a**.

Therefore, the predominant formation of **28** suggests that this indene adduct is correctly represented by the dihydrooxadiazine[36] structure **30** and not by the

(32) As it turned out later, **30** is the only dihydrooxadiazine, so far, which undergoes catalytic hydrogenation. This can be explained by the activation of the benzylic position, which is also responsible for the easy cleavage of benzyl ethers and esters on hydrogenation.[33]

(33) R. C. Fuson, "Advanced Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1953, p 261.

(34) Such a rearrangement would be analogous to that of, *e.g.*, N-benzoylaziridines to 2-oxazolines[35] by I^-. However, I^- did not have any effect on the indene azodiformate adduct, but rearranged[3] the diazetidine **10**.

(35) H. W. Heine, *Angew. Chem.*, **74**, 772 (1962).

(36) C. F. Huebner, E. M. Donoghue, C. J. Novak, L. Dorfman, and E. Wenkert, *J. Org. Chem.*, **35**, 1149 (1970), have also demonstrated the correctness of **30** by $LiAlH_4$ reduction to **28**, and have proven *cis* configuration for **28** by chemical means. Correspondence with Dr. Huebner, who kindly postponed the publication of his paper to allow the simultaneous appearance of our work is gratefully appreciated.

TABLE IV
IR DATA OF 30a AND 30b

Compd	Solvent	C=N (Cm⁻¹)	C=O (Cm⁻¹)	C=O (Cm⁻¹)
30a[a]	CH_3CN	1674	1700	1736
	CH_3NO_2	1672	1698	1732
	$C_6H_5NO_2$	1674	1699	1737
	C_5H_5N	1674	1698	1738
	C_6H_6	1675	1700	1743
	Dioxane	1675	1699	1743
	CCl_4	1674	1700	1743
	CH_2Cl_2	1672	1699 (sh)	1733
	$CHCl_3$	1671	1697 (sh)	1727
	$CHBr_3$	1667		1724
	C_2H_5OH	1667		1724
	KBr	1658	1683	1690
30b	$C_6H_5CH_3$	1675	1703	1745
	$CHCl_3$	1670	~1700 (sh)	1730

[a] See ref 39.

diazetidine structure **18**. A discussion of the nmr and ir data lends further support to this structural assignment.

The coupling constants in the nmr spectrum (Table III) of **21** closely resemble those in the cyclobutadiindene[37] **24**. Both compounds possess the same rigid arrangement of a four-membered ring fused to the five-membered ring of the indene moiety. J_{ax} and J_{bx} in the indene azodiformate adduct **30** are completely different from those in **21** and **24**. Inspection of molecular models reveals a dihedral angle close to 90° of H^bC–CH^x in **21**, thus explaining[38] the very small value of J_{bx}; the corresponding angle in **30** is much larger.

The ir spectrum of **30** shows three bands in the 1600–1800-cm^{-1} region whose positions have been studied in a variety of solvents (Table IV).[39] While the polarity of the solvent does not have a strong effect on these bands, their position is shifted to lower wavenumbers in those solvents which are capable of hydrogen bonding. Hydrogen bonding with chloroform could be demonstrated: the intensity of the C-D stretching vibration in $CDCl_3$ at 2254 cm^{-1} is strongly increased[40] by the presence of **30**. According to these solvent effects all three bands have to be attributed to >C=O or >C=N valence vibrations.

Up to four (possibly overlapping) >C=O bands could be expected[41] for the two possible configurational isomers of **18** by vibrational coupling.[42] However, according to our experience tetrahydropyridazine derivates resulting from the addition of azodiformates to dienes[43] show >C=O bands only at ≧1700 cm^{-1}. Three bands at the observed positions can be easily explained with the dihydrooxadiazine structure **30** on the basis of the experience with **5**–**8** as being due to the existence of two conformers (hindered rotation about the N–COOR bond). This conformational process can be directly observed by low temperature nmr.[22]

The chemical reactions carried out with **30** are compiled in Scheme II. The structures of the compounds shown are based on spectral evidence. The proposed[10] nonidentity of **29** and **35** (obtained from indan and DEAD) was confirmed by nmr.[44]

Attention should be drawn to the fact, that there is no evidence for any formation of the isomeric adduct **26**.

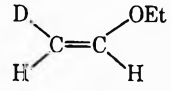
The formation of **30** at 20° is accelerated by several orders of magnitude, if mixtures of indene and azodiformates are irradiated with light of ≧350 mμ. The photochemical preparation of **30** gives very good yields of analytically pure material. Illumination has also been used for the preparation of **5** and **6**.

Mechanistic Considerations

Thermal Reactions.—The reaction constants listed in Table V show no considerable influence of solvent polarity on the rates of the addition of DEAD to indene (dihydrooxadiazine formation) and to vinyl ethyl ether, and of PTD to indene (diazetidine formation).

Retention of configuration (within the limits of detectability by nmr) was observed for the formation of the dihydrooxadiazines **7** and **8**, and excess *trans*- or *cis*-1,2-dimethoxy-ethylene is not isomerized in these reactions.[45,46]

The formation of only one diazetidine **13** from *cis*-1,2-dimethoxyethylene is not unequivocal, since no diazetidine was obtained with *trans*-1,2-dimethoxyethylene. DMAD and **36** gave **12**-D_1 under retention (see Table II) of configuration (stereospecificity > 90 % by nmr). The configuration of **37** remains unchanged in the addition of DMAD.



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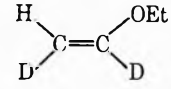


37

Are the dihydrooxadiazines and the diazetidines formed in one- or two-step reactions?

The following criteria are considered important for this distinction.[47] (1) Isolation, spectroscopic and kinetic detection, or scavenging with additives of an intermediate give positive proof for a two-step cycloaddition. (2) Stereospecificity is a necessary requirement for one-step cycloaddition. Stereoequilibration proves a two-step reaction.[45,48] However, several stereospecific two-step cycloadditions are known.[47,49] (3) Effects of substituents (orientation phenomena) are observed in one- and two-step reactions. A con-

(37) G. O. Schenck, W. Hartmann, S. P. Mannsfeld, W. Metzner, and C. H. Krauch, *Chem. Ber.*, **95**, 1642 (1962); A. G. Anastassiou and G. W. Griffin, *J. Org. Chem.*, **33**, 3441 (1968).

(38) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(39) We are grateful to Mr. R. E. Sacher, U. S. Army Natick Laboratories, for measuring these spectra on a Beckman IR-12.

(40) G. C. Pimentel and A. L. McClellan. "The Hydrogen Bond," W. H. Freeman and Co., San Francisco, Calif., 1960, p 197.

(41) Helpful discussions of this problem with Professor M. K. Wilson, Tufts University, are gratefully acknowledged.

(42) C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press Inc., New York, N. Y., 1963, p 265.

(43) B. T. Gillis, in "1,4-Cycloaddition Reactions," J. Hamer, Ed., Academic Press Inc., New York, N. Y., 1967, p 143.

(44) We are indebted to Dr. H. Niklas for a sample of **35**.

(45) E. Koerner von Gustorf and J. Leitich, *Tetrahedron Lett.*, 4689 (1968).

(46) E. Koerner von Gustorf, *ibid.*, 4693 (1968).

(47) R. Gompper, *Angew. Chem.* **81**, 348 (1969); *Angew. Chem. Int. Ed. Engl.*, **8**, 312 (1969); valuable discussions with Professor Gompper, who kindly provided a manuscript prior to publication, are gratefully appreciated.

(48) P. D. Bartlett, C. J. Dempster, L. K. Montgomery, K. E. Schueller, and E. H. Wallbillich, *J. Amer. Chem. Soc.*, **91**, 405 (1969).

(49) S. Proskow, H. E. Simmons, and T. L. Cairns, *ibid.*, **88**, 5254 (1966).

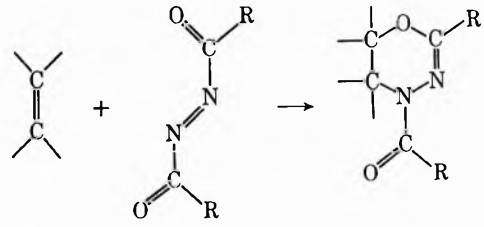
TABLE V

RATE CONSTANTS AND ACTIVATION PARAMETERS FOR THE ADDITION OF DEAD TO INDENE AND ETHYL VINYL ETHER, AND OF PTD TO INDENE

System	Solvent	Temp, °C	k (1/mol sec)	$\Delta H^{\pm}$ (kcal/mol)	$\Delta S^{\pm}$, eu
DEAD + indene	Acetonitrile	40	1.3×10^{-6}		
	Acetic anhydride	40	1.1×10^{-6}		
	Benzene	40	3.2×10^{-7}		
	Ethyl acetate	40	2.1×10^{-7}		
	Indene	20	4.2×10^{-7}	12.8 ± 0.4	-44 ± 2
	Indene	40	1.8×10^{-6}		
	Indene	60	6.6×10^{-6}		
DEAD + ethyl vinyl ether	Acetonitrile	20	2.0×10^{-5}		
	Acetic anhydride	20	1.7×10^{-5}		
	Benzene	20	6.0×10^{-5}		
	Ethyl acetate	20	4.4×10^{-5}		
	Ethyl vinyl ether	20	3.5×10^{-5}	11.0 ± 0.8	-46 ± 3
	Ethyl vinyl ether	25	4.6×10^{-5}		
	Ethyl vinyl ether	30	6.6×10^{-5}		
PTD + indene	Acetonitrile	20	1.5		
	Acetonitrile (+ 1.5 % H_2O)	20	4.9		
	Chlorobenzene	20	1.0		
	Acetone (dry)	20	1.6×10^{-1}		
	Acetone (+ 1.5% H_2O)	20	4.1×10^{-1}		
	Benzene	20	2.3×10^{-1}	7.2 ± 0.5	-36 ± 4
	Benzene	25	3.0×10^{-1}		
	Benzene	30	3.5×10^{-1}		
PTD + H_2O	Acetone (1.5% H_2O)	20	7.8×10^{-3}		

clusion (that it is a one-step reaction) is only possible if the orientation is contrary to the polarity of the substituents.[47] (4) Solvent effects are meaningful only (proving two-step cycloaddition), if rate constants increase several orders of magnitude going from an unpolar (*e.g.*, cyclohexane) to a polar (*e.g.*, acetonitrile) solvent.[47,49] Missing solvent effects (a requirement for one-step reactions) have been reported for several dipolar cycloaddition reactions.[47] (5) A small enthalpy of activation ($\Delta H^{\pm}$ 25 kcal/mol) and a highly negative activation entropy ($\Delta S^{\pm} \approx -35$ eu) are typical activation parameters of one-step cycloaddition (*e.g.*, Diels–Alder) reactions.[50,51] However, dipolar cycloadditions with similar data are known.[47] (6) Kinetic secondary isotope effects[52] allow an empiric distinction between one- and two-step cycloadditions.[50a,53,54]

The selection rules of Woodward and Hoffman[55,56] allow concerted oxadiazine formation (eq 2) by π^4s + π^2s addition. Water (which can add to dipolar intermediates) did not affect the formation of **30**. Therefore, the experimental criteria 1–5 are fulfilled for an one-step formation (eq 2) of dihydrooxadiazines.[57] Criterion 6 has not been checked for this reaction as yet.



(2)

Oxadiazine formation by addition of an electron-rich C=C bond (dienophile) to the electron-poor "diene" N=NC=O can be looked upon as a Diels–Alder reaction with inverse electron demand;[50,59] in accord with this, all attempted 1,4-additions failed with electron-poor olefins. The observed regiospecific[60] addition of indene suggests control by orientation phenomena possibly due to a slight polarity of the transition state.[47]

A concerted π^2s + π^2s diazetidine formation (eq 3) is forbidden by the Woodward–Hoffmann rules,[55,56] and it, indeed, proceeds in a different fashion. A dipolar intermediate **38** was trapped with water[61] in the reaction[62] of PTD with indene yielding **20**. A study[54] of the secondary α-deuterium kinetic isotope effect in the addition of DMAD to ethyl vinyl ether revealed an unsymmetric transition state: change of

(50) (a) J. Sauer, *Angew. Chem.*, **79**, 76 (1967); (b) R. Huisgen, R. Grashey, and J. Sauer, in "The Chemistry of Alkenes," S. Patai, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p 739.

(51) R. Huisgen, *Angew. Chem.*, **75**, 742 (1963).

(52) E. A. Halevi, *Progr. Phys. Org. Chem.*, **1**, 109 (1963).

(53) W. R. Dolbier and S.-H. Dai, *J. Amer. Chem. Soc.*, **90**, 5029 (1968).

(54) E. Koerner von Gustorf, D. V. White, J. Leitich, and D. Henneberg, *Tetrahedron Lett.*, 3113 (1969), and references therein.

(55) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 2046 (1965).

(56) R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968); R. B. Woodward and R. Hoffmann, *Angew. Chem.*, **81**, 797 (1969).

(57) With the *reservatio mentalis* that rotation in a (improbable) biradical intermediate should be fast as compared with ring closure.[48-51,58]

(58) P. D. Bartlett, R. Helgeson, and O. A. Wersel, *J. Appl. Chem.* (London), **16**, 187 (1968).

(59) W. E. Bachmann and N. C. Deno, *J. Amer. Chem. Soc.*, **71**, 3062 (1949).

(60) A. Hassner, *J. Org. Chem.*, **33**, 2684 (1968).

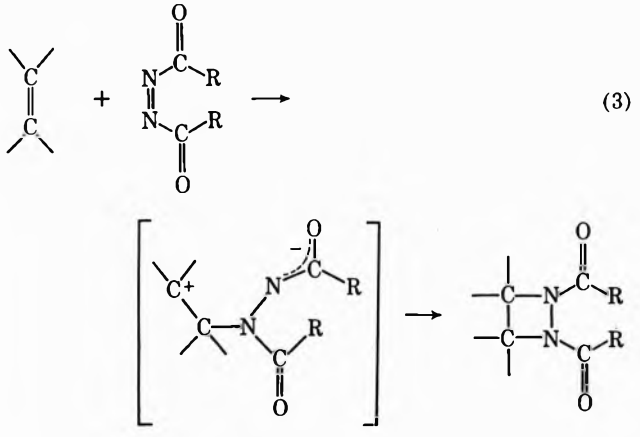
(61) It could be argued, that water changes the mechanism of this reaction. This appears very unlikely, since the ratios of the reaction constants in acetone and in acetonitrile are very similar with and without water.

(62) E. Fahr, and J. Flemming, as well as C. F. Huebner and his collaborators, have obtained **20** from indene and PTD in acetone according to private communications, but were unable to isolate **21**. We are grateful to Professor Fahr for a copy of the thesis of J. Flemming, Würzburg University, 1967. NOTE ADDED IN PROOF.—Compound **21** was obtained also by H. Helfert, Thesis, Würzburg University, 1969.

hybridization in the direction $sp^2 \rightarrow sp^3$ had occurred at $=CH_2$ but not at $=CH(OR)$.

Criteria 2–5 would have been in accord with a one-step process; an explanation could be "that, in certain stepwise cycloadditions by way of a dipolar ion, a coulombic orienting force in the first step eliminates or greatly diminishes this period in which the system searches for a favorable orientation for ring closure."[48]

It may appear surprising that the orbital symmetry-allowed concerted 1,4 addition (eq 2) of azodiformates to olefins can be completely overcome by the disconcerted 1,2 addition (eq 3). However, there are precedents;[63,64] there is no reason why the activation energy of the 1,2 addition should not be the lower one.



(3)

38

What factors are responsible for low activation energies of 1,2 cycloaddition? High polarity and polarizability of the olefin and high polarizing power of the cyclophile should facilitate the formation of a dipolar intermediate. Table VI shows that the electron polarizability[65] of the C=C bond of mono- and 1,2-disubstituted olefins indicates whether 1,2 or 1,4 addition of azodiformates has to be expected, increased polarizability favoring 1,2 addition. More data are needed to check possible predictions. The role of polarity, *e.g.*, in the reactions of 1,1-disubstituted olefins with azodiformates,[5,10,15,66] will be discussed elsewhere.

If the coulombic forces between the developing charge-carrying centers exceed repulsion early on the way from educt to product, the formation times of the two new bonds of a diazetidine may overlap to some extent (*e.g.*, ethyl vinyl ether + azodiformates). A fully developed two-step mechanism may be one extreme on a continuous scale with a completely symmetrical transition state as the other extreme.

Photochemical Reactions.—Illumination $\lambda \geqq 300$ mμ of the normally *trans*-configurated[67] azodiformates in inert solvents results in a partial conversion to *cis*-azodiformates;[68] the composition of the photoequilibrated mixtures depends on the wavelength used. *cis* Azodiformates are much more reactive in thermal cycloaddition reactions than the *trans*-configurated isomers;[68] even the products obtained may be different.[69] Therefore, the thermal reaction constants of the two geometrical isomers with an olefin and the composition of the photostationary state have to be known to allow a distinction, whether the acceleration is due to the photochemical formation of the *cis* isomer and its subsequent fast thermal reaction with the substrate, or whether it consists in a direct reaction of electronically excited azodiformate.

TABLE VI

EFFECT OF OLEFIN POLARIZABILITY ON CYCLOADDITION OF AZODIFORMATES

Olefin	Polarizability[a]	Cycloaddition
Ethyl vinyl ether	2.9	1.2
cis-1,2-Dimethoxyethylene	2.3	1.4 and 1.2
Vinyl acetate	2.1	1.4
Indene	2.1[b]	1.4
trans-1,2-Dimethoxyethylene	1.7	1.4
Dihydro-1,4-dioxine	1.2	1.4
Vinylene carbonate	1.1	1.4

[a] See ref 65. [b] Comparability with other values can be accidental.

The rate constants[68] for the thermal reactions of *cis*- and *trans*-DEAD with indene and ethyl vinyl ether are listed in Table VII; the photochemical acceleration (P) of the disappearance of DEAD achieved under conditions ($\lambda \geqq 370$ mμ) where only 2–4% *cis*-DEAD was present in the photostationary state has been compared with the value (for 3% *cis*-DEAD) calculated according to the following expression.

$$P = \frac{k_{cis}[cis\text{-DEAD}]}{k_{trans}\,[\text{DEAD}]} + 0.97$$

The intensity of illumination was sufficient to ensure that the formation of *cis*-DEAD was fast compared with its consumption.

According to the data given there is no necessity to postulate a direct reaction of electronically excited azodiformate in both cases.

Compound **30a** is obtained from indene and diethyl azodiformate in the dark, from the illumination of the mixture of both reactants, and from adding indene (16%) in the dark to a solution of DEAD, 16% of which had been transformed before into *cis*-DEAD by appropriate illumination. In this instance *cis*- and *trans*-DEAD yield the same product. The higher reactivity of *cis*-DEAD in comparison with the *trans* isomer toward indene can be attributed not only to its higher ground state energy, but also to a higher population of the cisoid conformations of the N=N-C=O system, owing to steric interactions of the OR groups in the transoid conformations as revealed by an inspection of molecular models. In this respect the azodiformates parallel other dienes, whose re-

(63) P. D. Bartlett and K. E. Schueller, *J. Amer. Chem. Soc.*, **90**, 6077 (1968).

(64) R. Huisgen and P. Otto, *Tetrahedron Lett.*, 4491 (1968); G. Binsch, L. A. Feiler, and R. Huisgen, *ibid.*, 4497 (1968).

(65) Difference between the experimentally determined molecular refraction and the calculated molecular refraction (using atomic refraction constants but omitting the C=C increment). For a detailed discussion of this experimental measure of the C=C bond polarizability see C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 119.

(66) 1,1-Dimethoxyethylene undergoes substitution with azodiformates; E. Koerner von Gustorf and D. V. White (1969), unpublished results.

(67) C. G. LeFévre, R. J. W. LeFévre, and W. T. Oh, *Aust. J. Chem.* **10**, 218 (1957); R. J. W. LeFévre, W. T. Oh, I. H. Reece, R. Roper, and R. L. Werner, *ibid.*, **11**, 92 (1958); A. Simon and H. Wagner, *Naturwissenschaften* **47**, 540 (1960).

(68) G. O. Schenck, H. R. Kopp, B. Kim, and E. Koerner von Gustorf, *Z. Naturforsch. B*, **20**, 637 (1965); E. Koerner von Gustorf and D. Hess, to be published, obtained *cis*-di-*t*-butyl azodiformate (95+ %) mp 32–34°.

(69) R. Askani, *Chem. Ber.*, **98**, 2551 (1965).

TABLE VII

PHOTOCHEMICAL ACCELERATION P OF THE ADDITION OF DEAD TO INDENE AND ETHYL VINYL ETHER

	$k_{cis(20°)}$, M^{-1} sec^{-1}	$k_{trans,(20°)}$, M^{-1} sec^{-1}	P_{obsd}[a]	P_{calcd}
DEAD + indene	1.0×10^{-3}	4.2×10^{-7}	76	75
DEAD + ethyl vinyl ether	6.2×10^{-4}	3.5×10^{-6}	3	6.5

[a] Ratio of the disappearance of DEAD (1.4×10^{-2} M in the neat olefins) under illumination (20 and 25 min; xenon high pressure lamp OSRAM XBO 2001 with UVG filter Spiegelglas AG Weilheim) to the dark reaction at 20 and 22.5°.

activity in Diels–Alder reactions increases with increasing population of the cisoid conformations.[46,50,70]

While **11** is formed from *trans*-DEAD and ethyl vinyl ether, the reaction of the latter with *cis*-DEAD in the dark, as well as with DEAD under illumination, yields similar mixtures of products resulting from hydrogen abstraction reactions, as demonstrated by NH absorption in ir; the structures of these products are currently being investigated.

We have not been able to observe any considerable acceleration of the addition of PTD to indene by illumination ($\lambda \geqq 500$ mμ). This finding points against a biradical intermediate in the corresponding thermal cycloaddition reaction; it also suggests the formation of *cis*-DEAD as being responsible for the photochemical acceleration of the reactions discussed above.

The photochemical observations are in accord with a concerted nature of the dihydrooxadiazine formation. The photochemical *cis–trans* isomerization of the azodiformates seems to be a much more important process than the addition of any electronically excited species to the unsaturated substrate in the systems investigated. A precedent is the photochemical addition of azobenzene to ketene, which consists of the photochemical formation of *cis*-azobenzene and its thermal addition to ketene; the thermal addition of pure *cis*-azobenzene to ketene is even slowed by illumination owing to the photochemical formation of the unreactive *trans*-azobenzene.[71]

Finally it should be noted that instances for reactions of electronically excited azodiformates with unsaturated substrates are known, *e.g.*, with cycloheptatriene[4,72] or cyclohexene;[73] in the former case it has been established that the thermal reaction follows a concerted path, but that the photochemical reaction proceeds in two steps.

Experimental Section[74]

Methyl 4a,6,7,8a-Tetrahydro-2-methoxy-4H-*p*-dioxino[2,3-*e*]-1,3,4-oxadiazine-4-carboxylate (5).—Dioxene[75] (0.71 g, 8.2 mmol) and 1.0 g (6.9 mmol) of DMAD in 12 ml of benzene were illuminated (3500 Å) for 67 hr in a Rayonet photochemical chamber reactor at 20°. Removal of the solvent from the colorless reaction mixture gave 1.6 g of solid material, mp 120–131°. Recrystallization from benzene–pentane yielded 0.35 g of pure **5**: mp 133–136°; mol wt 240 (232 mass spectrum); ir (CCl_4): no NH; 1723, 1755 cm^{-1} (C=O); 1681 cm^{-1} (C=N).

Anal. Calcd for $C_8H_{12}N_2O_6$ (232.2): C, 41.38; H, 5.21; N, 12.06. Found: C, 41.59; H, 5.35; N, 11.93.

Attempts to hydrogenate **5** catalytically in the presence of Raney Ni or Pd–$BaSO_4$ in ethyl acetate failed, and the starting material could be recovered.

Methyl 5,6-Dihydro-5,6-carbonato-2-methoxy-4H-1,3,4-oxadiazine-4-carboxylate (6).—Vinylene carbonate (0.69 g, 8.0 mmol) and 1.0 g (6.9 mmol) of DMAD in 12 ml of benzene were illuminated (as above) for 185 hr. Removal of the solvent and of polymeric material gave 0.069 g of **6**, mp 114–116°, after tedious recrystallization from chloroform and toluene: mol wt 232 (mass spectrum); ir ($CHCl_3$): no NH; 1840, 1762, 1730 cm^{-1} (C=O); 1680 cm^{-1} (C=N).

Anal. Calcd for $C_7H_8N_2O_7$ (232.2): C, 36.22; H, 3.47; N, 12.07. Found: C, 36.10; H, 3.60; N, 12.00.

Methyl *trans*-5,6-Dihydro-2,5,6-trimethoxy-4H-1,3,4-oxadiazine-4-carboxylate (7).—A solution of 1.25 g (8.5 mmol) of DMAD in 3 ml of C_6D_6 was added dropwise at 20° to 1.0 g (11 mmol) of *trans*-1,2-dimethoxy-ethylene[76] (98+% by preparative glpc) in 3 ml of C_6D_6. The reaction mixture was almost colorless after 30 min. On standing overnight a precipitate appeared. All volatile material was removed *in vacuo;* according to nmr analysis the C_6D_6 contained exclusively *trans*-1,2-dimethoxyethylene. The residue (2.0 g, 8.5 mmol), mp 126–128°, was pure (within the limits of nmr) **7** (recrystallization from benzene–*n*-hexane raised the melting point to 128–130°): mol wt 227; mass spectrum:[77] *m/e* (rel intensity) 234 (19), 235 (2), 203 (10), 175 (1), 159 (2), 149 (2), 118 (17), 89 (6), 88 (100), 86 (5), 85 (7), 75 (10), 73 (18), 70 (4); ir (KBr): no NH, 1727, 1688 cm^{-1} (C=O); 1660 cm^{-1} (C=N).

Anal. Calcd for $C_8H_{14}N_2O_6$ (234.2): C, 41.03; H, 6.03; N, 11.96. Found: C, 41.20; H, 6.16; N, 11.98.

Attempted catalytic hydrogenation of **7** with Raney Ni in ethyl acetate failed, and the starting material was recovered.

Methyl *cis*-5,6-Dihydro-2,5,6-trimethoxy-4H-1,3,4-oxadiazine-4-carboxylate (8) and Dimethyl *cis*-3,4-Dimethoxy-1,2-diazetidine 1,2-dicarboxylate (13).—DMAD (0.31 g, 2.1 mmol) in 1 ml of C_6D_6 was added to 0.26 g (2.4 mmol) of *cis*-1,2-dimethoxyethylene[76] (98+% by preparative glpc) in 1 ml of C_6D_6. Decolorization of the mixture took overnight. All volatile material was removed *in vacuo;* according to nmr analysis the C_6D_6 contained exclusively *cis*-1,2-dimethoxyethylene. The residue, a colorless oil (0.52 g, 2.2 mmol), was a 4:1 mixture of **8** and **13** according to nmr. Separation of these two compounds has not been achieved as yet: mol wt 260 (234 mass spectrum); ir ($CHCl_3$): no NH; 1725, 1705 cm^{-1} (C=O); 1665 cm^{-1} (b) (C=N).

Anal. Calcd for $C_8H_{14}N_2O_6$ (234.2): C, 41.03; H, 6.03; N, 11.96. Found: C, 40.87; H, 5.93; N, 11.78.

Ethyl 6-Acetoxy-2-ethoxy-5,6-dihydro-4H-1,3,4-oxadiazine-4-carboxylate (9).—DEAD (5.9 g, 34 mmol) and 28 g (0.33 mol) of vinyl acetate were refluxed under argon for 65 hr. The residue left after solvent removal was extracted with petroleum ether, 6.5 g remaining undissolved. The extract gave 3.2 g of a material, whose recrystallization from benzene–petroleum ether yielded 2.2 g (8.5 mmol) of **9**: mp 60–62°; mol wt 237; ir (CCl_4): no NH; 1770, 1750 (sh), 1705 cm^{-1} (C=O); 1675 cm^{-1} (C=N).

Anal. Calcd for $C_{10}H_{16}N_2O_6$ (260.3): C, 46.15; H, 6.20; N, 10.76. Found: C, 46.07; H, 6.23; N, 10.78.

(70) D. Craig, J. J. Shipman, and R. B. Fowler, *J. Amer. Chem. Soc.*, **83**, 2885 (1961).

(71) G. O. Schenck and N. Engelhard, *Angew. Chem.*, **68**, 71 (1956); G. O. Schenck, *Arbeitsgemeinsch. Forsch. Landes Nordrhein-Westfalen, Heft*, **120**, 27 (1963).

(72) E. Koerner von Gustorf, B. Kim, and D. Hess, unpublished work.

(73) G. Ahlgren, B. Akermark, and K. I. Dahlquist, *Acta Chem. Scand.*, **22**, 1129 (1968).

(74) Melting points are uncorrected. Ir spectra were taken with a grating spectrometer MH-2, SEM Brückl, Munich, and with a Beckman IR-12. The nmr spectra (τ) were recorded with a Varian A-60A and HA-100; the letter abbreviations used follow: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, o = octet, m = multiplet, b = broad; tetramethylsilane was used as internal standard. Molecular weights were determined cryoscopically or osmometrically (Mechrolab) in benzene. Indene, DEAD, and DMAD (all supplied by Aldrich) were purified by distillation. Illumination techniques have been described by G. O. Schenck, in A. Schönberg "Präparative Organische Photochemie," Springer-Verlag, Heidelberg, 1958, p 210.

(75) R. K. Summerbell and R. R. Umhoefer, *J. Amer. Chem. Soc.*, **61**, 3016 (1939).

(76) H. Baganz, K. Praefcke, and J. Rost, *Chem. Ber.*, **96**, 2657 (1963).

(77) We are grateful to Miss A. Egert for running the mass spectra on an Atlas CH-4 mass spectrometer (70 eV). The parent ion and at least the ten most intense fragment ions above *m/e* 60 have been listed.

Attempted catalytic hydrogenation of 9 with PtO_2 or Raney Ni in ethyl acetate failed; the starting material was recovered.

Dimethyl 3-Methoxy-1,2-diazetidine-1,2-dicarboxylate (10).—A solution of 2.0 g (14 mmol) of DMAD and 82 g (1.4 mol) of methyl vinyl ether (J. T. Baker Chemical Co.) in 100 ml of benzene was decolorized after 4 days at room temperature. After solvent removal 2.7 g of an oil remained, which was purified by short-path distillation at 40–50° and 10^{-5} mm, yielding 0.79 g (4 mmol) of **10** as a colorless oil: mol wt 208; mass spectrum: *m/e* (rel intensity) 204 (98), 205 (11), 173 (17), 172 (26), 145 (55), 130 (11), 128 (18), 118 (21), 113 (14), 101 (31), 86 (31), 85 (17), 75 (100), 71 (12); ir (CCl_4): no NH, 1725, 1735, and 1760 cm^{-1} (C=O).

Anal. Calcd for $C_7H_{12}N_2O_5$ (204.2): C, 41.18; H, 5.92; N, 13.72. Found: C, 41.43; H, 6.17; N, 13.35.

Dimethyl 3-Ethoxy-1,2-diazetidine-1,2-dicarboxylate (12).—A solution of 2.0 g (14 mmol) of DMAD and 5.0 g (70 mmol) of ethyl vinyl ether (Fluka) became colorless after 2 days at room temperature. The solvent was removed, and 2.4 g (11 mmol) of an oil remained, comprising pure **12** according to ir. A part of the material was short-path distilled at 10^{-5} Torr and 40–54°: mol wt 240; mass spectrum: *m/e* (rel intensity) 218 (100), 186 (16), 159 (21), 145 (37), 104 (16), 89 (57), 86 (26), 85 (30), 84 (42), 72 (62), 71 (22), 61 (21); ir (CCl_4): no NH, 1727, 1764 cm^{-1} (C=O).

Anal. Calcd for $C_8H_{14}N_2O_5$ (218.2): C, 44.03; H, 6.47; N, 12.84. Found: C, 43.90; H, 6.34; N, 12.72.

Diethyl 3-Ethoxy-1,2-diazetidine-1,2-dicarboxylate (11).—A solution of 12.0 g (69 mmol) of DEAD in 50.6 g (0.7 mol) of vinyl ethyl ether (Fluka) became colorless after 18 hr at room temperature. After removal of excess ethyl vinyl ether 16.6 g of an oil was left, whose distillation at 130° yielded 5.3 g (21 mmol) of **11**: bp 108° (3×10^{-5} mm); $n^{20}D$ 1.4581; mol wt 246; ir (CCl_4): no NH; 1715, 1760 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_{18}N_2O_5$ (246.3): C, 48.77; H, 7.37; N, 11.38. Found: C, 48.64; H, 7.22; N, 11.32.

Since 7.9 g of a brown resin was obtained as residue from the vacuum distillation, decomposition of **11** under these conditions was suspected. Inspection of the undistilled oil (11.1 g, 45 mmol) obtained from the reaction of 7.8 g (45 mmol) of DEAD and 22.0 g (0.31 mol) of ethyl vinyl ether showed this to be pure **11** according to ir and elemental analysis, mol wt 219.

Anal. Found: C, 48.69; H, 7.32; N, 11.48.

Diethyl N-(2-Ethoxy-1-ethyl)-bicarbamate (15).—Compound **11** (3.7 g, 15 mmol) in 120 ml of ethyl acetate took up 1 mol of H_2/mol in 7 hr on shaking with H_2–PtO_2. Filtration and solvent removal gave 3.4 g of colorless oil, distillation of which at 150° yielded 1.9 g (7.7 mmol) of **15**: bp 115° (0.5 mm); $n^{20}D$ 1.4468; mol wt 251; ir (CCl_4): 3410, 3300 cm^{-1} (NH); 1720, 1755 cm^{-1} (C=O); nmr (CCl_4): 2.40 (s, 1 H); 5.85 (q, 4 H), J = 7 cps; 6.4 (m), 6.51 (q), J = 7 cps, (6 H); 8.74 (t), J = 7 cps, 8.84 (t), J = 7 cps (9 H).

Anal. Calcd for $C_{10}H_{20}N_2O_5$ (248.3) C, 48.38; H, 8.12; N, 11.28. Found: C, 48.35; H, 7.90; N, 11.97.

***cis*-1-Deuterio-2-ethoxyethylene (36).**—Ethoxydeuterioacetylene was obtained with an isotopic purity of 80% (mass spectrum) by using D_2O instead of H_2O in the slightly modified standard procedure.[78]

Ethoxydeuterioacetylene (4.1 g, 58 mmol) in 50 ml of methyl benzoate took up 1 mol of H_2/mol in 45 min on shaking with 5 g of aged Raney Ni–H_2. Immediate filtration and distillation gave 2.4 g (33 mmol) of a product, bp 29–36°, which contained **36** and *trans*-1-deuterio-2-ethoxyethylene (T) in a 5.1:1 ratio, besides ~27% undeuterated ethyl vinyl ether (U), according to the gravimetric determination of the area underneath the C=C(O)H^x signals in the expanded nmr spectrum (neat). **36**: 3.54 (t), 3.65 (t), J_{ax} = 7 cps, J_{Dx} = 2.2 cps. T: 3.48 (obsc), 3.72 (obsc). U: 3.41, 3.52, 3.64, 3.76, J_{ax} = 7 cps, J_{bx} = 14 cps.

A solution of 0.56 g (7.8 mmol) **36** and 0.25 g (1.7 mmol) of DMAD in 12 ml of benzene became colorless in 4 days at room temperature and yielded 0.39 g (1.8 mmol) of adduct after solvent removal. This adduct contained according to nmr analysis (as above) **12**-D_1, the corresponding *trans* adduct in a 5.5:1 ratio, and **12**.

(*cis*-1,2-Dideuterio)-2-ethoxyethylene (37).—A solution of 4.4 g (63 mmol) of ethoxyacetylene in 50 ml of methyl benzoate was shaken with D_2–Raney Ni up to a consumption of 1 mol of D_2/mol. Distillation after filtration gave 1.7 g of product, bp 31–34°, which consisted mainly of **37**: nmr (neat) 1 olefinic H at 5.90 (t), J_{DH} = 2.2 cps.

The reaction of 1.0 g (13 mmol) of **37** with 0.25 g (1.7 mmol) of DMAD in 10 ml of benzene gave after 2 days at room temperature 0.36 g of adduct, with 1 H (four-membered ring) at 5.94 ($CDCl_3$).

2,3,4a,5,6,6a-Hexahydrodiazeto[3,4-*b*]dioxindicarboxylic Acid N-Phenylimide (14).—Solutions of 1.0 g (12 mmol) of dioxene in 80 ml of toluene and of 2.32 g of PTD (13 mmol) in 250 ml of toluene were both added dropwise to 100 ml of toluene with magnetic stirring at −40 to −60° over a period of 5 days. A white precipitate (1.76 g) was separated by filtration. Extraction of the material with $CHCl_3$ left 0.54 g (2.1 mmol) of **14** undissolved: mp 208–212°; mol wt (acetone) 279; mass spectrum: *m/e* (rel intensity) 261 (11), 149 (4), 142 (4), 120 (9), 119 (59), 92 (15), 91 (22), 87 (11), 86 (100), 85 (46), 83 (69), 78 (22); ir (KBr): no NH; 1702, 1729, and 1790 cm^{-1} (C=O).

Anal. Calcd for $C_{12}H_{11}N_3O_4$ (261.2): C, 55.17; H, 4.24; N, 16.08. Found: C, 54.84; H, 4.25; N, 15.98.

1-(1,4-Dioxan-2-yl)-4-phenyl-1,2,4-triazolidine-3,5-dione (16).—Compound **14** (0.22 g, 0.8 mmol) in ethyl acetate was shaken for 8 hr with H_2–Raney Ni. Cumbersome recrystallization of the residue, after filtration and solvent removal, gave 15 mg of **16**: mp 155–158° (from benzene–$CHCl_3$–*n*-hexane); mass spectrum: *m/e* (rel intensity) 263 (28), 228 (10), 177 (43), 168 (13), 149 (31), 119 (61), 91 (37), 88 (61), 87 (98), 86 (100), 84 (35), 77 (31), 73 (47), 69 (33); ir (KBr): 3300 cm^{-1} (NH); 1695–1720, 1788 cm^{-1} (C=O).

Anal. Calcd for $C_{12}H_{13}N_3O_4$ (263): C, 54.75; H, 4.98; N, 15.96. Found: C, 54.90; H, 5.60; N, 16.19.

1,2,2a,7b-Tetrahydro-3H-indeno[2,1-*c*]1,2-diazete-1,2-dicarboxylic Acid N-Phenylimide (21).—A solution of 5.0 g (29 mmol) of PTD[25] in 350 ml of benzene was added dropwise at 5–10° to 34 g (0.29 mol) of indene under an argon atmosphere. Compound **21** (2.88 g, 10 mmol) precipitated overnight on standing at ≤10°: mp 166–167.5° (from $CHCl_3$); mol wt 281; mass spectrum: *m/e* (rel intensity) 291 (23), 177 (27), 130 (10), 129 (43), 120 (18), 119 (100), 115 (14), 91 (42), 78 (15), 77 (17), 64 (29).

Anal. Calcd for $C_{17}H_{13}N_3O_2$ (291.3): C, 70.09; H, 4.50; N, 14.42. Found: C, 69.85; H, 4.61; N, 14.18.

1-(2-Indanyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (19).—Compound **21** (1.03 g, 3.4 mmol) in ethyl acetate yielded 0.93 g (3.2 mmol) of **19** on shaking with H_2–Raney Ni: mp 166.5–168° (from benzene–*n*-hexane); mass spectrum: *m/e* (rel intensity) 293 (3), 179 (4), 178 (36), 177 (14), 149 (5), 119 (4), 118 (4), 117 (41), 116 (100), 115 (18), 103 (4), 91 (11), 78 (9), 77 (5); ir (KBr): 3060, 3160 cm^{-1} (NH); 1675, 1770 cm^{-1} (C=O); nmr ($CDCl_3$): 2.57 (s, 5 H); 2.76 (b s, 1 H); 2.85 (s, 4 H); 4.95 (qui, 1 H), J = 7.7 cps; 6.83 (q, 4 H).

Anal. Calcd for $C_{17}H_{15}N_3O_2$ (293.3): C, 69.61; H, 5.15; N, 14.33. Found: C, 69.39; H, 5.21; N, 14.33.

1-(1-Hydroxy-2-indanyl)-4-phenyl-1,2,4-triazolidine-3,5-dione (20).—Compound **21** (0.50 g, 1.7 mmol) was dissolved in 43 ml of acetone containing 1.5 ml of concentrated aqueous HCl, and kept for 5 days at room temperature. After solvent evaporation and extraction with benzene 0.19 g (0.6 mmol) of benzene-insoluble **20** remained: mp 205–207° (from $CHCl_3$); mol wt (in $CHCl_3$) 312; mass spectrum: *m/e* (rel intensity) 309 (2), 291 (18), 178 (11), 133 (12), 132 (90), 119 (21), 117 (10), 116 (100), 115 (17), 91 (15), 83 (14); ir (KBr): 3450 cm^{-1} (OH); 3060, 3140 cm^{-1} (NH); 1685, 1710, 1768 cm^{-1} (C=O); nmr [$(CD_3)_2$-CO]: 2.6 (m, 10 H); 4.45 (d, 1 H) J = 8 cps; 5.28 (b, q, 1 H); 6.77 (b, d, 2 H); 7.2 (b, 1 H).

Anal. Calcd for $C_{17}H_{15}N_3O_3$ (309.3): C, 66.01; H, 4.89; N, 13.58. Found: C, 65.52; H, 4.90; N, 12.92.

Reaction of PTD with Indene in the Presence of Water.—A solution of 1.0 g (5.7 mmol) of PTD in 50 ml of dry acetone was added dropwise to a solution of 0.70 g (6.0 mmol) of indene in 50 ml of acetone containing 3% water. After 1 hr the solvent was removed and 0.53 g (1.7 mmol) of benzene insoluble **20** remained (mp 206–208° from $CHCl_3$–*n*-hexane). Its identity with the product fron the acid hydrolysis was proven by melting point and ir.

Anal. Calcd for $C_{17}H_{15}N_3O_3$ (309.3): C, 66.01; H, 4.89; N, 13.58. Found: C, 65.71; H, 4.93; N, 13.41.

In a control experiment 0.50 g (1.7 mmol) **21** was dissolved in 50 ml of acetone containing 3% water, and kept for 6 hr at room

(78) E. R. H. Jones, G. Eglinton, M. C. Whiting, and B. L. Shaw, *Org. Syn.*, **34**, 46 (1954). We extracted the crude ethoxyacetylene from the reaction mixture with *n*-butyl ether instead of distilling it at 100°.

temperature. Extraction with benzene after solvent removal did not yield any insoluble material; from the benzene solution 0.49 g of **21**, mp 166–168°, identical with the starting material according to ir, was recovered.

$LiAlH_4$ Reduction of 21.—Compound **21** (4.15 g, 14 mmol) in 300 ml of benzene was added dropwise to 10.8 g (0.3 mol) of $LiAlH_4$ in 500 ml of anhydrous ether. After refluxing for 1 hr excess $LiAlH_4$ was destroyed with water; the filtrate, dried over Na_2SO_4, yielded 2.06 g of a brown oil after solvent removal. A colorless liquid (0.73 g) could be separated from this oil by short-path distillation at room temperature and 10^{-2} mm in an apparatus equipped with a liquid N_2 cooled finger; glpc showed it to be a mixture of N-methylaniline (93%), indene (4.1 %), aniline (1.7 %), and N,N-dimethylaniline (<0.5 %). The residue from this distillation was separated by extraction into a pentane-soluble fraction (a) and a pentane-insoluble fraction (b).

Very cumbersome recrystallization of tarry fraction a gave 3 mg of colorless **1,2,3,3a,4,8b-hexahydro-1-(or 3)-methylindeno[2,1-*d*]imidazole (22)**, mp 75–85° dec (from pentane). Attempted purification by tlc was inadequate owing to decomposition: mass spectrum: *m/e* (rel intensity) 174 (26), 173 (42), 145 (69), 144 (100), 132 (24), 131 (28), 130 (50), 116 (21), 115 (33), 78 (20), 77 (22); ir (KBr): 3220 cm^{-1} (NH); 2780, 2840 cm^{-1} (NCH_3, NCH_2); no C=O; nmr ($CDCl_3$, microcell): 2.7 (m, 4 H); 5.2 (d, 1 H), $J \approx 6$–7 cps; 6.2 (m, 1 H); 6.7 (m), 6.95 (b, s, 4 H); 7.6 (s), 7.7 (b, 4 H).

From the pentane-insoluble dark brown oil (b) ~30 mg of colorless **1,2,2a,7b-tetrahydro-3H-indeno[2,1-*c*]1,2-diazete-1-carboxanilide (23)** could be separated by crystallization at <10°; it was purified by washing with benzene: mp 137–139°; mass spectrum:[79] *m/e* (rel intensity) 265 (2), 130 (32), 129 (43), 119 (47), 117 (28), 116 (100), 115 (44), 102 (23), 93 (31), 91 (28), 78 (15), 77 (15), 64 (19), 63 (17); calcd for $C_{16}H_{15}N_3O$: *m/e* 265.1215; found: *m/e* 265.1212 and 265.1215; ir (KBr): 3300, 3180 cm^{-1} (NH); 1662 cm^{-1} (C=O); 1515 cm^{-1} (amide II band); nmr ($CDCl_3$): 2.07 (b, 1 H); 2.6 (m, 9 H); 4.15 (d, 1 H) J = 5.5 cps; 5.0 (b, m, ~2 H); 6.75 (m, 2 H).

Photochemical Formation of 4a,9b-Dihydro-2-ethoxy-4H-indeno[2,1-*e*]-1,3,4-oxadiazine-4-carboxylic Acid Ethyl Ester (30a).—DEAD (20.1 g, 0.116 mol) and 40.0 g (0.345 mol) of indene were irradiated for 28 hr at room temperature using a high pressure xenon lamp Osram XBO-2001 placed in a Friesecke and Hoepfner cinema projector FH-X-66. The colorless reaction mixture yielded 30.5 g (0.105 mol) of **30a**, mp 105–106.5°, on trituration with pentane: mol wt 305; mass spectrum: *m/e* (rel intensity) 290 (23), 291 (4), 171 (3), 149 (4), 130 (3), 129 (3), 117 (17), 116 (100), 115 (16), 105 (3), 78 (3); ir (Table IV): no NH; uv_{max} (CH_3OH): 36930 cm^{-1} (ϵ 758), 37900 (850), 39000 (820).

Anal. Calcd for $C_{15}H_{18}O_4N_2$ (290.3): C, 62.06; H, 6.25; N, 9.65. Found: C, 62.10; H, 6.30; N, 9.59.

Photochemical Formation of 4a,9b-Dihydro-2-methoxy-4H-indeno[2,1-*e*]-1,3,4-oxadiazine-4-carboxylic Acid Methyl Ester (30b).—Illumination of 12.9 g (89 mmol) of DMAD and 158 g (1.36 mol) of indene for 48 hr with an immersed high pressure mercury lamp HPK 125 W (Solidex filter) at 20° gave 24 g of residue after removal of indene at 100° *in vacuo*. Extraction of the residue with 800 ml of pentane yielded 7.0 g (27 mmol) of **30b**: mp 110–112° (from CCl_4–pentane); mol wt 259; mass spectrum: *m/e* (rel intensity) 262 (27), 263 (5), 149 (6), 129 (6), 117 (14), 116 (100), 115 (21), 103 (2), 91 (2), 77 (2), 65 (2); ir (Table IV): no NH.

Anal. Calcd for $C_{13}H_{14}N_2O_4$ (262.3): C, 59.54; H, 5.38; N, 10.68. Found: C, 59.30; H, 5.29; N, 10.71.

Addition of Diethyl *cis*-Azodiformate (*cis*-DEAD) to Indene.—Illumination (40 hr, 3500 Å; Rayonet preparative photochemical reactor RPR-208) of 6.0 g (34 mmol) of DEAD in 500 ml of benzene at 20° afforded 0.64 g (3.7 mmol) of *cis*-DEAD according to titration with cyclopentadiene.[68] Reaction of this solution with 1.0 g (8.6 mmol) of indene in the dark yielded 1.0 g (3.5 mmol) of **30a**, mp 104–105.5°, its ir was identical with that of the photochemically prepared material.

Pyrolysis of 30a.—Compound **30a** (2.1 g, 7.3 mmol) was heated *in vacuo* to 300° with a bunsen burner. The reaction products were collected from the trap and the flask by rinsing with pentane; besides 0.42 g (1.4 mmol) of unreacted **30a** 0.48 g (4.1 mmol) of indene (identified by glpc) was obtained.

(79) High-resolution mass spectrum performed on a MS-9 through the courtesy of Dr. G. Schaden.

Diethyl-(2-Indanyl)bicarbamate (29).—Compound **30a** (8.7 g, 30 mmol) in 300 ml of ethyl acetate gave quantitatively **29** on shaking with H_2–PtO_2: mp 68–74°; mol wt 291; mass spectrum: *m/e* (rel intensity) 292 (0.4), 177 (9), 176 (16), 150 (5), 130 (13), 117 (25), 116 (100), 115 (8), 104 (14), 103 (6), 91 (5); ir (KBr): 3285 cm^{-1} (NH); 1710, 1750 cm^{-1} (C=O); 1517 cm^{-1} (amide II band); nmr (CCl_4): 2.97 (s), 3.1 (b, 4 H); 4.97 (qui, 1 H), J = 8 cps; 5.88 (q), 5.95 (q, 4 H); 6.98 (d, 2 H), J = 8 cps; 8.79 (t), 8.82 (t, 6 H).

Anal. Calcd for $C_{15}H_{20}N_2O_4$ (292.3): C, 61.63; H, 6.90; N, 9.58; 1 act H, 0.34. Found: C, 61.45; H, 7.02; N, 9.29; act H, 0.44.

Ethyl 3-(2-Indanyl)-3-methylcarbazate (27).—Compound **29** (1.29 g, 4.4 mmol) in 15 ml of benzene and 50 ml of ether were added to 0.75 g (20 mmol) of $LiAlH_4$ in 80 ml of ether. Refluxing for 2 hr, destruction of excess $LiAlH_4$ with water, filtration, and drying over K_2CO_3 gave 0.77 g (3.3 mmol) of **27**: mp 79–80° (from benzene–pentane); mol wt 231; ir (CCl_4): 3460, 3270 cm^{-1} (NH); 1750, 1735, 1705 cm^{-1} (C=O), 1500 cm^{-1} (amide II band); nmr (CCl_4): 3.00 (s, 4 H); 3.40 (b, s, 1 H); 5.95 (q, 2 H), J = 7 cps; 6.25 (m, 1 H); 7.11 (b, d, 4 H), J = 7.5 cps; 7.41 (s, 3 H); 8.81 (t, 3 H), J = 7 cps.

Anal. Calcd for $C_{13}H_{18}N_2O_2$ (234.3): C, 66.64; H, 7.74; N, 11.96. Found: C, 66.95; H, 7.95; N, 11.95.

2-(1,2-Dimethylhydrazino)-1-indanol (28).—Compound **30a** (5.85 g, 20 mmol) in 40 ml of benzene and 100 ml of ether was added to 3.90 g (0.1 mol) of $LiAlH_4$ in 150 ml of ether. After 2 hr refluxing, work-up with water, drying over K_2CO_3, and solvent removal 3.05 g (16 mmol) of **28** remained: mp 67–75° (from benzene–pentane); mol wt 186; mass spectrum: *m/e* (rel intensity) 192 (86), 193 (12), 162 (15), 144 (11), 133 (16), 132 (12), 119 (18), 117 (14), 116 (100), 115 (18), 105 (18), 103 (16), 91 (30), 77 (23), 73 (98); ir (CCl_4): 3430 cm^{-1} (OH); 3200 cm^{-1} (NH); 2780, 2830 cm^{-1} (NCH_3); nmr (CCl_4): 2.9 (m, 4 H); 5.14 (d, 1 H), J = 4.5 cps; 6.9 (m, 2 H); 7.1 (m, 3 H); 7.51 (s, 3 H); 7.54 (s, 3 H).

Anal. Calcd for $C_{11}H_{16}N_2O$ (192.3): C, 68.72; H, 8.39; N, 14.57; 2 act H, 1.04. Found: C, 68.50; H, 8.60; N, 14.48; act H, 1.03.

Diethyl (1-Hydroxy-2-indanyl)bicarbamate (31) and Ethyl 3-(2,3,3a,8b-Tetrahydro-2-oxo-4H-indeno[2,1-*d*]oxazolyl)carbamate (32).—Finely powdered **30a** (4.9 g, 17 mmol) was added with stirring over a period of 30 min to 27.5 ml of concentrated H_2SO_4, kept in an ice bath. After 20 more min the dark red solution was slowly poured into 650 g of ice–water. The mixture was allowed to warm up to room temperature and 0.3 g of a slimy precipitate was removed by filtration. Two fractions of crystals separated from the clear filtrate during 6 days at room temperature: (a) 0.42 g, mp 115–130°, on the surface of the solution, and (b) 1.74 g, mp 105–125°, on the bottom of the flask. Recrystallization of a from benzene–*n*-hexane gave **31**: mp 123–126°; mol wt 310; mass spectrum: *m/e* (rel intensity) 308 (4), 290 (8), 218 (11), 177 (29), 176 (94), 150 (40), 149 (12), 145 (12), 132 (71), 130 (37), 116 (49), 115 (43), 104 (26), 91 (12), 84 (100), 69 (23); ir (KBr): 3400 cm^{-1} (OH); 3230 cm^{-1} (NH); 1755, 1687 cm^{-1} (C=O); 1550 cm^{-1} (amide II); nmr ($CDCl_3$): 2.7 (m, 5 H); 4.70 (b, d, 1 H), J = 8–9 cps; 5.23 (m, 1 H); 5.76 (q, 4 H), J = 7 cps; 6.05 (b, ~1 H); 6.97 (m, 2 H); 8.72 (t 6 H), J = 7 cps.

Anal. Calcd for $C_{15}H_{20}N_2O_5$ (308.3): C, 58.43; H, 6.54; N, 9.09. Found: C, 58.25; H, 6.51; N, 9.02.

Recrystallization of fraction b from benzene–*n*-hexane yielded 1.14 g (4.4 mmol) of **32**: mp 131–132°; mol wt 275; mass spectrum: *m/e* (rel intensity) 262 (6), 218 (59), 145 (12), 130 (31), 129 (41), 126 (21), 117 (22), 116 (44), 115 (29), 113 (11), 84 (100), 69 (18); ir (KBr): 3250 cm^{-1} (NH); 1760–1770, 1722–1733 cm^{-1} (C=O); 1535 cm^{-1} (amide II band); nmr ($CDCl_3$): 2.6 (m, 4 H); 2.9 (b, s, 1 H); 4.12 (d, 1 H), J = 7.5 cps; 5.23 (m, 1 H); 5.77 (q, 2 H), J = 7 cps; 6.8 (m, 2 H); 8.75 (t, 3 H), J = 7 cps.

Anal. Calcd for $C_{13}H_{14}N_2O_4$ (262.3): C, 59.54; H, 5.38; N, 10.68. Found: C, 59.70; H, 5.20; N, 10.67.

Acid-Catalyzed Transformation 31 → 32.—Compound **31** (1.0 g, 3.2 mmol) was added over a 10-min period to 4.9 ml of concentrated H_2SO_4, kept in an ice bath. The solution was poured into 125 g of ice–water, and filtered. After 6 days at room temperature 0.23 g (0.9 mmol) of **32**, mp 129–131°, had precipitated, showing ir data as given above.

Ethyl 3-(2-Indanyl)carbazate (33).—Compound **32** (1.0 g, 3.8 mmol) in 150 ml of ethyl acetate yielded on 1.5-hr shaking with

H_2–Pd–$BaSO_4$, after filtration and solvent removal, 0.84 g (3.8 mmol) of **33**: mp 121–122° (from benzene–*n*-hexane); mol wt 224; ir (KBr): 3310, 3250 cm^{-1} (NH); 1700 cm^{-1} (C=O); 1508 cm^{-1} (amide II); nmr ($CDCl_3$): 2.86 (s, 4 H); 3.46 (b, 1 H); 5.83 (q) J = 7 cps, 6.1 (m, 4 H); 7.08 (m, 4 H); 8.75 (t, 3 H), J = 7 cps.

Anal. Calcd for $C_{12}H_{16}N_2O_2$ (220.3): C, 65.43; H, 7.32; N, 12.72. Found: C, 65.42; H, 7.24; N, 12.75.

Synthesis[80] of Ethyl 3-(2-Indanyl)carbazate (33).—Addition of 0.5 ml of glacial acetic to a solution of 5.0 g (38 mmol) of 2-indanone[81] and 4.3 g (41 mmol) of ethyl carbazate (purum Fluka) in 75 ml of ethanol (95%) at 50° gave the precipitation of 6.0 g (28 mmol) of 2-indanone-N-carbethoxyhydrazone (**34**) in 5 min: mp 176–177° (from benzene–acetone–*n*-hexane), lit.[80] mp 168–169.5°; mol wt (acetone) 215; ir (KBr): 3200, 3120 cm^{-1} (NH); 1700, 1655 cm^{-1} (C=O, C=N); nmr ($CDCl_3$): 2.0 (b, 1 H); 2.79 (s, 4 H); 5.70 (q, 2 H), J = 7 cps; 6.25 (m, 4 H); 8.67 (t, 3 H), J = 7 cps.

Anal. Calcd for $C_{12}H_{14}N_2O_2$ (218.3): C, 66.04; H, 6.47; N, 12.84. Found: C, 65.83; H, 6.47; N, 12.57.

Compound **34** (1.0 g, 4.6 mmol) in 75 ml of ethanol and 25 ml of glacial acetic acid was shaken with H_2–Pt–charcoal for 3.5 hr. Filtration, solvent removal *in vacuo*, and recrystallization of the remaining product from benzene–*n*-hexane afforded 0.38 g (1.7 mmol) of **33**: mp 121–122°, lit.[80] mp 120–120.5°; mol wt 227.

Anal. Calcd for $C_{12}H_{16}N_2O_2$ (220.3): C, 65.43; H, 7.32; N, 12.72. Found: C, 65.10; H, 7.07; N, 12.78.

Compound **33**, synthesized following this procedure, was identical with the product from the catalytic hydrogenation of **32** according to ir, nmr, and mixture melting point.

Kinetic Measurements.—Absorption spectroscopy (uv) at 24400–24700 cm^{-1} (DEAD) and 18400 cm^{-1} (PTD) was used to monitor the concentrations of DEAD and PTD in all the kinetic runs. The measurements were carried out with a Zeiss spectrophotometer PMQ II in 1-cm water-jacketted cells. Temperature was controlled to ±0.1° with a Haake ultrathermostat. The following initial concentrations were used in various solvents (Table V): system DEAD–indene, 2×10^{-2} M DEAD–1.4 M indene; system DEAD–ethyl vinyl ether, 2×10^{-2} M DEAD–1.4 M ethyl vinyl ether; system PTD–indene, 7×10^{-3} M PTD–7×10^{-3} M indene. All runs were at least duplicated.

Standard equations and graphic methods were applied to determine the orders of reaction, rate constants, and activation parameters. The maximum error observed for the rate constants was ± 7%; it was only exceeded for PTD + indene in acetonitrile (±16%).

(80) G. P. Marshall, P. A. McCrea, and J. P. Revell, British Patent 1,019,363; *Chem. Abstr.*, **64**, 12620c (1966).

(81) J. E. Horan and R. W. Schiessler, *Org. Syn.*, **41**, 53 (1961).

Registry No.—**5**, 23358-00-1; **6**, 23358-01-2; **7**, 23358-02-3; **8**, 23358-03-4; **9**, 23358-04-5; **10**, 23358-05-6; **11**, 23358-06-7; **12**, 23358-07-8; **12-D$_1$**, 23358-08-9; **13**, 23358-09-0; **14**, 23358-10-3; **15**, 23358-11-4; **16**, 23358-12-5; **19**, 23358-13-6; **20**, 23358-14-7; **21**, 23358-15-8; **23**, 23358-16-9; **24**, 23358-17-0; **27**, 23358-18-1; **28**, 23358-19-2; **29**, 23358-20-5; **30a**, 23358-21-6; **30b**, 23358-22-7; **31**, 23358-23-8; **32**, 23358-24-9; **33**, 5156-54-7; **34**, 5168-61-6; **36**, 23358-27-2; **37**, 23358-28-3; *cis*-DEAD, 4143-60-6; *trans*-DEAD, 4143-61-7; indene, 95-13-6; ethyl vinyl ether, 109-92-2; PTD, 4233-33-4; DMAD, 2446-84-6.

Acknowledgment.—The authors are grateful to Dr. G. Schomburg, F. Weeke, and H. Behlau for their support with preparative glpc, and to Dr. E. G. Hoffmann for helpful discussion of ir data. D. V. White is indebted to the Max-Planck-Gesellschaft for a predoctoral fellowship, and to Boston College for a University Travel Grant.

3,4-Disubstituted and Fused 1,2,5-Thiadiazole N-Oxides

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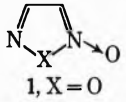
Received September 23, 1969

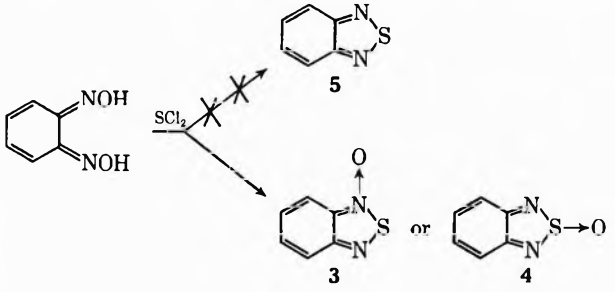
Acyclic and cyclic compounds containing the α-dioxime grouping are converted into mixtures of 3,4-disubstituted and fused 1,2,5-thiadiazoles and the corresponding N-oxides by reaction with sulfur dichloride.

Although furoxans (**1**) have been known for a long time, the corresponding 1,2,5-thiadiazole N-oxides (**2**) have not been definitely recognized. The reaction of

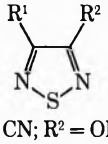


1, X = O
2, X = S

o-benzoquinone dioxime with sulfur dichloride has been reported,[1] but the structure of the reaction product was not determined unequivocally; the structures that were proposed are that of an N-oxide (**3**) and S-oxide (**4**); formation of 2,1,3-benzothiadiazole (**5**) was not observed.



Previous investigations of the action of sulfur monochloride and sulfur dichloride on aliphatic compounds containing an NCCN grouping also involved oximes and α-dioximes. α-Isonitrosocyanoacetamide and α-isonitrosophenylacetonitrile were converted into 3-cyano-4-hydroxy-1,2,5-thiadiazole[2] (**6**) and 3-chloro-4-phenyl-1,2,5-thiadiazole,[3] (**7**), respectively, while glyoxime and



6, R^1 = CN; R^2 = OH
7, R^1 = Cl; R^2 = C_6H_5
8, R^1 = R^2 = H and/or Cl
9, R^1 = R^2 = CH_3

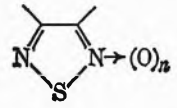
(1) V. G. Pesin, A. M. Khaletsky, and Chou-Chin, *J. Gen. Chem. USSR*, **28**, No. 7, 2131 (1958).

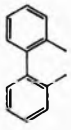
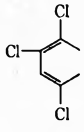
(2) J. M. Ross and W. C. Smith, *J. Amer. Chem. Soc.*, **86**, 2861 (1964).

(3) L. M. Weinstock, P. Davis, B. Handelsmann, and R. Tull, *J. Org. Chem.* **32**, 2823 (1967).

TABLE I

3,4-DISUBSTITUTED AND FUSED 1,2,5-THIADIAZOLES AND N-OXIDES



Compound	Group attached to basic structure	Method[a]	n	Yield, %	Mp or bp, °C	Analyses, % Nitrogen Calcd	Nitrogen Found	Sulfur Calcd	Sulfur Found	$\nu_{N\rightarrow O}$, cm^{-1}
5		A	0	38.1	43–44	20.6	20.9	23.5	23.2	
3			1	34.6	78–80	18.4	17.8	21.1	20.7	1365
10		C	0	22.7	163–164	11.9	11.8	13.6	13.2	
11			1	2.8	204–208	11.1	11.1	12.7	12.9	1375
13		A	0	7.3	123–124	11.7	11.8	13.4	13.2	
14			1	3.4	144–147	10.9	10.5	12.5	12.3	1370
15		B	0	67	65 (40 mm)	18.1	18.5	20.7	20.5	
16		C	0	5.7	83–84	11.8	11.8	13.4	13.1	
17			1	4.7	124	11.0	10.8	12.9	12.4	1360
18		C	0	23.0	132–133	13.3	13.2	15.3	15.8	
		B	0	81.9						

[a] (A) SCl_2 in benzene at 25°; (B) SCl_2 in DMF at 20–25°; (C) S_2Cl_2 in DMF at 5–25°.

dimethylglyoxime were converted into the 1,2,5-thiadiazoles **8**[3] and **9**;[3] formation of oxides analogous to **3** and **4** was not observed in these reactions.

Pesin's[1] report of an inability to distinguish between structures **3** and **4** and the failure of Ross and Smith,[2] and of Weinstock, *et al.*,[3] to observe formation of N-oxides or S-oxides in the reaction of acyclic oximes and α-dioximes with sulfur monochloride and sulfur dichloride prompted us to investigate the reaction of several aliphatic and aromatic α-dioximes with these reagents and determine the structures of the reaction products.

Results and Discussion

To elucidate the structure of the reaction product from *o*-benzoquinone dioxime and sulfur dichloride as that of **3** and **4**, it was decided to repeat Pesin's experiment. When *o*-benzoquinone dioxime[4] was allowed to react with sulfur dichloride in benzene at 25°, a 1:1 mixture of two products was obtained. Analytical, physical, and spectral data of the compound melting at 43–44° (see Table I) were in agreement with those of 2,1,3-benzothiadiazole (**5**). The compound that melted at 78–80° (lit.[1] mp 81–83°) has been assigned the N-oxide structure as shown in formula **3** rather than the S-oxide (**4**) structure. This assignment is based on its infrared spectrum which is consistent only with structure **3**. For example, the characteristic S → O stretching vibration of a sulfoxide[5] (*i.e.*, **4**) which occurs usually near 1050 cm^{-1} is absent, whereas a strong band at 1365 cm^{-1} indicates the presence of an heterocyclic N-oxide group. Support for this assignment comes from the infrared spectra of fused aromatic N-oxides:[6] the N → O stretching vibration of quinoxaline N-oxide which is isoelectronic with **3** has been assigned to the 1370-cm^{-1} band.[7]

9,10-Phenanthrenequinone dioxime[11] underwent reaction with excess sulfur monochloride at 25° in dimethylformamide (2 hr) to give a mixture of phenanthro[9,10-*c*]-1,2,5-thiadiazole (**10**) and the corresponding N-oxide (**11**). The structure of **10** was proven by independent, unequivocal synthesis from 9,10-diaminophenanthrene and thionyl chloride in the presence of triethylamine as scavenger for hydrogen chloride. The structure of **11** was indicated by the N–O band (ν 1375 cm^{-1}). To obtain additional support for the structure of **11** it was decided to prepare its only other positional isomer, namely the known[12] S-oxide (**12**) and establish their nonidentity. Reaction of phenanthrene-9,10-bis(trimethylsilyl)imine[12] with thionyl chloride afforded **12**, melting at 234–237° (lit.[12] mp 234.5–237°). Compounds **11** and **12** were not identical as shown by the differences in melting points. Consistent with the structure of **12** the infrared spectrum gave characteristic sulfoxide absorption at 1130 cm^{-1}, which is not present in **11**. The fact that **12** could readily be

(4) (a) Th. Zincke and P. Schwarz, *Justus Liebigs Ann. Chem.*, **307**, 28 (1899); (b) L. G. Green and F. W. Rowe, *J. Chem. Soc.*, 2452 (1912).

(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1954, Chapter 22, p 288.

(6) G. R. Clemo and A. F. Daglish, *J. Chem. Soc.*, 1481 (1950).

(7) The relatively high value of $\nu_{N\rightarrow O}$ 1370 cm^{-1} is not surprising since the $^{+}N–O^{-}$ band in heterocyclic N-oxides such as those of pyridine[8a,9] and pyrazine[8b,10] is found in the 1319–1230-cm^{-1} region, pyrazine N-oxide having its $\nu_{N\rightarrow O}$ stretching band at 1318 cm^{-1}, which is some 54 cm^{-1} higher than in pyridine N-oxide; in general, the band rises with increasing electron-acceptor properties of the substituent.[9]

(8) (a) H. Shindo, *Chem. Pharm. Bull. Jap.*, **6**, 117 (1958), and **7**, 791 (1951); (b) *ibid.*, **8**, 33 (1960).

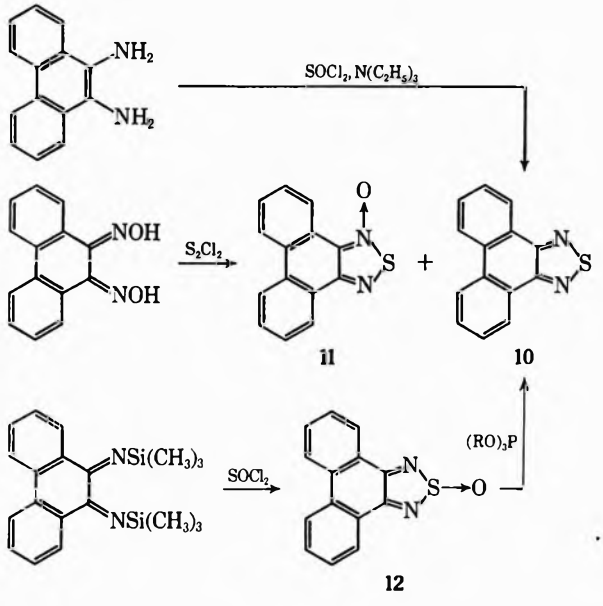
(9) A. R. Katritzky, J. A. T. Boulton, and N. A. Coats, *J. Chem. Soc.*, 3680 (1959).

(10) B. Klein and J. Berkowitz, *J. Amer. Chem. Soc.*, **81**, 5160 (1959).

(11) J. Schmidt and A. Soll, *Ber.*, **40**, 2459 (1907).

(12) G. Tuchtenhagen and K. Rühlmann, *Justus Liebigs Ann. Chem.*, **711**, 174 (1968).

reduced to the parent thiadiazole **10** under such mild conditions as warming a solution in excess triethyl phosphite at 60° for about 5 min is in marked contrast to the behavior of N-oxide **11** which underwent extensive decomposition under the same conditions; starting material (**11**) or reduced product (**10**) were not detectable in the dark reaction mixture.

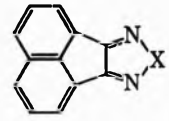


Reaction of 3,4,6-trichloro-*o*-benzoquinone dioxime with sulfur dichloride at 25° in benzene yielded two products in the approximate ratio of 2:1. The major component was identified as 4,5,7-trichloro-2,1,3-benzothiadiazole (**13**) by comparison of its physical and spectral data with those of an authentic sample prepared by the procedure reported by Van Daalen, *et al.*[13] The minor product was found to be 4,5(or 6),-7-trichloro-2,1,3-benzothiadiazole 1-oxide (**14**) by elemental analysis and its infrared spectrum (**14**, $\nu_{N\rightarrow O}$, 1370 cm^{-1}).

No reaction was observed between dichloroglyoxime[14] and sulfur dichloride in benzene at 25° after 2 hr. However, the reaction proceeded smoothly in dimethylformamide and was complete at 25–30° within 2 hr. Tlc indicated one major component along with one minor impurity. Purification by column chromatography afforded 67% 3,4-dichloro-1,2,5-thiadiazole (**15**) which was identical with the product obtained from cyanogen and sulfur dichloride according to the procedure of Vest.[15] The second (minor) component, presumably 3,4-dichloro-1,2,5-thiadiazole N-oxide, did not emerge from the column and therefore was not identified.

The reaction of diphenylglyoxime[16] with sulfur monochloride occurred also in dimethylformamide at 5° and gave 3,4-diphenyl-1,2,5-thiadiazole (**16**) and 3,4-diphenyl-1,2,5-thiadiazole N-oxide (**17**) in the approximate proportion of 1:1. Compound **16** was identical with the product obtained from 1,2-diphenylethane and tetrasulfur tetranitride (S_4N_4) according to the procedure of Bertini and Pino.[17] The structure of **17** follows from the value of $\nu_{N\rightarrow O}$ 1360 cm^{-1} and the absence of S → O, C=O, and OH stretching vibrations in the infrared spectrum. The H′ nmr spectrum has only a multiplet in the expected range of δ 7.7–8.7 ppm (phenyl H).

Reaction of acenaphthoquinone dioxime with sulfur monochloride or sulfur dichloride in dimethylformamide afforded acenaphtho[1,2-*c*]-1,2,5-thiadiazole (**18**); formation of the corresponding N-oxide was not observed. The ease of formation of **18** (23% with S_2Cl_2 and 82% with SCl_2) and its thermal stability are surprising in view of the structural similarity to the corresponding furazan analog **19** which is unknown. Attempts to prepare **19** by deoxygenation of the corresponding furoxan, which is prone to decompose violently at its melting point, have failed;[18] deoxygenation with trialkyl phosphites, which have proved to be efficient reagents for the reduction of furoxans to furazans,[19] gave instead naphthalene-1,8-dicarbonitrile.[18] Fusion of a furoxan or furazan nucleus to another five-membered ring apparently gives rise to an unfavorably strained situation,[20] whereas introduction of a larger sulfur atom in place of oxygen reduces ring strain.



18, X = S
19, X = O

The assignment of the 1,2,5-thiadiazole (D) and 1,2,5-thiadiazole N-oxide (C) structure to the products of these reactions allows the suggestion of a common reaction path for at least the early stages of all ring closure reactions involving α-dioximes and sulfur monochloride or sulfur dichloride. The formation of C and D has been rationalized according to Scheme I. It is plausible, for example, that the first step in all reactions is nucleophilic attack of nitrogen on the polarizable sulfur chloride to give A. The existence of compounds containing the chlorothio (ClS) group is well documented and, in several instances, compounds containing the chlorodithio (ClSS) group have been isolated.[21] Chlorodithio compounds as intermediates have also been postulated in the reaction of aliphatic amides[22] [to give bis(amido) sulfides and in the Herz reaction[23]]. Scheme I illustrates two possible routes to C and D. In the first (path a), nucleophilic attack of the nitrogen of the oxime group in A on the chlorothio group would

(13) J. J. Van Daalen, J. Daams, H. Koopmann, and A. Tempel, *Rec. Trav. Chim. Pays-Res.*, **86**, 1159 (1967); H. Koopmann, J. J. Van Daalen, and J. Daams, *Weed Res.* **7**, 200 (1967).

(14) (a) G. Ponzio and F. Baldracco, *Gazz. Chim. Ital.* **60**, 429 (1930); (b) H. E. Ungnade, G. Fritz, and L. W. Kissinger, *Tetrahedron*, **19**, *Suppl.* **1**, 245 (1963).

(15) R. D. Vest, U. S. Patent 3,115,497 (1963); *Chem. Abstr.*, **60**, 5512d (1964).

(16) K. v. Auwers and V. Meyer, *Ber.*, **22**, 547 (1889).

(17) V. Bertini and P. Pino, *Angew. Chem.* **77**, 262 (1965); *Angew. Chem., Int. Ed. Engl.*, **4**, 239 (1965).

(18) A. U. Rahman and A. J. Boulton, *Chem. Commun.*, 73 (1968).

(19) (a) C. Grundmann, *Ber.*, **97**, 575 (1964); (b) A. S. Bailey and J. M. Evans, *Chem. Ind.* (London), 1424 (1964); (c) T. Mukijama, N. Nambu, and M. Okamoto, *J. Org. Chem.*, **27**, 3651 (1962).

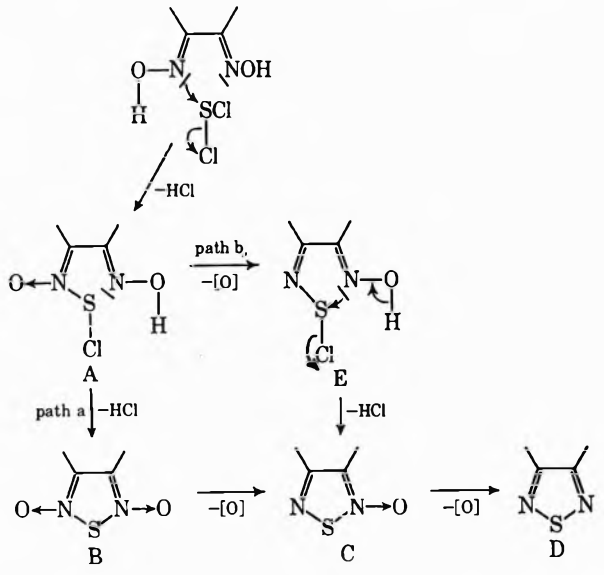
(20) H. J. Boyer in "Heterocylic Compounds," R. C. Elderfield, Ed., J. Wiley & Sons, Inc., New York, N. Y., 1961, p 462. The referee suggested that the stability difference between **18** and **19** may reflect a difference in aromaticity and not steric strain.

(21) Z. S. Ariyan and L. A. Wiles, *J. Chem. Soc.*, 4510 (1961); 1725 (1962).

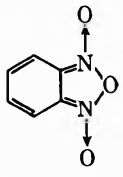
(22) P. Hope and L. A. Wiles, *ibid.*, 5679 (1964).

(23) P. Hope and L. A. Wiles, *Chem. Ind.* (London), 32 (1966).

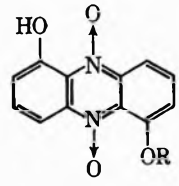
SCHEME I



lead to the di-N-oxide[24] (B) which is subsequently reduced to give C and, eventually, D. The second route (path b) would involve formation of the hypothetical intermediate E by loss of oxygen from A followed by nucleophilic attack of the nitrogen of the oxime group on sulfur of the chlorothio group to give the N-oxide C directly. If sulfur monochloride is employed in these reactions, the chlorodithio intermediates analogous to A and E are cleaved at the sulfur–sulfur bond during the ring clusure. Although at the present time we are unable to make a choice between these two mechanisms, we do favor path a. A possible explanation for the inability to detect the hypothetical B may be its inherent instability. For example, benzofurazan N,N-dioxide (**20**) has been shown to be unstable with respect to ring opening.[25] Another plausible explanation may be that the hypothetical B is easily reduced by any S^{+1} or S^{+2} source present in the reaction mixture before and after hydrolysis. The high oxidizing power of phenazine N,N-dioxides, such as the broad-spectrum antibiotics Jodinin[6] (**21**) and Myxin[26,27] (**22**), we regard as additional supporting evidence for path a.



20



21, Jodinin (R = H)
22, Myxin (R = CH_3)

Experimental Section

General.—Melting points were determined with a Thomas–Hoover capillary apparatus and are uncorrected. Infrared spectra were measured with a Perkin-Elmer Model 21 spectrometer. Nuclear magnetic resonance spectra were obtained on a Varian A-60 spectrometer.

α-Dioximes.—*o*-Benzoquinone dioxime prepared in 36.4% yield from benzofuroxan and hydroxylamine crystallized from aqueous ethanol and had mp 154° dec, lit.[4] mp 144° dec.

3,4,6-Trichloro-*o*-benzoquinone was prepared from 2,4,5-trichloroaniline *via* 2,4,5-trichloro-6-nitroaniline and 4,5,7-trichlorobenzofuroxan (47%, mp 104–105°) in 46% yield and melted at 193° dec.

Dichloroglyoxime from glyoxime by chlorination in 10% HCl at 0° had mp 198–199° dec, lit.[4] mp 198–199° dec.

The product obtained from benzil and hydroxylamine was *anti*-diphenylglyoxime, mp 244–246°, lit.[16] mp 244°.

9,10-Phenanthrenequinone dioxime from 9,10-phenanthrenequinone and hydroxylamine crystallized from methanol in 62.5% yield, mp 200–201°, lit.[11] mp 202°.

Acenaphthoquinone dioxime was prepared from acenaphthoquinone and hydroxylamine hydrochloric acid salt in refluxing ethanol (8 hr) and melted at 232°.

Anal. Calcd for $C_{12}H_8N_2O_2$:N, 13.2. Found: N, 12.9.

Reaction of o-Benzoquinone Dioxime with Sulfur Dichloride. Preparation of 2,1,3-Benzothiadiazole (5) and 2,1,3-Benzothiadiazole N-Oxide (3).—An adaptation of the procedure of Pesin, *et al.*,[1] was employed. A solution of 5 ml of sulfur dichloride in 25 ml of dry benzene was added dropwise at 25° and with constant stirring to a suspension of 5.0 g of o-benzoquinone dioxime in 100 ml of dry benzene. During the course of the mildly exothermic reaction, the dioxime dissolved. After 2 hr, the mixture was filtered and the filtrate was evaporated to dryness to give 4 g of product; tlc indicated two compounds. Separation was accomplished by column chromatography on deactivated silica gel[28] using hexane–ethyl acetate–tetrahydrofuran (40:8:2). The first fraction which emerged from the column was 2,1,3-benzothiadiazole(**5**), 1.88 g (38.1%), mp 43–44° (from hexane).

Anal. Calcd for $C_6H_4N_2S$: N, 20.6; S, 23.5. Found: N, 20.9; S, 23.2.

The second component (**3**) was obtained as yellow crystalline solid: mp 78–80°; 1.90 g (34.6%); ir spectrum: intense band at 1365 cm^{-1} (N→O); nmr spectrum, multiplet at δ 7.4 ppm (aromatic H).

Anal. Calcd for $C_6H_4N_2OS$: N, 18.4; S, 21.1. Found: N, 18.7; S, 20.8.

Reaction of 9,10-Phenanthrenequinone Dioxime with Sulfur Monochloride. Preparation of Phenanthro[9,10-*c*]-1,2,5-thiadiazole (10) and Phenanthro[9,10-*c*]-1,2,5-thiadiazole 2-Oxide (11).—A mixture of 10.0 g (0.042 mol) of phenanthrenequinone dioxime, 8 g (0.059 mol) of sulfur monochloride, and 20 ml of dimethylformamide was stirred for 2 hr at room temperature. The reaction mixture was poured into water and filtered. The crude mixture was separated by column chromatography over deactivated silica gel using a mixture of hexane–ethyl acetate–tetrahydrofuran (40:8:2) to give 2.07 g (22.7%) of **10** melting at 163–164°.

Anal. Calcd for $C_{14}H_8N_2S$: N, 11.9; S, 13.6. Found: N, 11.8; S, 12.9.

The fraction containing **11** was recrystallized from ethanol (5 times) to give 0.3 g (2.8%) of yellow brown solid, **11**: mp 204–208°; ir (KBr) 1375 cm^{-1} (N→O).

Anal. Calcd for $C_{14}H_8N_2OS$: N, 11.1; S, 12.7. Found: N, 11.1; S, 12.9.

Reaction of Phenanthro[9,10-*c*]-1,2,5-thiadiazole 1-Oxide (12) with Triethyl Phosphite.—A solution of 1.0 g (4 mmol) of **12** in 20 ml of triethyl phosphite was heated at 60° for 5 min. When the reaction mixture was allowed to cool to room temperature a brown solid melting at 158–159° crystallized out. Recrystallization from ethanol afforded 0.5 g (53%) of **10** as light brown solid, 163–164°. A mixture melting point with an authentic sample of **10** obtained from 9,10-diaminophenanthrene and thionyl chloride showed no depression.

Anal. Calcd for $C_{14}H_8N_2S$: N, 11.9; S, 13.6. Found: N, 11.9; S, 13.1.

Reaction of 3,4,5-Trichloro-o-benzoquinone Dioxime with Sulfur Dichlorodide. Preparation of 4,5,7-Trichloro-2,1,3-benzothiadiazole (13) and 4,5(or 6),7-Trichloro-2,1,3-benzothiadiazole 1-Oxide (14).—To a slurry of 11.1 g (0.046 mol) of 3,4,6-trichloro-*o*-benzoquinone dioxime in 100 ml of benzene was added in 15 min a solution of 5 ml (8.1 g, 0.79 mol) of sulfur dichloride

(24) The dioxide formulation was chosen for B to emphasize the symmetry of this type of molecule. Mallory, Schneller, and Wood[25] point out that a dioxide analogous to B would presumably be a resonance hybrid.

(25) F. B. Mallory, K. E. Schneller, and C. S. Wood, *J. Org. Chem.* **26**, 3312 (1961).

(26) O. E. Edwards and D. C. Gillespie, *Tetrahedron Lett.*, No. 40, 4867 (1966).

(27) M. Weigele and W. Leimgruber, *ibid.*, No. 8, 715 (1967).

(28) Deactivated by passing a stream of air through a layer of silica gel (Grace, grade 950, mesh size 60–200) for 12 hr.

in 25 ml of benzene. Stirring was continued for an additional 4 hr. The reaction mixture was poured over ice–water, extracted with 400 ml of ether and dried ($MgSO_4$). Evaporation of ether afforded a mixture of **13** and **14** which was separated by column chromatography over silica gel using the solvent mixture hexane–tetrahydrofuran–ethyl acetate (18:1:1). The first compound emerging from the column was identified as **13**, mp 123–124°, 0.8 g (7.3%).

Anal. Calcd for $C_6HCl_3N_2S$: N, 11.7; Cl, 44.5; S, 13.4. Found: N, 11.8; Cl, 44.4; S, 13.2.

The second fraction consisted of the N-oxide **14**: mp 144–147°; 0.4 g (3.4%); ir (KBr) 1370 cm^{-1} (N→O).

Anal. Calcd for $C_6HCl_3N_2OS$: N, 10.9; S, 12.5. Found: N, 10.5; S, 12.3.

Reaction of Diphenylglyoxime with Sulfur Monochloride. Preparation of 3,4-Diphenyl-1,2,5-thiadiazole (16) and 3,5-Diphenyl-1,2,5-thiadiazole N-Oxide (17).—Diphenylglyoxime, 30.0 g (0.125 mol), was added to a mixture of 32 ml (0.4 mol) of sulfur monochloride in 64 ml of dimethylformamide at 25°. The temperature of the reaction was maintained by external cooling with the aid of an ice bath. After 2 hr, the reaction mixture was poured onto 300 g of ice water and the precipitate was filtered and dried. Thin layer chromatography indicated the presence of three compounds in addition to large amounts of sulfur. The crude mixture was resolved by column chromatography on deactivated silica gel[28] using the solvent mixture hexane–tetrahydrofuran (9:1). Sulfur which emerged first from the column was discarded. After removal of the solvent, the second fraction was recrystallized from hexane to give 1.7 g (5.7%) of **16**: colorless, crystalline solid; mp 83–84°; nmr multiplet near 7.6 ppm (phenyl H).

Anal. Calcd for $C_{14}H_{10}N_2S$: N, 11.75; S, 13.45. Found: N, 11.8; S, 13.1.

The third fraction was recrystallized from hexane and afforded 1.5 g (4.7%) of **17**: colorless crystalline solid; mp 124°; ir (KBr pellet): 1360 cm^{-1} (N→O).

Anal. Calcd for $C_{14}H_{10}N_2OS$: N, 11.0; S, 12.9. Found: N, 10.8; S, 12.4.

A fourth compound, possibly the corresponding di-N-oxide, did not emerge from the column and therefore was not identified.

Preparation of Acenaphtho[1,2-*c*]-1,2,5-thiadiazole (18) from Acenaphthoquinone Dioxime. With Sulfur Dichloride.—Sulfur dichloride (20 ml, 32.4 g, 0.315 mol) was added dropwise with stirring at 25° to a solution of acenaphthoquinone dioxime (10.6 g, 0.05 mol) in dimethylformamide (150 ml). After 2.5 hr, the mixture was poured over ice–water and filtered. The solid was dissolved in methylene chloride, charcoaled, and dried ($MgSO_4$). Evaporation to dryness afforded a dark residual solid which was extracted with 500 ml of boiling hexane. This solution was concentrated to 150 ml and cooled to give 8.6 g (81.9%) of **18** as white solid melting at 132–133°. The nmr spectrum shows complex lines near 7.8 ppm (aromatic H).

Anal. Calcd for $C_{12}H_6N_2S$: N, 13.3; S, 15.3. Found: N, 13.2; S, 15.8.

With Sulfur Monochloride.—The reaction of acenaphthoquinone dioxime (10.6 g, 0.05 mol) with sulfur monochloride (25 ml, 42.5 g, 0.315 mol) which was carried out under the same reaction conditions (see above) afforded **18** in 23% yield with recovery of about 18% of acenaphthoquinone dioxime.

Registry No.—**3**, 23431-06-3; **5**, 273-13-2; **10**, 1143-73-3; **11**, 23431-09-6; **13**, 1982-55-4; **14**, 23431-11-0; **15**, 5728-20-1; **16**, 4057-61-8; **17**, 23431-14-3; **18**, 437-40-1; 3,4,6-trichloro-*o*-benzoquinone, 23431-16-5; acenaphthoquinone dioxime, 1932-08-7.

Acknowledgment.—The author expresses his appreciation to Mr. G. E. Pollard and Mr. P. M. Saliman and their associates for spectral and analytical data.

Notes

Reactions of Trihalopropionitriles with Trialkyl Phosphite. A Convenient Synthesis of 2-Haloacrylonitriles

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Received August 27, 1969

Vicinal dihalides react with trialkyl phosphites to yield either of two products, depending on the structure of the dihalide. In the absence of electron-withdrawing groups on the carbon atoms bearing the halogen atoms, phosphonate esters are formed (eq 1).[1]

$$(RO)_3P + BrCH_2CH_2Br \longrightarrow (RO)_2P(O)CH_2CH_2Br + RBr \quad (1)$$

If, however, both halogen atoms are on carbon atoms bearing electron-withdrawing groups, dehalogenation occurs (eq 2), giving a high yield of olefin.[2]

$$C_6H_5C(O)CHBrCHBrC(O)C_6H_5 + (RO)_3P \longrightarrow C_6H_5C(O)CH{=}CHC(O)C_6H_5 + (RO)_2P(O)Br + RBr \quad (2)$$

In the presence of an electron-withdrawing group on only one carbon atom, the usual course of reaction with trialkyl phosphites is formation of a phosphonate ester, as illustrated by the reaction of 2,3-dichloropropionitrile with triethyl phosphite (eq 3).[3]

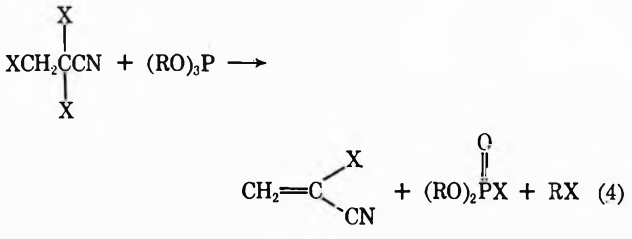
$$ClCH_2CHClCN + (EtO)_3P \longrightarrow ClCH_2CH(CN)P(O)(OEt)_2 + EtCl \quad (3)$$

However, styrene dibromide has been found to undergo dehalogenation when allowed to react with triethyl phosphite to give styrene in 50% yield.[4]

(1) G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **66**, 109 (1944).
(2) S. Dershowitz and S. Proskauer, *J. Org. Chem.*, **26**, 3595 (1961).
(3) U. S. Abramov and N. A. Il'ina, *J. Gen. Chem. USSR*, **26**, 2014 (1956); *Chem. Abstr.*, **51**, 1822 (1957).
(4) B. A. Arbuzov and B. P. Lugovkin, *J. Gen. Chem. USSR*, **21**, 99 (1951); *Chem. Abstr.*, **45**, 7002 (1951).

We wish to report another reaction of preparative value, where dehalogenation has been shown to occur from a system containing vicinal halide groups.

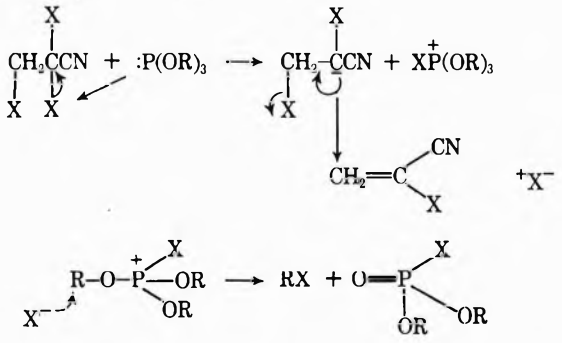
From the reaction of 2,2,3-trichloro- or tribromopropionitrile with triethyl or trimethyl phosphite below room temperature, almost quantitative yields of 2-haloacrylonitriles, halophosphates, and alkyl halides can be readily isolated, (eq 4).



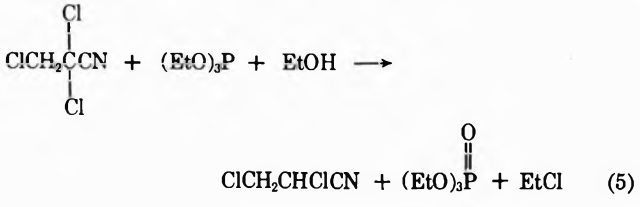
R = Et or Me, X = Cl or Br

The dialkyl chlorophosphates and 2-haloacrylonitriles were characterized by their boiling points, vpc retention times, and ir and nmr spectra. The dialkyl bromophosphates could not be distilled without decomposition. The identity of these compounds was verified by conversion into their anilino derivatives according to a known method.[5]

These results can be explained by nucleophilic attack of phosphorus on an α halogen, followed by elimination of β halogen from the resulting carbanion. Subsequent Arbuzov cleavage of the resultant phosphonium species by halide ion would explain the other products.

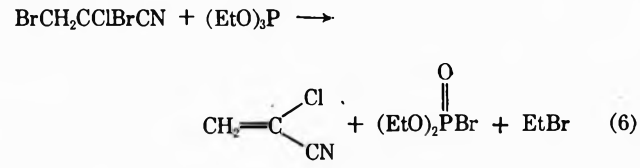


Attack by phosphorus on halogen is well established.[6] The intermediacy of the carbanion in these dehalogenation reactions was confirmed by reacting 2,2,3-trichloropropionitrile and triethyl phosphite in ethanol. Ethanol served as a proton donor and the reaction took the following course (eq 5).

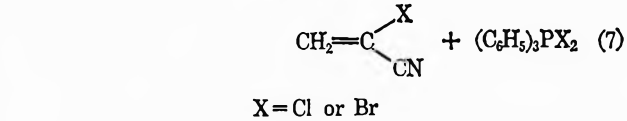


Comparing the reactions of trialkyl phosphites with those of 2,3-dichloropropionitrile and 2,2,3-trichloropropionitrile, it appears that the phosphite can attack the α carbon, giving the normal Arbuzov product (eq 3), or the α chlorine, giving the dehalogenation product. Attack at the α carbon is apparently favored, but is prevented in the 2,2,3-trichloro derivative presumably by the bulky geminal chlorine atoms. Attack on chlorine is, therefore, favored in the latter case.

The reaction of 2-chloro-2,3-dibromopropionitrile and triethyl phosphite also gives high yields of 2-chloroacrylonitrile (eq 6), indicating that attack of trivalent phosphorus esters on bromine is favored over attack on chlorine.



Substituted phosphines such as triphenylphosphine have also been found to react with 2,2,3-trihalopropionitriles in ether solution to give 2-haloacrylonitriles in good to moderate yields (eq 7).



X = Cl or Br

Experimental Section

General Comments.—All the reactions were carried out in a three-necked flask equipped with magnetic stirrer assembly, dropping funnel, and a condenser connected to a cold trap. Infrared spectra were recorded on a Beckman IR 7. Nmr spectra ($CDCl_3$) were obtained on a Varian A-60A instrument. Vpc analysis was carried out isothermally, using a Beckman Model 2 with a 10-ft column packed with silicon gum on Chromosorb W.

Reaction of 2,2,3-Trichloropropionitrile and Triethyl Phosphite.—Triethyl phosphite (33.0 g, 0.2 mol) was added dropwise to 2,2,3-trichloropropionitrile (32.0 g, 0.2 mol). The temperature of the reaction mixture was maintained at 5–10° by external cooling. After complete addition of the phosphite, the reaction mixture was fractionated to give ethyl chloride (12.0 g), 2-chloroacrylonitrile (16.0 g, 90%), bp 88–90°, and diethyl chlorophosphate, bp 55° (1.5 mm).

Reaction of 2,2,3-Tribromopropionitrile and Triethyl Phosphite.—The addition of triethyl phosphite (33.0 g, 0.2 mol) to 2,2,3-tribromopropionitrile (58.0 g, 0.2 mol) was carried out as described above and fractionated to give ethyl bromide (17.0 g, collected in the cold trap), 2-bromoacrylonitrile (20.0 g, 77%), bp 52–53° (85 mm), and a light yellow residue (*ca.* 50.0 g). This residue was identified as O,O'-diethyl bromophosphate by converting a portion of the residue into its anilino derivative as described in the literature to give diethyl anilinophosphonate, mp 93° (lit.[6] mp 96.5°).

Reaction of 2,3-Dibromo-2-chloropropionitrile and Triethyl Phosphite.—The reaction was carried out by slow addition of triethyl phosphite (16.6 g, 0.1 mol) to 2,3-dibromo-2-chloropropionitrile (24.5 g, 0.1 mol) at 5–10°, followed by fractionation. The reaction yielded ethyl bromide (8.0 g) and 2-chloroacrylonitrile (7.5 g, 86%), bp 84–89°. The undistilled material was converted into its anilino derivative to give diethyl anilinophosphonate, mp 93°.

Reaction of 2,2,3-Trichloropropionitrile and Trimethyl Phosphite.—Trimethyl phosphite (24.8 g, 0.2 mol) was added to 2,2,3-trichloropropionitrile (32.0 g, 0.2 mol) at 5–10°. During the course of the exothermic reaction, methyl chloride (21.0 g) was collected in the cold trap. On fractionation, the reaction mixture gave 2-chloroacrylonitrile (14.5 g, 82%), bp 86–88°.

Reaction of 2,2,3-Trichloropropionitrile and Triethyl Phosphite in the Presence of Dry Ethanol.—To an ethanol (25.0 g) solution of 2,2,3-trichloropropionitrile (16.0 g, 0.1 mol) was added

(5) H. McCombie, B. C. Saunders, and G. J. Stacey, *J. Chem. Soc.*, 380 (1945).

(6) M. Grayson and E. Griffith, "Topics in Phosphorus Chemistry," Vol. 2, Interscience Publishers, Inc., New York, N. Y., 1965, pp 135–195.

triethyl phosphite (16.6 g, 0.1 mol) at 15–20°. After the complete addition of the phosphite, the reaction mixture was fractionated to give ethyl chloride (5.0 g), 2,3-dichloropropionitrile (10.5 g, 80%), bp 63–65° (35 mm), and triethyl phosphate (15.5 g), bp 85–87° (20 mm).

Reaction of 2,2,3-Trichloropropionitrile and Triphenylphosphine.—Triphenylphosphine (26.2 g, 0.1 mol) in dry ether (100 ml) was added dropwise to the 2,2,3-trichloropropionitrile (16.0 g, 0.1 mol) in dry ether (70 ml) under constant stirring. An exothermic reaction resulted and a white precipitate was formed. After complete addition of the triphenylphosphine, the white precipitate (31.0 g) was filtered. The filtrate on fractionation yielded 2-chloroacrylonitrile (6.0 g, 70%), bp 88–89°. The white precipitate, on treatment with water, gave triphenylphosphine oxide, mp 151–153° (lit.[7] mp 152–153°).

Reaction of 2,2,3-Tribromopropionitrile and Triphenylphosphine.—This reaction was carried out in the manner described above, using 2,2,3-tribromopropionitrile (29.2 g, 0.1 mol) in dry ether (30 ml) and triphenylphosphine (26.2 g, 0.1 mol) in dry ether (100 ml). The reaction gave 2-bromoacrylonitrile (77 g, 60%) and triphenylphosphine dibromide, which was then converted into triphenylphosphine oxide (20.0 g), mp 152–153°.

Registry No.—2,2,3-Trichloropropionitrile, 813-74-1; triethyl phosphite, 122-52-1; 2,2,3-tribromopropionitrile, 22929-17-5; 2,3-dibromo-2-chloropropionitrile, 22929-18-6; trimethyl phosphite, 121-45-9; triphenylphosphine, 603-35-0; triphenylphosphine oxide, 791-28-6; 2-chloroacrylonitrile, 920-37-6; diethyl chlorophosphate, 814-49-3.

(7) G. M. Kosolapoff, "Organo-Phosphorus Compounds," John Wiley & Sons, Inc., New York, N. Y., 1950.

Amino Acid Insertions in Solid-Phase Peptide Synthesis[1a,b]

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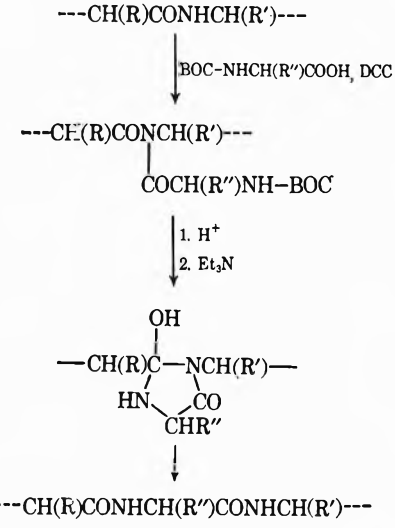
Received July 3, 1969

In solid-phase peptide synthesis,[2–4] peptide bonds are most frequently formed through the reaction of excess N-protected amino acid and N,N′-dicyclohexylcarbodiimide[5] with amino acid or peptide derivatives of polystyrene. Brenner[6] has stated that acylation of peptide bonds, followed by aminoacyl insertion,[7] may be possible under such conditions (Scheme I). The occurrence of insertion reactions would yield side products closely resembling the desired product. Since the use of solid-phase peptide synthesis is increasing,[8–12] it is of interest to establish whether or not

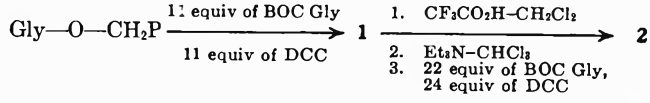
SCHEME I



amino acid insertions can occur in this method of peptide synthesis.

As insertion reactions should be most favored in the absence of bulky side chains (R = R′ = R″ = H) a model system utilizing glycine was devised (Scheme II).

SCHEME II



Large excesses of N-*t*-butoxycarbonylglycine[13] and N,N′-dicyclohexylcarbodiimide were used in both coupling reactions in an attempt to promote acylation of the peptide bond.

When a portion of product **1** was treated with trifluoroacetic acid in methylene chloride, then with triethylamine in chloroform, and finally with hydrogen bromide in trifluoroacetic acid, the products were glycine (54.8%) and glycylglycine (45.2%), as determined with an amino acid analyzer calibrated with glycine, diglycine, triglycine, and tetraglycine. Had aminoacyl insertion occurred, some triglycine would have been formed.

Product **2** was treated in the manner described for product **1** yielding glycine, diglycine, and triglycine upon paper chromatography of the cleavage products. The chromatogram from the amino acid analyzer indicated the presence of glycine (6.0%), diglycine (46.1%), triglycine (47.7%), and two trace peaks. One of these peaks emerged at the position of tetraglycine and represented 0.2% of the total products. The presence of tetraglycine would indicate that amino acid insertions can occur during solid-phase peptide synthesis when very large excesses of acylating agents are used. On the basis of these experiments it appears

(1) (a) This work was supported in part by grants from the U. S. Public Health Service (GM-10591), the American Heart Association, the National Science Foundation, and by a Heart Research Center Grant (HE-06308). (b) The following abbreviations are used in this paper: BOC = *t*-butyloxycarbonyl; DCC = N,N′-dicyclohexylcarbodiimide; P = polystyrene–2% divinylbenzene copolymer. (c) Research Career Development Awardee of the U. S. Public Health Service.

(2) R. B. Merrifield, *J. Amer. Chem. Soc.*, **85**, 2149 (1963).

(3) R. B. Merrifield, *Biochemistry*, **3**, 1335 (1964).

(4) J. M. Stewart and J. D. Young, "Solid Phase Peptide Synthesis," W. H. Freeman and Co., San Francisco, Calif., 1969.

(5) J. C. Sheehan and G. P. Hess, *J. Amer. Chem. Soc.*, **77**, 1067 (1955).

(6) M. Brenner in "Peptides," H. C. Beyerman, A. Van De Linde, and W. Maassen Van Den Brink, Ed., John Wiley & Sons, Inc., New York, N. Y., 1967, pp 1–7.

(7) M. Brenner, *J. Cell Comp. Physiol.*, **54**, 221 (1959).

(8) R. B. Merrifield in "The Handbook of Biochemistry with Selected Data for Molecular Biology," H. A. Sober Ed., The Chemical Rubber Co., Sandusky, Ohio, 1968, pp C83–C90.

(9) H. Takashima, V. du Vigneaud, and R. B. Merrifield, *J. Amer. Chem. Soc.*, **90**, 1323 (1968).

(10) J. Meienhofer and Y. Sano, *ibid.*, **90**, 2996 (1968).

(11) J. Blake and C. H. Li, *ibid.*, **90**, 5882 (1968).

(12) B. Gutte and R. B. Merrifield, *ibid.*, **91**, 501 (1969).

(13) E. Schnabel, *Ann. Chem.*, **702**, 188 (1967).

that amino acid insertions, though possible, are not significant side reactions under the usual conditions of solid phase peptide synthesis.

Experimental Section[14]

Glycyl Resin.—A solution of N-*t*-butyloxycarbonylglycine[13] (1.31 g, 7.48 mmol) and triethylamine (1.04 ml, 7.48 mmol) in 60 ml of ethanol was added to 10.00 g of chloromethylated polystyrene–2% divinylbenzene copolymer, 200–400 mesh[2] (0.374 mmol of Cl/g). The mixture was stirred under reflux for 46 hr and filtered. The resin was washed with ethanol and acetic acid followed by treatment with trifluoroacetic acid for 15 min. The resin was washed with chloroform, ethanol, and methylene chloride. The trifluoroacetate was neutralized by treatment with triethylamine (10%) in chloroform followed by washes of chloroform, ethanol, and methylene chloride. A sample was hydrolyzed in 1:1 dioxane–12 *N* HCl for 24 hr at 110°. Amino acid analysis gave a glycine content of 0.128 mmol/g.

Coupling Reaction I.—Glycyl resin (3.00 g, 0.384 mmol) was placed in a reaction vessel and treated in the following manner: (1) washed (three 30-ml portions) with methylene chloride, (2) introduced N-*t*-butyloxycarbonylglycine (0.740 g, 4.22 mmol) in 30 ml of methylene chloride and mixed for 10 min, (3) introduced N,N′-dicyclohexylcarbodiimide (0.910 g, 4.42 mmol) and allowed to react for 24 hr, (4) washed (three 30-ml portions) with methylene chloride, (5) washed (three 30-ml portions) with dimethylformamide, (6) washed (three 30-ml portions) with acetic acid, (7) washed (three 30-ml portions) with ethanol, (8) washed (three 30-ml portions) with methylene chloride, and (9) dried *in vacuo* to yield product **1**.

Coupling Reaction II.—A portion (1.00 g) of product **1** was treated in the manner described above for the conversion of N-*t*-butyloxycarbonylglycyl resin to glycyl resin. The resulting resin was then treated according to the procedure used for coupling reaction I, with the exception that a 22-fold excess of N-*t*-butyloxycarbonylglycine and a 24-fold excess of N,N′-dicyclohexylcarbodiimide were used to prepare product **2**.

Characterization of Products 1 and 2.—Portions (0.500 g) of **1** and **2** were treated in the following manner: (1) washed (three 15-ml portions) with methylene chloride, (2) mixed with trifluoroacetic acid–methylene chloride (2:3) for 15 min, (3) washed (three 15-ml portions) with methylene chloride, (4) washed (three 15-ml portions) with ethanol, (5) washed (three 15-ml portions) with chloroform, (6) mixed with triethylamine (10%) in chloroform, (7) washed (three 15-ml portions) with chloroform, (8) washed (three 15-ml portions) with methylene chloride, (9) suspended in trifluoroacetic acid (20 ml) and treated with a stream of hydrogen bromide for 30 min, (10) washed (two 15-ml portions) with trifluoroacetic acid, (11) washed (two 15-ml portions) with trifluoroacetic acid–methylene chloride (1:1), and (12) washed (two 15-ml portions) with methylene chloride. The filtrates from steps 9–12 were pooled and evaporated *in vacuo* at 20°. The resultant residues were dissolved in 1% HCl and subjected to paper chromatography and ion exchange chromatography using an amino acid analyzer.

The presence of only glycine (R_f 0.26) and diglycine (R_f 0.38) was indicated by paper chromatography of the cleavage products from **1**. The amino acid analyzer indicated the presence of 38.4 μmol glycine/g (54.8%) and 31.6 μmol diglycine/g (45.2%) in **1**. The cleavage products from **2** were glycine (R_f 0.27), diglycine (R_f 0.37), and triglycine (R_f 0.50), as determined by paper chromatography. The amino acid analyzer indicated the presence of 5.3 μmol glycine/g (6.0%), 40.4 μmol diglycine/g (46.1%), 41.8 μmol triglycine/g (47.7%), 0.2 μmol tetraglycine (0.2%), and an unidentifiable trace peak equal in area to that of the presumed tetraglycine.

(14) Reference 5 gives detailed instructions on the methodology used for solid phase peptide synthesis. Paper chromatography was performed using the ascending method on Whatman No. 1 filter paper developed with phenol–water in a ratio of 75:25. Ninhydrin was used for revealing the chromatograms. Amino acids and peptides were quantitatively determined with a Technicon amino acid autoanalyzer as described by A. R. Mitchell and R. W. Roeske, *J. Chromatogr.*, **43**, 266 (1969). A buffer gradient from pH 3.10 to pH 3.80 allowed the resolution of glycine, diglycine, triglycine, and tetraglycine at elution times of 95, 189, 199, and 172 min, respectively. Glycine, diglycine, triglycine, and tetraglycine were purchased from Mann Research Laboratories, New York, N. Y.

Products of the Action of Peracetic Acid on Isolongifolene

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Received August 18, 1969

Treatment of isolongifolene[1] with perbenzoic acid has been reported to give the corresponding epoxide.[2] We have attempted to carry out this reaction using peracetic acid. Commercial peracetic acid brought to pH 3.6 with sodium acetate reacted sluggishly with isolongifolene. A 65% yield of the isolongifolene was recovered, and the remainder consisted of a mixture of a ketone (VI),[2] a lactone (V),[2] and an alcohol (VII) in a ratio of 14:1:4 along with a trace of an epoxide (III).[2] The alcohol, $C_{15}H_{24}O$, was assigned the structure VII on the basis of the following considerations.

(a) The infrared spectrum exhibits a hydroxy stretching vibration at 2.94 μ (Nujol), indicating the presence of alcohol.

(b) The nuclear magnetic resonance spectrum of VII is in accord with the assigned structure. It exhibits the following resonances: δ 5.51 (d, 1 H, corresponding to one olefinic proton, >=CH—C, J = 3 cps), 3.7 (t, 1 H, HCOH, J = 7.5 cps), 0.89, 0.86, 0.80, and 0.70 (4 s, 12 H, four methyl groups), 1.0–1.58 (m, 8 H, $>CH_2$), and 2.1 (m, 1 H, corresponding to the group C=C—CH—C).

(c) The mass spectrum shows a parent peak at m/e 220, 177 (M − 43), 164, etc.

The structure is further supported by the chemical evidence. Oxidation by the Jones reagent gave a ketone to which the structure VIII is assigned on the basis of the spectral data.

(a) The infrared spectrum (film) exhibits a carbonyl stretching band at 5.87 μ, indicating a six-membered unconjugated ketone.

(b) The ultraviolet spectrum exhibits λ_{max} 221 (ϵ_{max} 300), ruling out the possibility of a conjugated ketone.

(c) The nuclear magnetic resonance spectrum of VIII supports the above-assigned structure, indicating signals at δ 5.6 (d, 1 H, assigned to olefinic proton, >C=C—C, J = 3 cps), 0.68, 0.80, 0.82, and 0.86 (4 s, 12 H, *gem*-dimethyls), and 1.0–1.57 (m, 8 H, $>CH_2$).

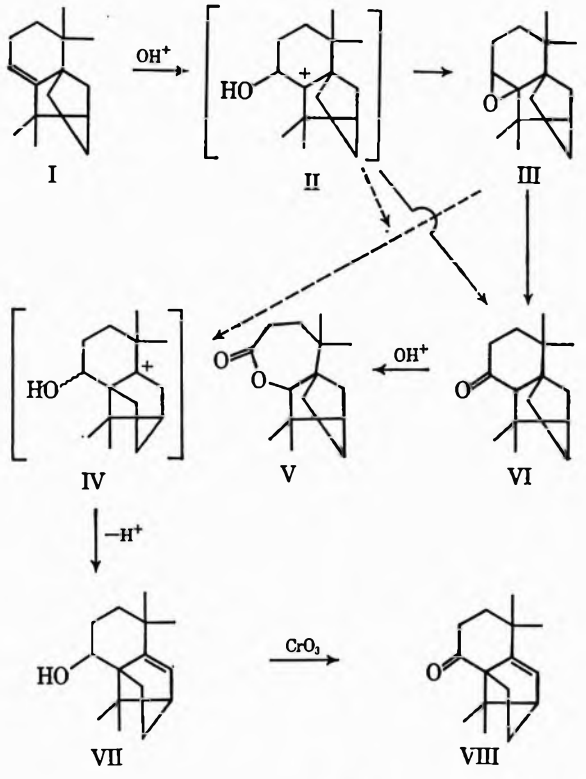
(d) The mass spectrum shows ions at m/e 218 (parent peak), 175 (M − 43), etc.

It was of interest to see if epoxide III, when treated with peracetic acid under the same conditions, would give the same products. Isolongifolene epoxide (III) was treated with peracetic acid buffered at pH 3.6 and gave at 60° three major products. They were shown by spectral analysis to be VI, V, and VII in a ratio of 15:1:5. These products suggest that the epoxide III could be an intermediate to give all the products shown in Scheme I.

(1) U. Ramdas Nayak and Sukh Dev, *Tetrahedron*, **8**, 42 (1960).

(2) S. Dev, J. Prahlad, R. Ranganathan, U. Ramdas Nayak, and T. S. Santhanakrishnan, *Tetrahedron Lett.*, No. 8, 417 (1964).

SCHEME I



Experimental Section[3]

Reaction of Isolongifolene (I) with Peracetic Acid.—In a 500-ml flask fitted with stirrer, condenser, and addition funnel was placed 100 g (0.5 mol) of isolongifolene and 12.5 g (0.15 mol) of sodium acetate. The mixture was heated to 60° and 95 g (0.5 mol) of 40% peracetic acid was added dropwise over a period of 45 min, while the temperature was maintained at 60°. After the addition, the mixture was stirred at 60° for 3 hr. It was then cooled, washed with water and 1% sodium sulfite solution, and extracted with toluene. The organic layer was washed once with water and dried over magnesium sulfate. The solvent was removed *in vacuo*. After 65 g of the starting material had been recovered *in vacuo*, the product obtained in an overall yield of 30% consisted of a mixture of previously unknown alcohol VII, ketone VI,[2] and lactone V[2] in a ratio of 4:14:1, respectively.[4] The compounds were isolated by preparative glpc using an 8 ft × 0.25 in., 20% SE-30 column at 200°. Alcohol VII had a melting point of 143–144°.

Anal. Calcd for $C_{15}H_{24}O$: C, 81.57; H, 10.90. Found: C, 81.37; H, 10.89.

Ketone VIII.—In a flask fitted with stirrer, condenser, and addition funnel was placed 42.0 g (0.19 mol) of alcohol VII and 300 ml of acetone. To this mixture was added 85 ml (0.18 mol) of Jones reagent at 15° during a period of 45 min, and the solution was then further stirred at the same temperature for 45 min. After the solids had been filtered off, the acetone was removed *in vacuo* and the crude product was distilled to give 29.0 g of the ketone VIII, 70% yield, bp 106–107° (3.7 mm).

Anal. Calcd for $C_{15}H_{22}O$: C, 82.50; H, 10.10. Found: C, 82.31; H, 9.90.

The 2,4-dinitrophenylhydrazone had mp 181–182°.

Anal. Calcd for $C_{21}H_{26}N_4O_4$: C, 62.29; H, 6.51; N, 14.10. Found: C, 62.89; H, 6.48; N, 13.90.

Reaction of Isolongifolene Epoxide (III) with Peracetic Acid.—Isolongifolene oxide, 1.1 g, mixed with 0.28 g of sodium acetate, was treated with 0.96 g of 40% peracetic acid. The mixture was heated slowly to 60°, and stirred at 60° for 3 hr. The mixture was cooled and extracted with chloroform, and the extract was washed with water and dried over magnesium sulfate. The solvent was removed *in vacuo*, and the products were separated by preparative glpc (8 ft × 0.25 in., SE-30 column, 20%, 200°). The three products were shown by spectral analysis to be V, VI, and VII.

(3) All the nmr spectra were run on a Varian HA-100 spectrometer. Tetramethylsilane was used as an internal standard. The C and H analyses were run by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

(4) The ratio of the products varies with the varying amounts of sodium acetate used.

Registry No.—Peracetic acid, 79-21-0; I, 1135-66-6; VII, 22979-29-9; VIII, 22979-30-2; VIII-2,4-dinitrophenylhydrazone, 22979-31-3.

Acknowledgment.—The authors express their thanks to Dr. W. I. Taylor for his helpful suggestions and continued interest. We are also thankful to the Analytical Group for running various spectra and for their help in gas chromatography.

The Reactions of Organophosphorous Compounds with α- and β-Diphenylacyl Bromides

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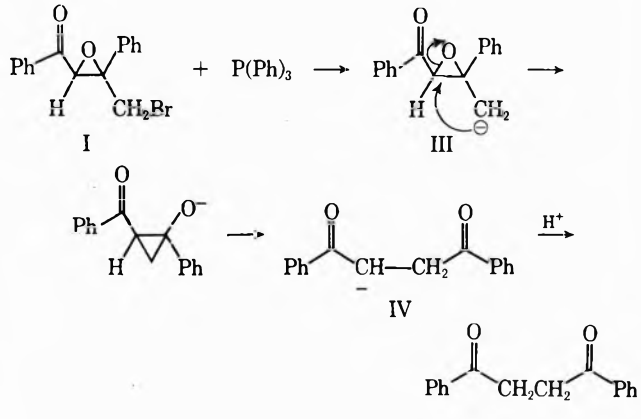
Received September 15, 1969

Relatively little attention has been directed to the preparation and reactions of organophosphorous compounds that possess an epoxide function in the β,γ position.[2] In the course of a study on the reactivity of small-membered rings, we investigated the reactions of *cis*- and *trans*-1,3-diphenyl-2,3-epoxy-4-bromo-1-butanone (I and II) with several organophosphorous compounds in an attempt to prepare a β,γ-epoxy phosphorous ylide.



In our studies, we have found that the reaction of *cis*-1,3-diphenyl-2,3-epoxy-4-bromo-1-butanone (I) with triphenylphosphine in refluxing toluene affords dibenzoylethane (55%), *trans*-dibenzoylethylene (5%), phenacyltriphenylphosphonium bromide (30%), benzoylmethylenetriphenylphosphorane (8%), and some triphenylphosphine oxide. Similar results were obtained with the *trans* epoxide (II).

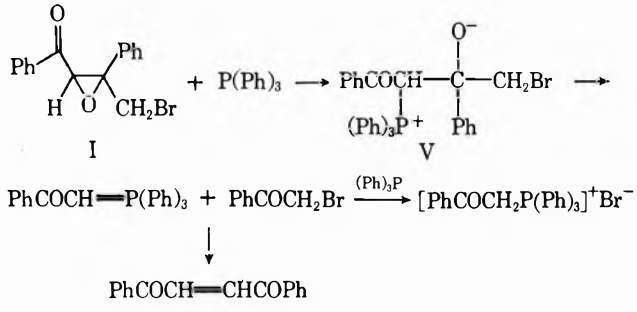
A plausible explanation for the formation of dibenzoylethane involves attack of triphenylphosphine on bromine leading to anion III, which then rearranges to

(1) Alfred P. Sloan Foundation Fellow, 1968–1970

(2) For some pertinent references, see C. E. Griffin and S. K. Kundu, *J. Org. Chem.*, **34**, 1532 (1969).

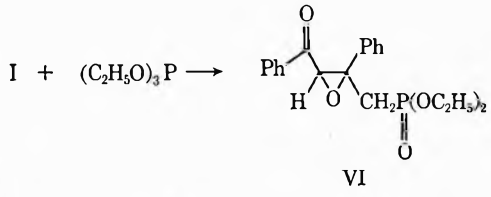
the more stable anion IV.[3] This transformation is related to the debromination of I with zinc in methanol.[4]

The formation of the remaining products can be pictured as proceeding through the intermediacy of an internal phosphonium alkoxide (V), produced by initial displacement at carbon. This intermediate subsequently collapses to phenacyl bromide and benzoylmethylenetriphenylphosphorane which are known to react to form *trans*-dibenzoylethylene.[5,6] It is also known that primary α-bromo ketones such as phenacyl bromide react with triphenylphosphine in aprotic solvents to give α-keto phosphonium bromides.[7] This would account for the isolation of phenacyltriphenylphosphonium bromide in the above reaction.



The formation of an intermediate of type V finds confirmation in work by Speziale and Bissing in their studies on the opening of epoxides with tertiary phosphines.[8] The fact that dibenzoylethane is the major product in this reaction can be attributed to the preference of trivalent phosphorous compounds to carry out displacements at a halogen center as opposed to attack at a sp^3-hybridized carbon atom.[9]

In contrast to the results outlined above, we find that reaction of I with triethyl phosphite at 120° goes to completion and gives diethyl *cis*-1,3-diphenyl-2,3-epoxybutan-1-one phosphonate (VI) as the only isolable material. Similarly, reaction of II with triethyl phosphite gives diethyl *trans*-1,3-diphenyl-2,3-epoxybutan-1-one phosphonate (VII) in high yield. The spectral data obtained for these compounds are summarized in the Experimental Section.



With the expectation that the reaction of VI (or VII) with base would generate a phosphonate anion which could be used for further reaction,[10] we treated VI with sodium hydride. The reaction was carried out at room temperature in dimethoxyethane as solvent. Addition of benzaldehyde or acetone to the mixture gave a dark brown solution. The reaction mixture, upon work-up, gave black tars with ill-defined spectra, unresolved by careful chromatography. In view of the difficulty of isolating characterizable products from this reaction, we abandoned further study on the generation of phosphonate carbanions from these systems.

Experimental Section[12]

***cis*- and *trans*-1,3-diphenyl-2,3-epoxy-4-bromo-1-butanone** were prepared by the method of Wasserman, Aubrey, and Zimmerman using phenacyl bromide and sodium ethoxide in ethanol.[4]

Reaction of *cis*-1,3-Diphenyl-2,3-epoxy-4-bromo-1-butanone (I) with Triphenylphosphine.—A mixture of triphenylphosphine (8.4 g) and I (5.0 g) in toluene (330 ml) was heated at reflux for 36 hr. The resultant precipitate which separated was triturated with boiling acetone to give phenacyltriphenylphosphonium bromide as a white solid, mp 279–280 (lit.[13] mp 279–280°). To the solvent was added benzophenone (1.0 g) and the mixture was heated at reflux for 8 hr. At the end of this time the solvent was removed and the residue was chromatographed on a Florisil column. The column was eluted with benzene and then with 1% ethyl acetate–benzene. The eluent, in 50-ml fractions, was concentrated and dried *in vacuo*. Benzophenone was recovered from elution of the column with benzene. Three major fractions were obtained from elution with 1% ethyl acetate–benzene and were identified as dibenzoylethane (55%), *trans*-dibenzoylethylene (5%), and β-phenylbenzalacetophenone (8%) by comparison with authentic samples.

The isomeric epoxide II gave similar results when it was treated under comparable reaction conditions.

Preparation of Diethyl *cis*-1,3-Diphenyl-2,3-epoxybutan-1-one Phosphonate (VI).—A mixture of *cis* epoxide I (5.0 g) and triethyl phosphite (18 ml) was heated at 120° for 3 hr. During this time ethyl bromide was allowed to distil from the reaction flask. The excess triethyl phosphite was removed *in vacuo* and the crude residue obtained was chromatographed on a Florisil column to give 5.1 g of VI as a colorless oil.

Anal. Calcd for $C_{20}H_{23}PO_5$: C, 64.16; H, 6.19. Found: C, 64.42; H, 6.28.

The infrared spectrum showed bands at 5.9, 8.0, 8.52, 9.6, and 10.25 μ. The nmr spectrum (CCl_4) showed multiplets at τ 1.93 (2 H) and 2.67 (3 H), a singlet at τ 5.15 (1 H), two overlapping quartets at τ 5.92 (4 H), a double doublet at τ 7.37 (J = 20, 5.3 Hz, 2 H), and two overlapping triplets at τ 8.72 (6 H).

Preparation of Diethyl *trans*-1,3-Diphenyl-2,3-epoxy-butan-1-one Phosphonate (VII).—A mixture of *trans* epoxide II (1.8 g) and triethyl phosphite (6 ml) was heated at 110° for 3 hr. During this time ethyl bromide distilled from the reaction mixture. The excess triethyl phosphite was removed by distillation and the crude residue was chromatographed on a Florisil column to give 1.5 g of VII as a mobile oil.

Anal. Calcd for $C_{20}H_{23}PO_5$: C, 64.16; H, 6.19. Found: C, 63.97; H, 6.24.

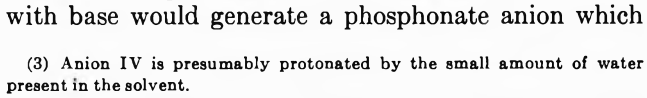
The infrared spectrum showed strong bands at 5.89, 8.10, 8.53, 9.65, and 10.20 μ. The nmr spectrum ($CDCl_3$) showed multiplets at τ 1.95 (2 H) and 2.42 (8 H), a doublet at τ 5.70 (J = 1.7 Hz, 1 H), two overlapping quartets at τ 6.12 (4 H), a double doublet at τ 7.48 (J = 19.5, 9.0 Hz, 2 H), and two overlapping triplets at τ 8.95 (6 H).

(3) Anion IV is presumably protonated by the small amount of water present in the solvent.

(4) H. H. Wasserman, N. E. Aubrey, and H. E. Zimmerman, *J. Amer. Chem. Soc.*, **75**, 96 (1953).

(5) M. Slemiatycki and H. Strzelecka, *Compt. Rend.*, **250**, 3489 (1960).

(6) Another possible route to dibenzoylethylene is the following.



(7) I. J. Borowitz, K. C. Kurby, and R. Virkhaus, *J. Org. Chem.*, **31**, 4031 (1966).

(8) D. E. Bissing and A. J. Speziale, *J. Amer. Chem. Soc.*, **87**, 2683 (1965).

(9) A. J. Kurby and S. G. Warren, "The Organic Chemistry of Phosphorous," Elsevier Publishing Co., New York, N. Y., 1967, p 111.

(10) The reaction of phosphonate carbanions with aldehydes or ketones in an aprotic solvent is a useful supplement to the well-known "Wittig" reaction.[11]

(11) W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1732 (1961).

(12) All melting points are uncorrected. The infrared absorption spectra were determined on a Perkin-Elmer Infracord spectrometer, Model 137. The nuclear magnetic resonance spectra were determined at 60 MHz with the Varian Associates high-resolution spectrometer. Tetramethylsilane was used as an internal standard.

(13) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 41 (1957).

Registry No.—I, 23265-28-3; II, 23265-29-4; VI, 23265-30-7; VII, 23265-31-8; triphenylphosphine, 603-35-0; triethyl phosphite, 122-52-1.

Acknowledgment.—Support of this work by the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged.

Base-Catalyzed Deuterium Exchange in Pyridine N-Oxides[1]

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In connection with another study, we observed that 4-benzylpyridine N-oxide (I), recovered after a reflux period of 24 hr in equimolar triethylamine and excess deuterium oxide, exchanged hydrogen for deuterium in excess of the calculated amount for the two benzylic hydrogens.[2] The nuclear magnetic resonance spectrum of the deuterated compound compared well with that of the reference compound, differing only in that a small peak appeared at τ 6.06 replacing the sharp singlet for the benzylic hydrogens. Integration of the peak areas, however, indicated that the doublet at τ 1.89 for the two α hydrogens of the pyridine ring and the multiplet with a sharp peak at τ 2.76 for the two β hydrogens and five phenyl hydrogens were not in a 2:7 ratio. By assuming nonexchange of the β and the phenyl hydrogens, we calculated 95% exchange of the benzylic hydrogens and 17% exchange of the α hydrogens from the integration of the respective peak areas (this is consistent with the elemental analysis of an exchange of 21.00 atom % excess deuterium).[3]

Considerable attention of late has been given to H–D exchange in heterocyclic N-oxide systems. Substituted pyridine N-oxides and similar compounds exchange rapidly in the α position of the ring under basic conditions; for a review of the literature see ref 5. Under acidic conditions similar systems exhibited exchange at the β position when the species reacting was in the conjugate acid form.[6]

In this note we wish to report H–D exchange in the aromatic ring and the side chain of alkylpyridine N-oxides[7] and, qualitatively, the dependence of the exchange on base strength; this is readily seen from the data in Table I for the benzylpyridine N-oxides. Our investigation of the isomeric picoline N-oxides revealed ring-proton exchange as well as side-chain exchange. Prior studies of Zatsepina[8] reported exchange of the protons of the side chains of 2- and 4-picoline N-oxides (III and IV) but not ring-proton exchange. For 2-picoline N-oxide (III), α-proton exchange accompanied methyl-proton exchange in the presence of sodium carbonate and sodium deuteroxide. The relative amount of ring- and side-chain exchange varied with reaction time and base. Typical results follow: for sodium carbonate, 0.5-hr reaction time, α-proton exchange, 12%, 2-methyl proton, 66%; 5-hr reaction time, α-proton exchange, 45%, 2-methyl proton, 97%; for sodium deuteroxide, 0.5 hr, 86% for both ring and methyl protons. The 4 isomer, 4-picoline N-oxide (IV), presented an interesting contrast insofar as the amount of ring exchange exceeded side-chain proton exchange in the presence of triethylamine and sodium carbonate. Typical results follow: for triethylamine, 72 hr, α-proton exchange, 40%, 4-methyl proton exchange, 20%; for sodium carbonate, 0.5 hr, 80 and 50%, respectively, for α-proton and 4-methyl proton exchange; for sodium deuteroxide the amount of side chain and ring exchange was equivalent. As reported previously,[8] 3-picoline N-oxide (V) exhibited both ring- and methyl-proton exchange. Since ring exchange for 2- and 4-picoline N-oxides (III and IV) was not taken into account in the prior publications,[8] the velocity constants given for III and IV are in error in those references; exchange, however, was noted for V and appropriate corrections were made in the velocity constant.

The conditions used for the exchange reactions were mild and yields were good (87%, average). Since deoxygenation of the N-oxides under specific conditions is reported to be facile,[9] deuterated pyridine derivatives may be conveniently prepared by this procedure.

TABLE I

DATA FOR BASE-CATALYZED EXCHANGE OF BENZYLPYRIDINE N-OXIDES IN HEAVY WATER[a]

N-Oxide	Expt	Base	Time, hr	Exchange,[b] % α protons	Exchange,[b] % Side-chain protons
4-Benzylpyridine N-oxide (I)	1	Et_3N[c]	20	17	95
	2	Na_2CO_3[d]	0.5	18	94
	3[e]	Na_2CO_3	5	100	100
2-Benzylpyridine N-oxide (II)	4	Et_3N	21	3	100
	5	Na_2CO_3	0.5	3	78
	6	Na_2CO_3	5	30	100

[a] All nmr spectra were determined in deuteriochloroform solutions. [b] Calculated on the basis of the assumption that only the α protons of the hetero ring readily exchange. Electronic integration of peak intensities was used for the calculations. [c] Reflux temperature, 76°. [d] Reflux temperature, 100°. [e] Good correlation of 2–5 intensity ratio was obtained in the case of 4-benzylpyridine N-oxide (I); the singlet at τ 2.98 and the singlet at τ 2.76, representing the β and the phenyl protons, respectively, were the only signals in the nmr spectrum.

(1) A preliminary report of this work was presented: Abstracts, Second Middle Atlantic Regional Meeting, of the American Chemical Society, New York, N. Y., Feb 1967, p 65.

(2) V. J. Traynelis and S. A. I. Gallagher, unpublished results. *Anal.* Calcd for $C_{12}H_9D_2NO$: D, 18.18 atom % excess deuterium. Found: D, 21.00 atom % excess deuterium. This analysis was performed by Josef Nemeth, Urbana, Ill.

(3) We were prompted to make this assumption on the evidence of results obtained in expt 3, Table I, footnote *e*. Also, extremely slow or no exchange in the β position has been reported for 3-bromopyridine N-oxide in the presence of sodium deuteroxide at 150° [4] and deuterated 3-chloropyridine N-oxide in the presence of sodium methoxide–methanol.[5]

(4) R. A. Abramovitch, G. M. Singer, and A. R. Vinutha, *Chem. Commun.*, 55 (1967).

(5) J. A. Zoltewicz and G. M. Kauffman, *J. Org. Chem.*, **34**, 1405 (1969).

(6) P. Bellingham, C. D. Johnson, and A. R. Katritzky, *J. Chem. Soc., B*, 1226 (1967), and references cited therein.

(7) A referee called to our attention the kinetic studies of Zatsepina, *et al.*,[8] on the H–D exchange of methyl derivatives of pyridine N-oxide. Qualitatively, our findings are in agreement with the reported data except where noted below.

(8) (a) N. N. Zatsepina, I. F. Tupitsyn, and L. S. Efros, *J. Gen. Chem. USSR*, **33** (8), 2636 (1963); (b) *ibid.*, **34** (12), 4124 (1964).

(9) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., New York, N. Y., 1967, p 184.

Experimental Section

The liquid N-oxides were purified by vacuum distillation prior to use, and the melting points of the picrates matched those reported in the literature. The melting points of the solid N-oxides and their picrates were in agreement with literature values except in the following cases: 4-benzylpyridine N-oxide (I), mp 105–107° (lit.[10] mp 151°); the picrate of 4-picoline N-oxide (IV), mp 154° (lit.[11] mp 159–160°).

General Procedure for Exchange Reactions.—An equimolar mixture of the N-oxide (*ca.* 5 g) and base in deuterium oxide (15 ml) was refluxed for the appropriate amount of time. After the reflux period, the mixture was extracted with chloroform (200–300 ml) and the extract was dried over anhydrous sodium sulfate. After removal of the drying agent, the chloroform and organic base when present were removed by flash evaporation. The N-oxides so recovered were placed in a vacuum desiccator for drying, since most of the N-oxides are hygroscopic. Most of the deuterated N-oxides were of sufficient purity to be directly submitted for nmr analysis.[12] All recovered N-oxides had melting points which matched the literature values for the undeuterated analogs (or were slightly higher). The ir spectra exhibited a weak C–D stretch at 4.3–4.4 μ with variation of the O–H out-of-plane region at 11–15 μ. Yields of the recovered deuterated pyridine N-oxides averaged 87%.

Registry No.—I, 7259-53-2; II, 20531-86-6.

(10) A. R. Hands and A. R. Katritzky, *J. Chem. Soc.*, 1754 (1958). We were never able to duplicate the reported melting point for this compound. *Anal.* Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99. Found: C, 77.51; H, 5.99. Analysis was performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points are uncorrected.

(11) V. Boekelheide and W. J. Linn, *J. Amer. Chem. Soc.*, **76**, 1286 (1954).

(12) All nmr spectra were obtained through the courtesy of Dr. Vincent J. Traynelis, West Virginia University, Morgantown, W. Va., to whom we wish to express our gratitude.

Preparation and Ring Opening of 1,2,3,4-Tetrahydro-2-oxopyrimido-[2,1-*b*]benzothiazol-5-ium Chloride[1]

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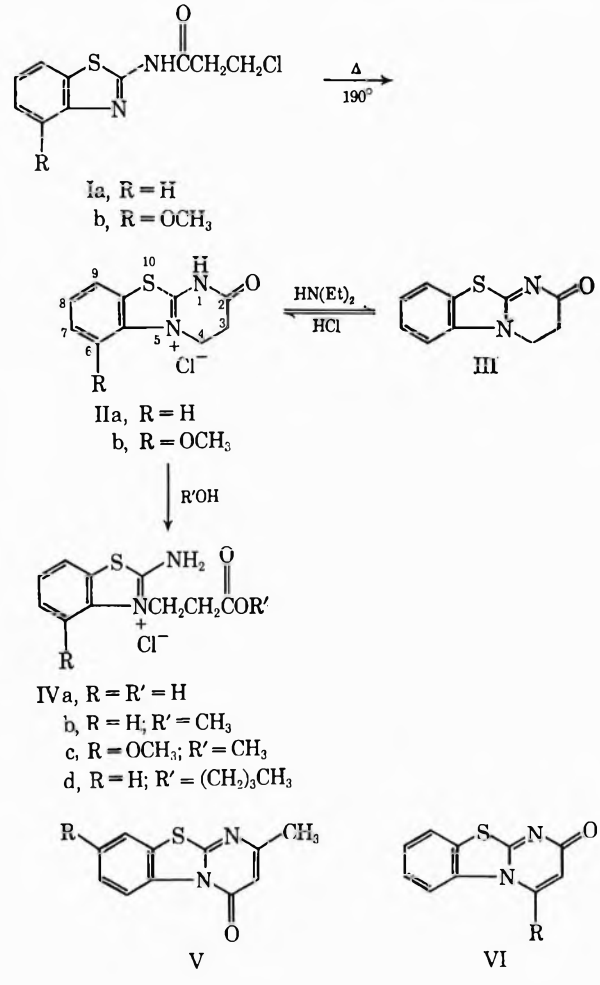
Received August 28, 1969

The synthesis of 1,2,3,4-tetrahydro-2-oxopyrimido-[2,1-*b*]benzothiazol-5-ium chloride (IIa) by fusion of 2-(3-chloropropionylamino)benzothiazole (Ia) has been recently reported.[3] These studies were carried out in the course of our investigations with 3-aminoisoquinoline and the 1,3-diazatricyclic ring system, such as VII, which could be similarly prepared by fusion of 3-chloro-N-(isoquinolin-3-yl)propionamide. We now wish to report the details of the synthesis and spectral characteristics of the benzothiazolium salts (II) and the observed facile ring-opening reaction which occurs when II is treated with water or alcohol to form the novel amino acids IV.

Compounds of structure V have been prepared by Antaki and Petrov[4] by heating 2-aminobenzothiazoles with β-aminocrotonic ester. Schrader[5] indicated that



acylacetamidobenzothiazoles could be dehydrated to VI, but no details were given and the structure remains uncertain.

We have found that 1,2,3,4-tetrahydro-2-oxopyrimido[2,1-*b*]benzothiazol-5-ium chloride (IIa) can be readily prepared by fusion of 2-(3-chloropropionylamino)benzothiazole (Ia) at 190°. Treatment of the quaternary halide IIa with anhydrous diethylamine resulted in the isolation of a halogen-free compound, which was assigned structure III. Tsatsas and Costakis[6] isolated III as a side product by treatment of equimolar quantities of 2-aminobenzothiazole and β-chloropropionyl chloride in alkaline medium. We could readily convert III into II with chloroform saturated with hydrogen chloride. The spectra (nmr and uv) and the elemental analyses of II and III confirm the proposed structures and agree with the structure for III as previously suggested.[6] These authors[6] claimed that the insolubility of their compound III kept them from obtaining an nmr spectrum. We had no difficulty in obtaining an nmr spectrum of this compound in deuteriochloroform.

In attempting to obtain nmr spectra of IIa in deuterium oxide solution, however, we found that a mixture of IIa and the ring-opened amino acid IVa was obtained. Spectral evidence indicated that, after the solution had stood at room temperature for 12 hr, the hydrolysis had gone to completion and pure IVa

(1) Presented in part at the First Northeast Regional Meeting of the American Chemical Society, Boston, Mass., Oct 1968.

(2) To whom inquiries should be addressed: Department of Medicinal Chemistry, College of Pharmacy, Northeastern University, Boston, Mass. 02115.

(3) J. L. Neumeyer and K. K. Weinhardt, *Chem. Commun.*, 1423 (1968).

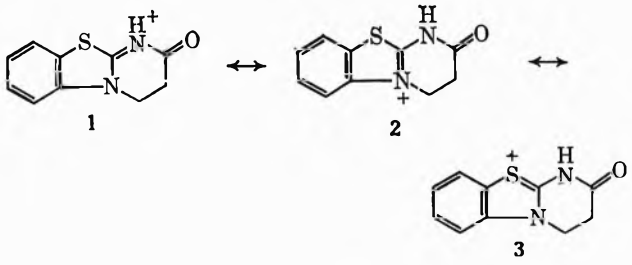
(4) H. Antaki and V. Petrov, *J. Chem. Soc.*, 551 (1951).

(5) G. Schrader, German Patent 603,623 (1937); Friedländer's Fortschritte der Teerfarbenfabrikation und verwandter Industriezweige, Vol. 21, Julius Springer, Berlin, 1937, p 317.

(6) G. Tsatsas and E. Costakis, *Chem. Commun.*, 991 (1967).

was obtained. It was not possible to obtain an nmr spectrum of either IIa or IIb owing to their insolubility in organic solvents and their rapid hydrolysis in water. The hydrolysis of IIa on a preparative scale with water, methanol, and 1-butanol resulted in the isolation of the corresponding acid IVa, or esters IVb and IVd, respectively, the structures of which were confirmed on the basis of spectral evidence (nmr, ir, and uv) and elemental analysis.

The unusual ease of the ring opening of II with nucleophiles can be explained by the activating influence of the neighboring quaternary nitrogen and the unbonded pair of electrons on the sulfur atom, which contribute to a resonance stabilization of the positive charge on the amide nitrogen and on the bridgehead nitrogen (**1** ↔ **2** ↔ **3**). This would result in the amide carbonyl being more electrophilic, facilitating hydrolysis.



1 **2** **3**

The stability of the pyrimido[2,3,-*b*]isoquinoline[3] (VII) under such mild hydrolytic conditions can be thus rationalized. The positive charge of the quaternary salt is largely localized on the isoquinoline nitrogen. A resonance form having the positive charge on the amide nitrogen, such as in VIIa, would require a less energetically favorable quinoid-type arrangement.

VII VIIa

Experimental Section[7]

1,2,3,4-Tetrahydro-6-methoxy-2-oxopyrimido[2,1-*b*]benzothiazol-5-ium Chloride (IIb).—A mixture of 4.6 g (0.0255 mol) of 2-amino-4-methoxybenzothiazole and 1.2 g of 56% sodium hydride in oil was stirred in 200 ml of refluxing benzene for 6 hr. The mixture was then cooled to 5° and 3.8 g (0.030 mol) of 3-chloropropionyl chloride in 10 ml of benzene was added at once. The mixture was stirred at ice-bath temperature for 0.5 hr and at room temperature for 3 days. Treatment with 50 ml of water, collection of the off-white solid on a Büchner funnel and air drying gave 2.69 g of Ib, mp 150–152° (resolidification). The 3-chloropropionamide Ib was not identified as such, but cyclized to IIb by heating to 190°. No recrystallizing solvent for the crude product could be found and it was purified by trituration with hot dioxane to yield 2.44 g (35%) of product IIb: mp 273°;[8] uv λ_{max}^{EtOH} 262 mμ (ε 8800) and 305 (15,200); ir (KBr) 1730 cm^{-1} (C=O).

Anal. Calcd for $C_{11}H_{11}ClN_2O_2S$: C, 48.80; H, 4.09; Cl, 13.10; N, 10.35; S, 11.84. Found: C, 48.87; H, 4.02; Cl, 13.04; N, 10.38; S, 11.85.

(7) All melting points were recorded on a Thomas–Hoover melting point apparatus unless otherwise specified and were uncorrected; the microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. The infrared spectra were recorded on a Perkin-Elmer Model 521 grating spectrophotometer; the nmr spectra were determined on a Varian A-60 spectrophotometer with tetramethylsilane as the internal standard; uv spectra were recorded with a Beckman Model DK-1A.

(8) The melting point was determined on a Du Pont Model 900 Thermo Analyzer.

1,2,3,4-Tetrahydro-2-oxypyrimido[2,1-*b*]benzothiazol-5-ium Chloride (IIa).—2-(3-Chloropropionylamido)benzothiazole[3,6] (Ia, 16.0 g, 0.066 mol) was divided into portions of 2–3 g. Each portion was packed tightly into a large test tube which was then immersed for *ca.* 15 min in a 190° hot oil bath. The resulting orange solid was powdered and treated with 250 ml of water. The insoluble impurities were removed by filtration. The filtrate was divided into a 200-ml and a 50-ml aliquot. The 200-ml aliquot was lyophilized. The remaining yellow solid was carefully triturated with ethanol, which dissolved the hydrolysis product IVa and gave 10.5 g (82%) of IIa: mp 279° dec; uv λ_{max}^{EtOH} 251 mμ (ε 9200) and 301 (19,800); ir (KBr) 1740 cm^{-1} (C=O).

An nmr spectrum in D_2O solution showed the presence of large amounts of IVa, as a result of hydrolysis of IIa in the nmr solvent. The following assignment was made for IIa: δ 3.37 (triplet, $-COCH_2-$), 4.82 (triplet, $=\overset{+}{N}CH_2-$), and 7.3–8.17 (multiplet, aromatic H). The methylene protons were shifted in the acid IVa to δ 2.98 as a triplet ($-COCH_2-$) and to δ 4.45 as a triplet ($=\overset{+}{N}CH_2$).

Anal. Calcd for $C_{10}H_9ClN_2OS$: C, 49.90; H, 3.77; Cl, 14.73; N, 11.64; S, 13.32. Found: C, 50.05; H, 3.84; Cl, 14.52; N, 11.51; S, 13.52.

3,4-Dihydro-2H-pyrimido[2,1-*b*]benzothiazol-2-one (III).—A suspension of 2.0 g (0.0083 mol) of the quaternary salt IIa in 25 ml of anhydrous diethylamine was stirred at room temperature for 15 min. The insoluble residue was collected on a Buchner funnel, washed with small amounts of ethanol, and recrystallized from 25 ml of ethanol to give 0.9 g (53%) of pure III: mp 218–219.5° (lit.[6] mp 214–217°); uv λ_{max}^{EtOH} 308 mμ (ε 28,000); ir (KBr) 1655 cm^{-1}. The following assignment was made for III in $CDCl_3$: δ 7.04–7.7 (multiplet, aromatic H), 4.23 (triplet, $-\overset{|}{N}CH_2-$), and 2.84 (triplet, $-COCH_2-$).

Anal. Calcd for $C_{10}H_8N_2OS$: C, 58.82; H, 3.95; N, 13.72; S, 15.68. Found: C, 59.08; H, 3.88; N, 13.84; N, 15.36.

A small amount of III was reconverted into its hydrochloride salt IIa by treatment of a cold chloroform solution with anhydrous hydrogen chloride.

2-Amino-3-(2-carboxyethyl)benzothiazolium Chloride (IVa).—The 50-ml aliquot from the foregoing step (preparation of IIa) was warmed on a steam bath for 2 hr and the water was removed *in vacuo* to yield 3.5 g of crude amino acid IVa, mp 163–167° dec. Two recrystallizations from ethanol gave pure IVa: mp 169–170° dec; uv λ_{max}^{EtOH} 253 mμ (ε 10,300), 277 (9600), and 285 (10,400).

Anal. Calcd for $C_{10}H_{11}ClN_2O_2S$: C, 46.42; H, 4.29; Cl, 13.70; N, 10.83; S, 12.37. Found: C, 46.65; H, 4.39; Cl, 13.51; N, 10.64; S, 12.13.

2-Amino-3-[2-(methoxycarbonyl)ethyl]benzothiazolium Chloride (IVb).—A solution of IIa [obtained by the fusion of 3 g (0.0125 mol) of Ia] in 50 ml of methanol was heated at reflux for 15 hr and cooled. Addition of 100 ml of ether caused the separation of an oil that solidified slowly. Recrystallization from dioxane–methanol and from tetrahydrofuran–acetonitrile gave 1.0 g (34%) of IVb: mp 154–157° dec; uv λ_{max}^{EtOH} 259 mμ (ε 8200), 286 (sh), 292 (4000), and 298 (sh); ir (KBr) 1740 cm^{-1} (C=O). A nmr spectrum in D_2O solution was recorded: δ 7.3–7.95 (multiplet, aromatic H), 4.6 (triplet, $=\overset{+}{N}CH_2$), 3.07 [triplet, $CH_2(C=O)O-$], 3.88 (singlet, $O=COCH_3$).

Anal. Calcd for $C_{11}H_{13}ClN_2O_2S$: C, 48.44; H, 4.80; N, 10.27. Found: C, 48.22; H, 4.61; N, 10.19.

2-Amino-3-[2-(*n*-butoxycarbonyl)ethyl]benzothiazolium Chloride (IVd).—Using conditions similar to those described above for the methyl ester IVb, 1.5 g (0.0063 mol) of the quaternary salt IIa in 10 ml of 1-butanol was stirred for 20 hr at 90°. Treatment of the cooled solution with 10 ml of ether yielded 1.68 g (85%) of IVd, mp 170–171° (acetonitrile). The following assignment was made for the nmr spectrum (DMSO-d_6 solution): δ 7.2–8.05 (multiplet, aromatic H), 4.69 (triplet, $\overset{+}{N}CH_2$), 2.91 [triplet, $-CH_2(C=O)O-$], 10.3 (board, exchanges with D_2O, NH_2), 3.99 (triplet, $O=COCH_2-$), 1.0–1.8 (multiplet, $O=CO-CH_2CH_2CH_3$), and 0.83 (triplet, CH_3).

Anal. Calcd for $C_{14}H_{19}ClN_2O_2S$: C, 53.41; H, 6.08; N, 8.90. Found: C, 53.45 H, 6.05; N, 8.94.

2-Amino-4-methoxy-3-[2-(methoxycarbonyl)ethyl]benzothiazolium Chloride (IVc).—A solution of 1 g (0.0037 mol) of

the methoxypyrimidobenzothiazolium chloride IIb in 20 ml of methanol was refluxed for 3 hr. The excess solvent was removed *in vacuo*. The solid residue was treated with 50 ml of boiling acetonitrile and the mixture was filtered to separate 0.46 g of solid insoluble in the acetonirile. After the filtrate had stood for 2 days, 0.26 g (26%) of IVc were collected, mp >125° (slow dec).

An additional 0.4 g (36%) of IVc was obtained when the acetonitrile-insoluble solid was dissolved in methanol and ether was added carefully. The following assignment was made for the nmr spectrum (DMSO-d_6 solution): δ 7.2–7.72 (multiplet, aromatic H), 9.91 (broad, exchanges, NH_2), 4.81 (triplet, $\overset{+}{N}CH_2$), 3.97 (singlet, $-OCH_3$), 3.67 (singlet, $O{=}COCH_3$), and 2.91 [triplet, $-CH_2(C{=}O)O-$].

Anal. Calcd for $C_{12}H_{15}ClN_2O_3S$: C, 47.61; H, 4.99; N, 9.25. Found: C, 47.73; H, 5.08; N, 9.22.

Registry No.—IIa, 21140-01-2; IIb, 23230-61-7; III, 17326-07-7; IVa, 23230-63-9; IVb, 23230-64-0; IVc, 23230-65-1; IVd, 23230-66-2.

Acknowledgment.—We wish to thank Dr. K. Stevenson and Professor R. E. Lyle for helpful discussions and Dr. P. L. Levins for the spectral data.

Transformation Products of 2-(2-Imidazolin-2-yl)benzophenone

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Received September 8, 1969

2-(2-Imidazolin-2-yl)benzophenone, which has been shown to exist in two tautomeric forms (**1** and **2**),[2] was treated with *p*-toluenesulfonic acid in refluxing xylene to give the dehydrated compound **3** (Scheme I). It was found that **3** underwent a slow oxidation with air in refluxing ethanol using platinum on carbon as a catalyst to give the ketoimidazo compound **5**. This compound, on reduction with sodium borohydride, gave the imidazolylbenzhydrol **4**, which on dehydration gave the original imidazoisoindole **3**. The known reaction of dimethylsulfoxonium methylide with ketones to give epoxides *via* methylene transfer[3] prompted us to treat both compounds **1** and **5** with this reagent. The synthesis of other small heterocyclic ring systems by the use of this reagent has recently received some attention in the literature.[4] As anticipated, methylene transfer took place. The intermediates (such as A) were not isolated but cyclized in the reaction medium to give the observed products. Thus compound **1** gave the imidazoisoquinoline **6**. The corresponding ketone **5** gave the expected unsaturated product **9**. Further dehydration of **9** in boron trifluoride etherate in acetic acid gave the fully saturated derivative **8**. This compound was also obtained from compound **6**, first by dehydration with thionyl chloride to give the intermediate **7**, followed by dehydrogenation in refluxing tetralin with palladium on carbon as a catalyst. The structure of compound **7** was readily confirmed by an independent synthesis from isocoumarone (**10**) by treatment with ethylenediamine in the presence of *p*-toluenesulfonic acid. Similarly, compound **8** could be prepared by the catalytic dehydrogenation of **12**. This, in turn, was prepared in one of three ways. Treatment of either the dihydroisocoumarone **11** or 3-methyl-3-phenylphthalide (**13**) or its isomer **16** with ethylenediamine in the presence of *p*-toluenesulfonic acid all gave compound **12**.

Experimental Section[5]

5-Phenyl-5H-imidazo[2,1-*a*]isoindole (3). A. From Compound 1.—A mixture of 2.5 g (50 mmol) of 1[2], 0.5 g of *p*-toluenesulfonic acid, and 250 ml of *m*-xylene was heated under reflux for 1 hr in a 500-ml flask equipped with a Dean–Stark trap and condenser. Xylene was removed under reduced pressure, 40 ml of 0.1 *N* sodium hydroxide was added, and the mixture was extracted with methylene chloride. The extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated to leave a pale pink solid. The solid was dissolved in 70 ml of hot ethyl acetate, treated with Norit, and filtered. The solution was concentrated to a volume of 40 ml, followed by the addition of 100 ml of petroleum ether and cooling. Filtration gave 8.9 g (76.7%) of **3** as a pale pink solid, mp 145–148° dec. Recrystallization twice from ethyl acetate–petroleum ether gave colorless prisms: mp 147–150° dec; uv max 224 mμ (inflection, ϵ 14,700), 280 (14,200), and 295 (inflection, 10,400); nmr ($CDCl_3$) δ 5.90 (singlet, 1 H) and multiplets centered at δ 7.20 (10 H) and 7.90 (1 H).

Anal. Calcd for $C_{16}H_{12}N_2$: C, 82.73; H, 5.21; N, 12.06. Found: C, 82.82; H, 4.85; N, 12.03.

B. From Compound 4.—A solution of 0.5 g (2 mmol) of **4** and 0.1 g of *p*-toluenesulfonic acid in 50 ml of xylene was heated at reflux for 46 hr, using a Dean–Stark trap to collect the water formed. Solvent was removed under reduced pressure, 20 ml of 0.1 *N* sodium hydroxide was added, and the mixture was extracted with methylene chloride. The extracts were washed with water, dried over sodium sulfate, and evaporated to leave a yellow oil which crystallized upon scratching. The solid was dissolved in 25 ml of hot ethyl acetate, treated with Norit, filtered, and concentrated to a volume of 5 ml. Petroleum ether (5 ml) was added and the solution was cooled. Filtration gave 250 mg (53.9%) of **2** as colorless crystals, mp (and mixture melting point with a sample prepared as in A above) 146–148°.

2-(2-Imidazolyl)benzophenone (5).—A mixture of 11.6 g (50 mmol) of **3**, 5.0 g of a 10% platinum on carbon catalyst, and 300 ml of ethanol was heated at reflux, with a gentle stream of air bubbling through the mixture, for 16 hr. The mixture was filtered and the filtrate was evaporated under reduced pressure to leave a pale yellow solid. Recrystallization from ethyl acetate gave 8.2 g (66.1%) of **5**, mp 155–158° dec. Recrystallization gave the analytical sample as colorless prisms: mp 158–160° dec; uv max 251 mμ (ϵ 20,200) and 315 (2350); ir ($CHCl_3$) 1658 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.20; H, 4.85; N, 11.25.

2-(2-Imidazolyl)benzhydrol (4).—A solution of 4.96 g (20 mmol) of **5** and 1.89 g (50 mmol) of sodium borohydride in 75 ml of ethanol was heated under reflux for 2 hr. Ethanol was removed under reduced pressure and 50 ml of water was added. The mixture was extracted with methylene chloride and the extracts were washed with water, dried over sodium sulfate, and evaporated to leave a pale yellow oil. The oil was crystallized

(1) To whom correspondence should be addressed.

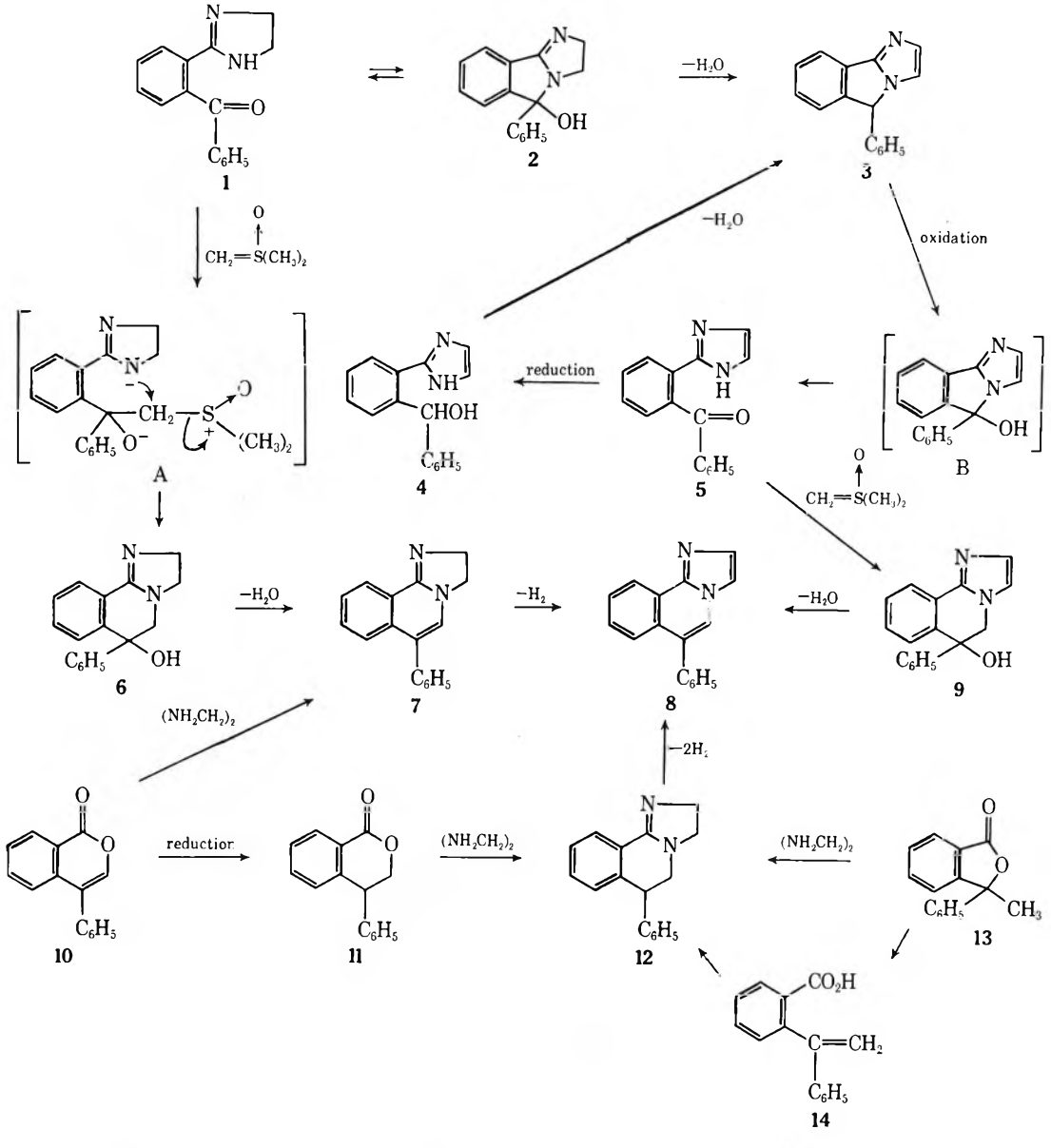
(2) W. Metlesics, T. Anton, M. Chaykovsky, V. Toome, and L. H. Sternbach, *J. Org. Chem.*, **33**, 2874 (1968).

(3) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 867 (1962).

(4) See P. Bravo, G. Gaudiano, and A. Umani-Rochi, *Tetrahedron Lett.*, No. 9, 679 (1969), and references cited therein.

(5) All melting points were determined microscopically on a hot stage and are corrected. The uv spectra were determined in 2-propanol on a Cary Model 14 spectrophotometer, nmr spectra with a Varian A-60 instrument, and ir spectra on a Beckman IR-9 spectrophotometer. Petroleum ether refers to a fraction of bp 30–60°.

SCHEME I



from 20 ml of ethyl acetate. Filtration gave 4.0 g (80%) of the alcohol **4** as a white solid. Recrystallization from ethyl acetate gave colorless prisms, mp 155–156°, uv max 267 mμ (ε 11,400). The near-ir ($CHCl_3$) shows NH absorption at 1.47 μ (ε 0.8), and OH absorption at 1.43 μ (ε 0.18).

Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.77; H, 5.56; N, 11.23.

6-Hydroxy-6-phenyl-2,3,5,6-tetrahydroimidazo[2,1-*a*]isoquinoline (6).—Sodium hydride (12.0 g of 60% oil dispersion, 0.30 mol) was placed in a 1-l., three-necked flask and swirled with 50 ml of petroleum ether. The petroleum ether was decanted, 250 ml of dry dimethyl sulfoxide [distilled from calcium hydride, bp 64° (4 mm)] was added and the system was placed under nitrogen. With stirring, 68 g (0.31 mol) of trimethyloxosulfonium iodide[3] was added, in portions over a period of 20 min, through a piece of Gooch tubing connected to the flask. After the mixture had been stirred for 1 hr, 25.0 g (0.1 mol) of **1** was added, as the solid, over a period of 5 min. The reaction mixture was then heated at 100° for 30 min, cooled, and poured into 1 l. of ice–water. Filtering gave 21.2 g (80.4%) of **6** as a tan solid which was recrystallized from methanol–chloroform (Norit) to give colorless prisms: mp 264–266° dec; uv max 237 mμ (ε 13,300), 282 (3620), and 302 (inflection, 2600); ir ($CHCl_3$) 1618 cm^{-1} (sharp, strong).

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.10; H, 6.06; N, 10.85.

6-Phenyl-2,3-dihydroimidazo[2,1-*a*]isoquinoline (7). A. From Compound 6.—A suspension of 10.6 g (0.04 mol) of **6** in 105 ml of pyridine was stirred and cooled while 24 g (14.5 ml, 0.2 mole) of thionyl chloride was added at 25–30°. When the addition was completed, stirring was continued at room temperature for a total of 1.5 hr. The orange solution was poured into 1.6 l. of ice–water with stirring, basified with 50% sodium hydroxide solution, and diluted to 2 l. with water to give a yellow solid. After 30 min, the solid was collected by filtration and dried partially on the funnel. The damp solid was dissolved in chloroform which was dried over sodium sulfate and evaporated to give 7.3 g (74%) of **7** as a pale yellow solid, mp 155–159°. Recrystallization from benzene–hexane solution (Norit) gave pure **7** as pale yellow needles: mp 160–161° dec; uv max 207 mμ (ε 42,300), 267 (10,750), 272 (15,300), and 340 (9500); ir ($CHCl_3$) 1640 cm^{-1} (strong).

Anal. Calcd for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37. Found: C, 38.24; H, 5.94; N, 11.42.

B. From Compound 10.—A mixture of 11.1 g (0.05 mol) of **10**[6] and 58 g (0.25 mol) of ethylenediamine *p*-toluenesulfonate was stirred in an open flask at 190–200° for 6 hr. After cooling, the pale yellow, hard mass was covered with 200 ml of hot water, broken up with a spatula, and stirred for 30 min. The pale yellow solid was collected by filtration, air dried partially on the funnel, and dissolved in 200 ml of chloroform. The chloroform solution was washed twice with 75-ml portions of 1 *N* sodium

(6) F. Daro and P. Condorelli, *Boll. Sedute Accad. Gioenia Sci. Nat. Catania*, **6**, 606 (1960); *Chem. Abstr.*, **58**, 9010 (1963).

hydroxide solution and once with water. After having been dried over sodium sulfate, the solution was evaporated *in vacuo* to give 12.3 g (100%) of pale yellow solid, mp 150–160°. Recrystallization from benzene gave **7** as pale yellow needles, mp (and mmp with a sample prepared by method A), 160–161°.

6-Phenylimidazo[2,1-*a*]isoquinoline (8). A. From Compound 9.—A solution of 850 mg (3.24 mmol) of **9** and 0.5 ml of boron trifluoride etherate in 10 ml of acetic acid was heated under reflux for 5 hr and poured into 30 ml of water which was then basified with 50% aqueous sodium hydroxide. The mixture was extracted with chloroform and the extracts were combined, washed with water, dried over sodium sulfate, and evaporated to yield 700 mg (88.5%) of **8** as a white solid. Recrystallization from benzene–hexane gave the pure product as colorless needles: mp 152–153.5°; uv max 250 mμ (inflection, ε 41,700), 257 (52,800), 287 (inflection, 9000), and 324 (1400); nmr ($CDCl_3$) δ 7.47 (center of 10 H multiplet), 7.74 (1 H, singlet), and 8.67 (1 H, multiplet).

Anal. Calcd for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47. Found: C, 83.39; H, 4.95; N, 11.39.

B. From Compound 7.—A mixture of 24.6 g (0.1 mol) of **7** and 5 g of 25% palladium on carbon in 200 ml of tetraline was stirred under reflux for 2 hr. After cooling, the mixture was diluted with 150 ml of chloroform and filtered. The pale yellow filtrate was treated with 80 ml of 2.4 *N* methanolic hydrogen chloride solution and extracted into water (five 100-ml portions). The aqueous extracts were combined, basified with 2 *N* sodium hydroxide solution, and extracted with chloroform (three 100-ml portions). The light purple chloroform extract was dried over sodium sulfate and evaporated to give an oil which solidified on cooling to give a tan solid. Recrystallization from benzene–hexane (charcoal) gave 10.9 g (45%) of **8** as colorless needles, mp and mmp 150–151°.

C. From Compound 12.—A mixture of 2.5 g (0.01 mol) of **12** and 0.5 g of 25% palladium on carbon in 10 ml of tetralin was stirred at reflux for 5 hr. The warm mixture was filtered and the catalyst was rinsed with tetralin. The filtrate was diluted with petroleum ether until cloudy and cooled in an ice bath with occasional scratching. Tan crystals were collected after 15 min and air dried to yield 1.3 g (54%) of **8**, mp 142–147°. Recrystallization from benzene gave **8** as colorless needles, mp (and mixture melting point with a sample as prepared in A above) 152–153.5°.

6-Hydroxy-6-phenyl-5,6-dihydroimidazo[2,1-*a*]isoquinoline (9).—Sodium hydride (6.0 g of a 60% oil dispersion, 0.15 mol) was placed in a 1-l., three-necked flask and swirled with 50 ml of petroleum ether. The petroleum ether was decanted, 250 ml of dry dimethyl sulfoxide [distilled from calcium hydride, bp 64° (4 mm)] was added, and the system was placed under nitrogen. With stirring, 36.8 g (0.16 mol) of trimethyloxosulfonium iodide was added, in portions over a period of 15 min, through a piece of Gooch tubing connected to the flask. After the solution had been stirred for 45 min, 12.2 g (0.0492 mol) of **5** was added over a period of 5 min. Stirring was continued for 2 hr at room temperature and then at 70–80° for 1 hr. The reaction mixture was poured into 1 l. of ice–water which was then extracted with chloroform. The extracts were combined, washed with water, dried over sodium sulfate, and evaporated to leave a yellow, semisolid mass. Trituration with 40 ml of ethyl acetate, cooling, and filtering gave 2.8 g (21.7%) of white crystals, which were recrystallized from ethanol to give **9** as colorless prisms, mp 231–233° dec. The mother liquors were shown, by thin layer chromatography to consist mainly of starting material with several impurities: uv max 286 mμ (ε 14,840) and 300 (inflection, 10,000); nmr (CD_3COOD) δ 4.72 (2 H, quartet), 7.18 (10 H, multiplet), and 8.18 (1 H, multiplet).

Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.60; H, 5.47; N, 10.45.

6-Phenyl-2,3,5,6-tetrahydroimidazo[2,1-*a*]isoquinoline (12). A. From 3-Phenyl-3-methylphthalide (12).[7]—A mixture of 11.2 g (0.05 mol) of **13** and 58 g (0.25 mol) of ethylenediamine *p*-toluenesulfonate was heated in an oil bath at 190–200° with stirring for 20 hr. The melt was cooled, stirred with warm water, and extracted with 100 ml of chloroform. The chloroform extract was washed twice with 50-ml portions of 1 *N* hydrochloric acid, dried over sodium sulfate, and evaporated to dryness. The resulting orange oil was warmed with 50 ml of benzene with occasional scratching to give the toluenesulfonic acid salt of **12** as white crystals, mp 170–175°. The crude salt was dissolved in chloroform. The chloroform solution was washed twice with 50-ml portions of 1 *N* sodium hydroxide solution and once with water. After having been dried over sodium sulfate, the chloroform solution was evaporated to give 7.3 g (59%) of **12** as nearly colorless crystals. Recrystallization from benzene–hexane solution (Norite) gave colorless crystals: mp 133–134°; uv max 273 mμ (ε 13,800) and 280 (4100); ir ($CHCl_3$) 1615 cm^{-1} (strong).

Anal. Calcd for $C_{17}H_{16}N_2$: C, 82.23; H, 6.50; N, 11.28. Found: C, 82.55; H, 6.68; N, 11.28.

B. From o-(δ-Methylenebenzyl)benzoic acid (14).[8]—A mixture of 4.5 g (0.02 mol) of **14** and 23.2 g (0.1 mol) of ethylenediamine *p*-toluenesulfonate was heated with stirring in an oil bath at 190–200° for 20 hr. The melt was cooled, dissolved in 75 ml of warm water, and extracted with 100 ml of chloroform. The chloroform extract was washed twice with 50-ml portions of 1 *N* hydrochloric acid, dried over sodium sulfate, and evaporated to dryness to give an orange oil. The oil was warmed with 30 ml of benzene with occasional scratching to give the toluenesulfonic acid salt of **12** as tan crystals, mp 170–175°. The salt was converted into the base as above to give 3 g (60%) of **12**, mp and mmp 133–134°.

C. From 3,4-Dihydro-4-phenylisocoumarin (11).—A mixture of 1.7 g (0.008 mol) of **11** and 9.3 g (0.04 mol) of ethylenediamine *p*-toluenesulfonate was stirred at 190–200° for 6 hr and cooled to give a pale yellow solid. The mass was covered with 50 ml of warm water and broken up with a spatula. The mixture was extracted with chloroform. The chloroform extract was washed twice with 1 *N* hydrochloric acid, dried over sodium sulfate, and evaporated to dryness to give an orange oil. The oil was warmed with 10 ml of benzene with scratching to give the toluenesulfonic acid salt of **12** as nearly colorless crystals, mp 175–178°. The salt was converted into the base as for A above to give 1 g (53%) of **12** as pale yellow crystals. Recrystallization from benzene–hexane solution (charcoal) gave colorless crystals, mp and mmp 133–134°.

3,4-Dihydro-4-phenylisocoumarin (11).—To a suspension of 3.3 g (0.09 mol) of sodium borohydride in 150 ml of ethanol was added in portions 7.2 g (0.03 mol) of *o*-(α-formylbenzoyl)benzoic acid, which was prepared from 4-phenylisocoumarin by the method of Berti.[8] The mixture became hot and hydrogen was evolved. When the exothermic reaction had abated, the mixture was stirred and refluxed for 3 hr. The turbid, white solution was evaporated under reduced pressure to give a gummy, white solid. This solid was stirred with 300 ml of water, acidified with 6 *N* hydrochloric acid, and extracted with chloroform. After having been dried over sodium sulfate, the chloroform extract was evaporated under reduced pressure to give a colorless oil. The oil was stirred with aqueous sodium bicarbonate solution until it became viscous. The sodium bicarbonate solution was decanted and the gum was stirred with cold water until it solidified. The yield of waxy, white solid after air drying was 6.1 g (91%). Crystallization from hexane (40 ml/g) gave 3,4-dihydro-4-phenylisocoumarin (**11**) as white prisms: mp 58–60°; uv max 232 mμ (ε 11,100), and 282 (1800); ir ($CHCl_3$) 1725 cm^{-1} (strong).

Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.33; H, 5.39. Found: C, 80.35; H, 5.51.

Registry No.—**3**, 23293-85-8; **4**, 23293-86-9; **5**, 23293-87-0; **6**, 23293-88-1; **7**, 23293-89-2; **8**, 23293-90-5; **9**, 23293-91-6; **11**, 23293-92-7; **12**, 23293-93-8.

Acknowledgment.—We are indebted to the following members of the Physical Chemistry Department under the direction of Dr. P. Bommer: Dr. Toome for the uv spectra, Dr. T. Williams for nmr spectra, Mr. S. Traiman for ir spectra, and Dr. F. Scheidl for the microanalyses. We also wish to thank Professor G. Büchi for helpful discussions.

(7) R. Reinschneider, H. G. Kaahn, and L. Horner, *Monatsh. Chem.*, **91**, 1034 (1960); J. Tironflet, *Bull. Soc. Sci. Bretagne, Spec. Publ. No. 26*, 7 (1951); *Chem. Abstr.*, **47**, 8694 (1953).

(8) G. Berti, *Gazz. Chim. Ital.*, **87**, 707 (1957); *Chem. Abstr.*, **52**, 15536 (1958).

Synthesis of Isoquinolines. XI. Dibenzo[c,f]-1-azabicyclo[3.3.1]nonanes and 4-Phenyl-1,2,3,4-tetrahydroisoquinolines[1]

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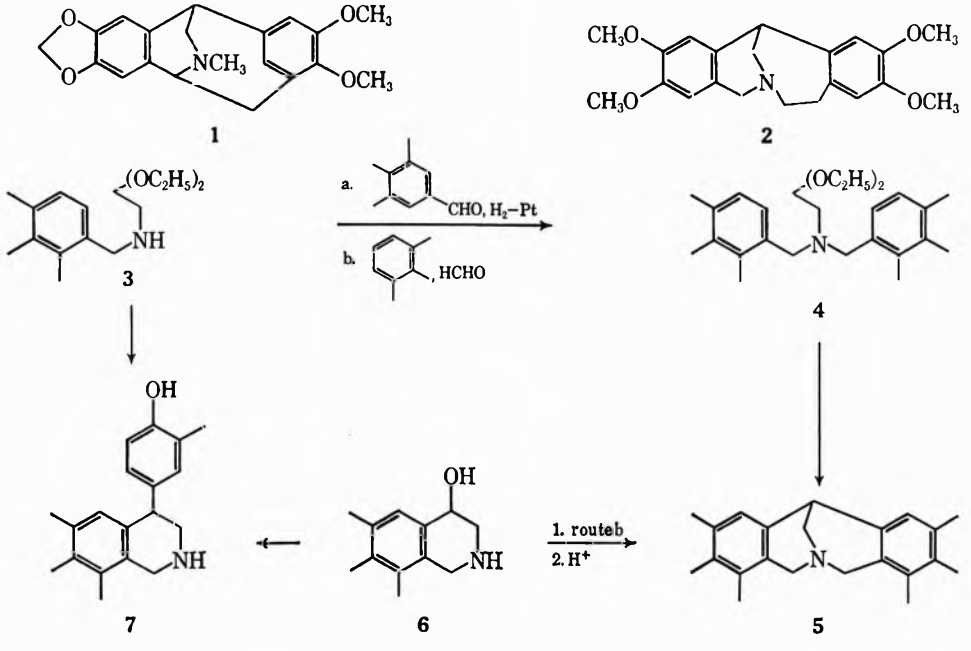
Received October 2, 1969

The facile syntheses of 4-hydroxy-1,2,3,4-tetrahydroisoquinolines[2] appears to have made available a versatile intermediate for the preparation of a number of interesting compounds. In addition to the conversions reported in papers II–VIII of this series, they have been converted into 4-benzylisoquinolines,[3] 4-alkoxy-1,2,3,4-tetrahydroisoquinolines,[4] and 4-alkylamino-1,2,3,4-tetrahydroisoquinolines.[5] They have been converted into two bicyclic systems, the pavine system (**1**)[6] and the azabicyclodecane (**2**).[7] It would seem that the 4-hydroxy compounds can react in at least three ways: simple nucleophilic displacement (4-alkoxy and 4-alkylamino compounds and bicyclic structures);[4-7] dehydration to an enamine followed by alkylation at the 4 position;[3] and dehydration followed by nucleophilic attack at the 3 position.[8] Furthermore, 4-hydroxy-1,2,3,4-tetrahydroisoquinolines have been suggested[6] as biosynthetic intermediates. In this paper, we would like to report two additional nucleophilic displacement reactions of the hydroxyl group leading to the title compounds.

N,N-Bisbenzylaminoacetals (**4**) were prepared from **3**[9] by reductive benzylation in acetic acid over a platinum catalyst (route a) or by a Mannich reaction (route b).[10] These compounds were cyclized in 6 *N* HCl to yield the azabicyclononanes (**5**). The results are shown in Table I. The yields are based upon crude **3**[9] and were slightly erratic, although never low. The structures of **5** are based upon the mode of formation and the usual spectra and analytical data. The mass spectra showed the correct molecular ions and reasonable cracking patterns. Compounds **5a** and **5b** were methylated with diazomethane to give **5h**, which was the major compound for nmr studies. The spectrum is extremely simple, indicating a highly symmetrical structure. The aromatic protons show up as two sharp singlets (4 protons) at τ 3.5 and 3.29, as do the methoxyl protons (12 protons) at τ 6.21 and 6.19. The protons on the methylene groups between the nitrogen and the rings (5 and 7 positions) appear as an AB pattern (J = 17.5 cps) centered at τ 5.8, and the remaining protons appear in the general region of τ 6.7–6.4. The other compounds in Table I have similar and predictable spectra.



When the appropriately substituted benzylaminoacetals (crude)[9] were allowed to stand in 6 *N* HCl at room temperature in the presence of various phenols, the 4-(*p*-hydroxyphenyl)-1,2,3,4-tetrahydroisoquinolines (**7**) resulted. These compounds could also be obtained from the purified 4-hydroxy compounds (**6**)[2] as could the azabicyclononanes, but quite satisfactory yields were obtained from the acetals. The results are shown in Table II. The yields are based upon crude **3**.[9]

The structures of the 4-phenyl derivatives are based upon their mode of formation, their predictable nmr spectra, and the synthesis by this method of a known

(1) Part X: J. M. Bobbitt, A. S. Steinfeld, K. H. Weisgraber, and S. Dutta, *J. Org. Chem.*, **34**, 2478 (1969). This work was sponsored in part by Research Grant CA-10494 from the National Cancer Institute of the National Institutes of Health.

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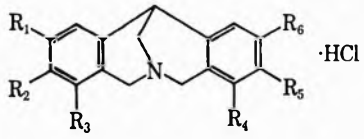
(10) J. M. Bobbitt and C. P. Dutta, *ibid.*, **34**, 2001 (1969).

TABLE I

DIBENZO[c,f]-1-AZABICYCLO[3.3.1]-NONANE HYDROCHLORIDES[a]



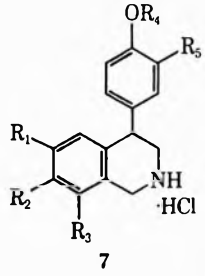
5

Compd	R_1	R_2	R_3	R_4	R_5	R_6	Yield, %	Mp, °C
5a	OCH_3	OH	H	H	OH	OCH_3	70	278–280
5b	OH	OCH_3	H	H	OCH_3	OH	75	170–173
5c	OCH_3	OCH_3	H	OH	OCH_3	OCH_3	60	270–272
5d[b]	OCH_3	OCH_3	H	H	OH	OCH_3	72	118–120
5e	OCH_3	OH	H	OH	OCH_3	OCH_3	70	288–290
5f[c]	H	OCH_3	OH	H	OH	OCH_3	65	265–267
5g	H	OCH_3	OH	OH	OCH_3	H	70	279–281
5h[d]	OCH_3	OCH_3	H	H	OCH_3	OCH_3	95	280–282

[a] Analytical values (±0.35%) for C, H, and N were reported for all compounds except 5c (C found, 0.46% low) and 5g (C found 0.55% low) (Ed.). [b] Purified as free base after basification of the hydrochloride. The data given refer to the free base. [c] Crystallized with 1 mol of water. [d] Prepared from 5a and 5b by methylation.

TABLE II

4-PHENYL-1,2,3,4-TETRAHYDROISOQUINOLINE HYDROCHLORIDES[a]



7

Compd	R_1	R_2	R_3	R_4	R_5	Yield, %	Mp, °C
7a	OCH_3	OCH_3	H	CH_3	OCH_3	10	238–240[b]
7b[c]	OCH_3	OCH_3	H	H	OCH_3	70	131–133
7c	OCH_3	OCH_3	H	H	OH	65	126–128.5
7d	OCH_3	OH	H	H	OCH_3	70	261–263
7e	OCH_3	OH	H	H	CH_3	60	280–281
7f	H	OCH_3	OH	H	CH_3	78	286–288
7g	H	OCH_3	OH	H	OH	75	276–278

[a] Analytical values (±0.30) for C, H, and N were reported for all compounds except 7g, for which C and N values (found) were 0.5 and 0.4% high (Ed.). [b] Literature (ref 11) mp 240°. [c] The compound was purified as the free base from crude hydrochloride. The data given apply to the free base; analysis indicated 1 mol of water.

compound, 4-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1,-2,3,4-tetrahydroisoquinoline (**7a**).[11] The condensation always appeared to go in the position *para* to the phenol group of the ring destined to be the 4-phenyl group. The reaction does take place on activated systems which contain no phenol group, as for **7a**, but the yields are low.

Experimental Section[12]

Dibenzo[c,f]-1-azabicyclo[3.3.1]nonanes. General Procedure.—Substituted N-benzylaminoacetaldehyde diethyl acetals (**3**) were prepared on 0.02-mol amounts from aminoacetal and the appropriate benyaldehydes as described.[9,13] The acetals, in ethanol over platinum as formed, were combined with 0.02 mol of the second aldehyde and 6 ml of glacial acetic acid and hydrogenated until hydrogen uptake ceased (8–10 hr). The catalyst was removed, the solvent was removed under vacuum, and the residue was taken up in 80 ml of 6 *N* HCl. After 12–15 hr at room temperature, the solvent was evaporated under vacuum. During the evaporation, compounds **5a**, **5b**, **5f**, and **5g** crystallized and were recrystallized from ethanol–ether to give the final products. Compound **5d** was obtained by basifying the solid from the evaporation and extracting with $CHCl_3$. The analytical sample was crystallized from ethanol–ether.

Compound 5e.—N-Isovanillylominoacetaldehyde diethyl acetal (1 g, 0.0037 mol) in 30 ml of ethanol was allowed to stand with 1.4 ml (0.18 mol) of 40% HCHO and 0.41 g (0.0037 mol) of 2,3-dimethoxyphenol for 24 hr at room temperature. The solvent was removed and the residue was taken up in 50 ml of 6 *N* HCl and allowed to stand at room temperature for 12 hr. Evaporation of solvent under vacuum and crystallization from ethanol–ether yielded 0.98 g (70%) of **5e** hydrochloride.

Compound 5c.—Crude 6,7-dimethoxy-4-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (0.5 g, 0.002 mol), prepared by the reported procedure,[2] was allowed to stand for 24 hr at room temperature in 20 ml of ethanol with 1 ml (0.01 mol) of 40% HCHO and 0.27 g (0.002 mol) of 2,3-dimethoxyphenol. The solvent was removed and the residue was allowed to stand for 15 hr at room temperature in 20 ml of 6 *N* HCl. Evaporation of the solvent under vacuum and crystallization from ethanol gave 0.48 g (60%) of **5c**.

Methylation of 5a and 5b to 5h.—Compounds **5a** and **5b** (0.3 g), converted into the free bases, were methylated with an excess of distilled ethereal diazomethane (*ca.* 100 ml, from 5 g

(11) R. Quelet, M. Mansouri, and R. Pineau, *Compt. Rend.*, **245**, 537 (1957).

(12) Melting points were taken on a Kofler hot-stage apparatus and are corrected. The analyses were carried out by Baron Consulting Co., Orange, Conn. The nmr spectra were measured on a Varian A-60 instrument using tetramethylsilane as a standard.

(13) Actually, this means that the yields are based upon the benzaldehydes originally used to prepare the benzylaminoacetals,[9] since the acetals are not purified.

of N,N′-dimethyl-N,N′-dinitrosoterrephthalamide) in 20 ml of methanol–ether (1:2). The reaction was allowed to stand for *ca.* 36 hr. Evaporation and purification through the hydrochloride (prepared with HCl in ethanol) gave **5h** in *ca.* 95% yield from both compounds.

4-Phenyl-1,2,3,4-tetrahydroisoquinolines. General Procedure.—Crude substituted N-benzylaminoacetaldehyde diethyl acetals[9,13] (**3**, 0.01 mol) were allowed to stand with 0.011 mol of the appropriate phenols in 20 ml of 6 *N* HCl at room temperature for 12–15 hr. The product (**7**) precipitated. Concentration of the reaction mixtures yielded additional amounts of product. They were combined and recrystallized from ethanol or ethanol–ether.

Registry No.—**5a**, 23230-67-3; **5b**, 23282-29-3; **5c**, 23230-68-4; **5d**, 23230-69-5; **5e**, 23230-70-8; **5f**, 23230-71-9; **5g**, 23230-72-0; **5h**, 23230-73-1; **7a**, 23230-74-2; **7b**, 23263-77-6; **7c**, 23263-78-7; **7d**, 23230-75-3; **7e**, 23230-76-4; **7f**, 23230-77-5; **7g**, 23230-78-6.

Rearrangement of a 2,3-Alkylene-2,3-dihydro-1,5-benzoxazepine into a 2-Substituted Benzoxazole

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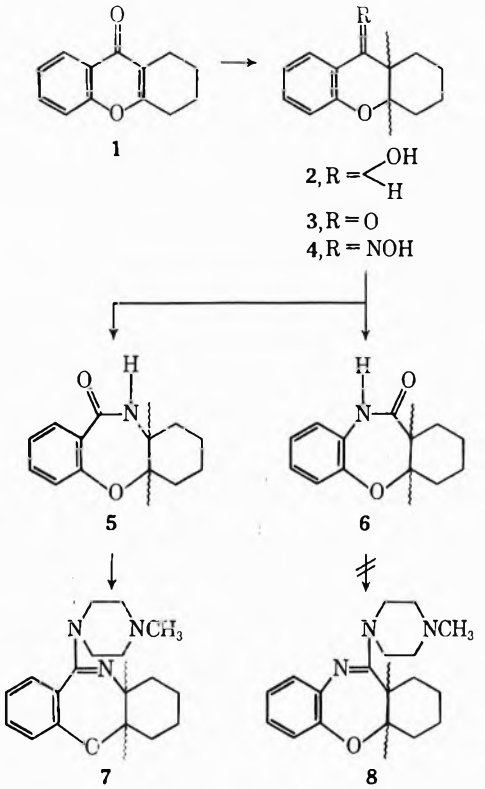
Received October 10, 1969

Discussion

Laboratory[1] studies have suggested that 2-chloro-11-(4-methyl-1-piperazinyl)dibenz[*b*,*f*][1,4]oxazepine[1c,2] possesses potential psychotropic utility. In view of the interest of our laboratories in this agent,[1b–d] we undertook the preparation of partially saturated congeners of this compound. During this study we observed a facile rearrangement of a 2,3-alkylene-2,3-dihydro-1,5-benzoxazepine into a 2-substituted benzoxazole, which is the subject of this report.

1,2,3,4-Tetrahydroxanthone (**1**)[3] served as the starting material for this investigation (see Scheme I). Catalytic reduction of **1** gave the hexahydro alcohol **2**, which afforded ketone **3** on treatment with chromium trioxide–pyridine.[4] Beckmann rearrangement of the derived oxime **4** furnished a separable mixture of lactams **5** and **6**. Consonant with earlier studies,[5] lactam **6**, the product of aryl migration, predominated. Treatment of **5** with phosphorus oxychloride gave a chloroimidate, which reacted with 1-methylpiperazine to give 5a,6,7,8,9,9a-hexahydrodibenz[*b*,*f*][1,4]oxazepine (**7**).

SCHEME I



Application of this sequence to the isomeric lactam **6** failed to afford hexahydrodibenz[*b*,*f*][1,4]oxazepine (**8**); instead a product with composition $C_{13}H_{13}NO$ was isolated. This material appeared to result from a skeletal rearrangement in view of its distinctive ultraviolet spectrum (λ_{max} 265, 285, and 290 mμ). In contrast, the spectrum of **7** shows only weak end-absorption. The identity of the ring system present in the $C_{13}H_{13}NO$ substance was indicated by dehydrogenation in boiling decalin with palladium on carbon, which afforded the known 2-phenylbenzoxazole.[6] Although thermally induced rearrangement under the stringent conditions of dehydrogenation could not yet be eliminated from consideration, this observation suggested that the $C_{13}H_{13}NO$ substance was 2-(1-cyclohexenyl) benzoxazole (**11**). Thus the formation of **11** from the intermediate chloroimidate **9** could be interpreted as proceeding *via* a base-induced elimination to give phenoxide **10**, which then undergoes intramolecular displacement of chloride to afford **11** (see Scheme II). The well-known intermolecular reaction of phenoxides with chloroimidates constitutes ample precedent for this last stage.[7]

The 2-substituted benzoxazole **11** was synthesized independently by ring closure of anilide **12** with phosphorus pentachloride.[8] The identity of **11** prepared in this manner with the $C_{13}H_{13}NO$ product established the structure of the latter material and confirmed that base treatment of chloroimidate **9** results in rearrangement of the 2,3-dihydro-1,5-benzoxazepine system into a benzoxazole.

(1) (a) G. Stille, H. Lauener, E. Eichenberger, F. Hunziker, and J. Schmutz, *Arzneim.-Forsch.*, **15**, 841 (1965); (b) C. N. Latimer and L. C. Malone, *Fed. Proc.*, **27**, 438 (1968); (c) C. F. Howell, N. Q. Quinones, E. N. Greenblatt, A. C. Osterberg, and R. A. Hardy, Jr., Abstracts of Papers, 1st Northeast Regional Meeting of the American Chemical Society, Boston, Mass., Oct 1968; (d) C. N. Latimer, *J. Pharmacol. Exp. Ther.*, **166**, 151 (1969).

(2) J. Schmutz, F. Künzle, F. Hunziker, and R. Gauch, *Helv. Chim. Acta*, **50**, 245 (1967).

(3) Prepared by the procedure of L. A. Paquette and H. Stucki, *J. Org. Chem.*, **31**, 1232 (1966).

(4) C. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

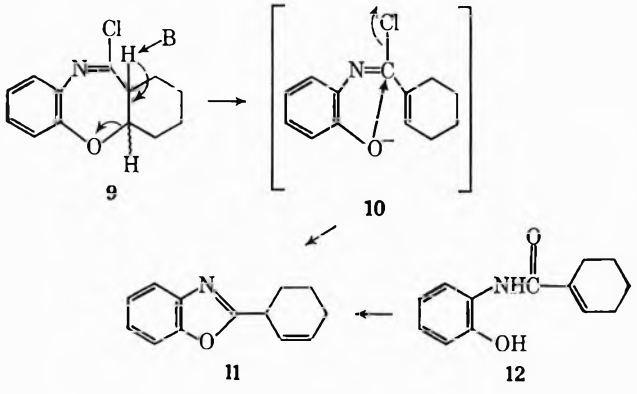
(5) I. G. Donaruma and W. Z. Heldt, *Org. React.*, **11**, 17 (1960).

(6) H. L. Wheeler, *Amer. Chem. J.*, **17**, 400 (1895).

(7) J. W. Schulenberg and S. Archer, *Org. React.*, **15**, 38 (1965).

(8) J. W. Cornforth in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley & Sons, Inc., New York, N. Y., 1957, p 420.

SCHEME II



Experimental Section

General.—Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Infrared spectra were determined in potassium bromide discs on a Perkin-Elmer Model 21 spectrophotometer, and the ultraviolet spectra were measured with a Cary recording spectrophotometer. Nmr spectra were determined in the indicated solvent on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. The mass spectrum was determined on an AEI MS-9 spectrometer. All evaporations were carried out at reduced pressure.

1,2,3,4,4a,9a-Hexahydro-9-xanthenol (2).—To a solution of 10.3 g of 1,2,3,4-tetrahydroxanthone (1)[3] in 150 ml of absolute ethanol was added 20 g of wet commercial Raney nickel catalyst.[9] The mixture was shaken under hydrogen for 2 hr, during which time 2 equiv of hydrogen were absorbed and crystals separated from solution. The mixture was filtered through diatomaceous earth and the filter cake was washed with 100 ml of acetone. The combined filtrate and washes were evaporated and the residue was crystallized from acetone–hexane, affording in two crops 7.4 g of white needles, mp 161–165°. A similar preparation, twice recrystallized from acetone–hexane, melted at 165–167°, ν 3350 and 3290 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.67; H, 8.24.

1,2,3,4,4a,9a-Hexahydro-9-xanthone (3).—To a stirred, ice-cooled slurry of 1.0 g of chromium trioxide in 10 ml of pyridine was added a solution of 500 mg of 1,2,3,4,4a,9a-hexahydro-9-xanthenol (2) in 2 ml of pyridine. The mixture was stirred at 25° for 18 hr and then poured into 100 ml of water. The aqueous solution was extracted with ethyl acetate, and this extract was washed with water and dried with magnesium sulfate and the solvent was removed to give 480 mg of pale yellow oil which absorbed at 1680 cm^{-1} in its infrared spectrum. This material was utilized for preparation of the oxime without further purification.

1,2,3,4,4a,9a-Hexahydro-9-xanthenone Oxime (4).—A solution of 480 mg (2.38 mmol) of 1,2,3,4,4a,9a-hexahydro-9-xanthenone (3) and 480 mg (6.9 mmol) of hydroxylamine hydrochloride in 5 ml of pyridine was heated at reflux temperature for 18 hr. The mixture was cooled and poured into 50 ml of water. The resulting gum was rubbed to a solid and collected to afford 380 mg of oxime: mp 164–166° (two recrystallizations from methanol–water raised the melting point to 165–167°); λ_{max} 254 mμ (ϵ 9765), 305 (5425), and 317 (4665); ν 3250, 992, 968, and 948 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.17; H, 7.12; N, 6.71.

Beckmann Rearrangement of Oxime 4.—A suspension of 3.75 g (17.3 mmol) of 1,2,3,4,4a,9a-hexahydro-9-xanthenone oxime (4) in 60 g of polyphosphoric acid was placed in an oil bath preheated to 135° and stirred with a glass rod until solution was complete (*ca.* 5 min). The heating was continued for an additional 15 min. The reaction mixture was cooled, and 200 ml of water was added slowly with stirring and cooling. The resulting mixture of lactams was collected as 3.40 g of tan crystals, mp 117–120°. The lactams were separated by chromatography on 60–100 mesh magnesia–silica adsorbent. Elution with 1.5% acetone–methylene chloride and crystallization from acetone–water afforded 2.02 g of **1,2,3,4,4a,11a-hexahydrodibenz[*b*,*f*]-[1,4]oxazepine-11(10H)-one (6)**, mp 149–150°. A similar preparation gave the following data: λ_{max} 244 mμ (ϵ 9114) and 275 (2821); ν 3180 and 1675 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.64; H, 6.66; N, 6.68.

Elution was continued with 5% acetone–methylene chloride to give a mixture of the lactams, as determined by thin layer chromatography; *ca.* 80 mg of mixture was eluted. The column was then washed with 30% acetone–methylene chloride to afford 0.97 g of 5a,6,7,8,9,9a-hexahydrodibenz[*b*,*f*][1,4]oxazepine-11-(10H)-one (5). Crystallization from acetone–hexane gave shiny plates, mp 196–198°. A similar preparation gave the following data: λ_{max} 225 mμ (ϵ 8140) and 282 (1410); ν 3175 and 1660 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.84; H, 6.56; N, 6.68.

5a,6,7,8,9,9a-Hexahydro-11-(4-methyl-1-piperazinyl)dibenz-[*b*,*f*][1,4]oxazepine (7).—To a solution of 280 mg (1.29 mmol) of 5a,6,7,8,9,9a-hexahydrodibenz[*b*,*f*][1,4]oxazepin-11(10H)one (5) in 10 ml of benzene was added 300 mg (1.44 mmol) of phosphorus pentachloride. The solution was heated at reflux temperature for 2 hr and then evaporated. The residual gum was dissolved in 5 ml of N-methylpiperazine and the solution was heated at reflux for 2 hr. The cooled solution was diluted with water and extracted with ethyl acetate. The organic solution was extracted with three 15-ml portions of 1 *N* hydrochloric acid. The acid extract was washed with ethyl acetate and then made alkaline with 10% sodium hydroxide solution to give 220 mg of tan crystals: mp 114–116° (two recrystallizations from methanol–water raised the melting point to 117–119°); λ_{max} 233 mμ (ϵ 7775); ν 1608 and 1592 cm^{-1}.

Anal. Calcd for $C_{18}H_{25}N_3O$: C, 72.20; H, 8.42; N, 14.04. Found: C, 72.61; H, 8.74; N, 14.26.

2-(1-Cyclohexenyl)benzoxazole (11). A.—A suspension of 110 mg (0.53 mmol) of phosphorus pentachloride and 100 mg (0.46 mmol) of 1,2,3,4,4a,11a-hexahydro[*b*,*f*][1,4]oxazepin-11(10H)-one (6) in 5 ml of dry benzene was stirred and heated at reflux temperature for 2 hr and then evaporated. The residual gum was dissolved in 5 ml of benzene, and a solution of 0.3 ml (*ca.* 3 mmol) of N-methylpiperazine in 2 ml of benzene was added. The solution was heated at reflux temperature for 90 min and then evaporated. The resultant gum was crystallized from acetone–water to give 30 mg of white crystals: mp 55–57°; λ_{max} 230 mμ (ϵ 7450), 265 (13,000), 285 (16,400), and 290 (17,400); ν 2525, 2840, 1640, 1535, 1450, 1240, and 747 cm^{-1}; mass spectrum *m/e* 199.

A similar preparation, recrystallized twice from acetone–water, melted at 62–63°.

Anal. Calcd for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.09; H, 6.86; N, 6.93.

B.—A solution of 300 mg (1.39 mmol) of 2′-hydroxy-1-cyclohexene-1-carboxanilide (12) and 0.30 ml (3.37 mmol) of phosphorus oxychloride in 7.5 ml of benzene was stirred at reflux temperature for 90 min and then evaporated. The residue was treated with 15 ml of ice–water and extracted with ethyl acetate. The extract was washed with 10 ml of 10% sodium hydroxide solution and water, dried with magnesium sulfate, and evaporated. The residue was dissolved in methylene chloride and passed through a magnesia–silica column. The product was collected by evaporation of the first five 50-ml fractions of eluate and crystallized from acetone–water to give 60 mg of white needles, mp 63–64°. Admixture with the previously described product from 1,2,3,4,4a,11a-hexahydrodibenz[*b*,*f*][1,4]-oxazepine-11(10H)-one showed no depression of melting point.

2-Phenylbenzoxazole.—A solution of 50 mg (0.25 mmol) of 2-(1-cyclohexenyl)benzoxazole in 2 ml of decalin and 50 mg of 10% palladium on charcoal was stirred at reflux temperature for 18 hr. The cooled solution was diluted with methylene chloride, filtered, and evaporated. The residue was dissolved in a water–ethanol mixture and this solution was evaporated. This process was repeated and the residue was crystallized from acetone–water to give 7.5 mg of 2-phenylbenzoxazole, mp 100°. The identity of this material with an authentic specimen[6] was shown by mixture melting point and comparison of infrared spectra.

(9) Raney active nickel catalyst (No. 28) as supplied by W. R. Grace and Co.

2′-Hydroxy-1-cyclohexene-1-carboxanilide (12).—To a solution of 1.26 g (10 mmol) of 1-cyclohexenecarboxylic acid in 5 ml of benzene was added dropwise 0.87 ml (12 mmol) of thionyl chloride. The mixture was allowed to stand at room temperature for 1 hr, heated on the steam bath for 30 min, and evaporated. The evaporation was repeated several times with toluene, leaving the 1-cyclohexenecarboxylic acid chloride as an oil. The acid chloride was added dropwise to a stirred, ice-cooled solution of 545 mg (0.5 mmol) of *o*-aminophenol in 2 ml of pyridine. The solution was stirred at room temperature for 2 hr and then poured into 30 ml of ice–water. The resulting oil was rubbed to a solid, which was collected and washed successively with 1 *N* hydrochloric acid, water, and saturated sodium bicarbonate solution to afford 1.05 g of a brown solid. The solid was dissolved in 20 ml of 10% sodium hydroxide solution, treated with activated charcoal, and filtered. The filtrate was acidified with acetic acid to afford 700 mg of white solid, mp 158–160°. A sample of this material, twice recrystallized from acetone–hexane, melted at 163–164°: λ_{max} 215 mμ (ε 20,600), 256 (8250), and 292 (8470); ν 3400, 3030, 2670, 1665, 1630, 1615, 1590, and 1538 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.82; H, 7.07; N, 6.35.

Registry No.—**2**, 23386-10-9; **4**, 23386-11-0; **5**, 23386-12-1; **6**, 23386-13-2; **7**, 23386-14-3; **11**, 23386-15-4; **12**, 23386-16-5.

Acknowledgment.—We wish to thank Mr. L. Brancone and his staff for the microanalyses and Mr. W. Fulmor and his associates for the spectral data.

Oxazoline Formation from N-Acylaziridines. Isolation of an Intermediate in an Octahydrophenanthrene System

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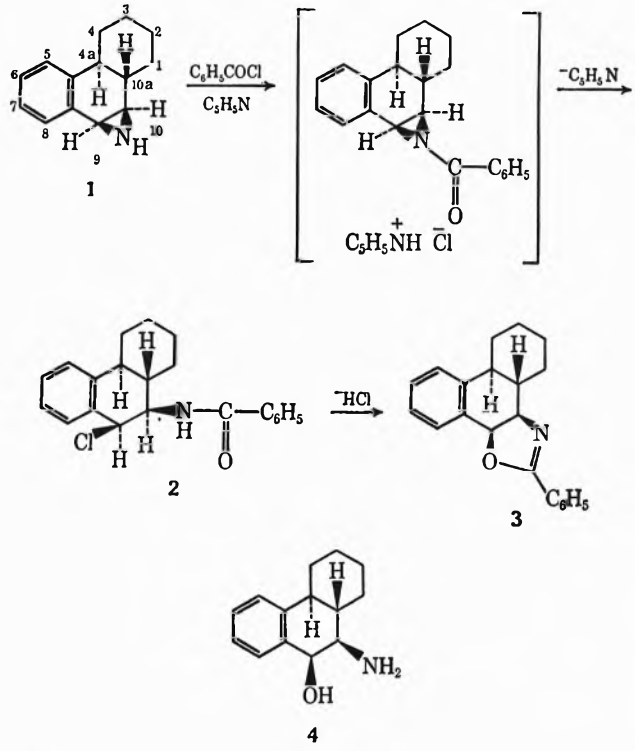
Received July 22, 1969

Opening of styrylaziridines and -aziridinium ions has been shown to afford products characteristic of both carbonium ion and displacement mechanisms,[2-4] while the isomerization of N-acylaziridines to oxazolines has been reported to occur under the influences of nucleophilic catalysis or heat.[5] The latter process is thought to involve formation of an intermediate β-halobenzamide in which carbonyl oxygen displacement of the halide occurs.[6] We wish to report a case of opening of an N-acylaziridine capable of forming an intermediate carbonium ion which affords a *cis*-β-halobenzamide stereoselectively, and which is readily converted into the corresponding oxazoline, probably through a solvolytic process.

In a study of amino alcohols in the octahydrophenanthrene system, we attempted the N-benzoylation of *syn*-aziridine **1**.[7,8] Aziridine **1** was prepared by the addition of iodoisocyanate (INCO) to 1,2,3,4,4a,10a-(*trans*-4a,10a)-hexahydrophenanthrene, followed by methanolysis, and aqueous potassium hydroxide treatment of the resulting β-iodocarbamate.

Attempted N-benzoylation of **1** with benzoyl chloride in pyridine at 60° afforded only small amounts of the oxazoline **3**. However, when the reaction was performed using a single equivalent of the acyl halide, and of the pyridine in ether, below 10°, an intermediate, 9(*a*)-chloro-10(*e*)-benzamido-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene[9] (**2**), was readily isolated.



Structural assignment of **2** is based primarily on infrared and nmr data.[10] The infrared spectrum showed an NH stretching band at 3330 cm^{-1} and amide I and II carbonyl bands at 1630 and 1520 cm^{-1}. The nmr spectrum (60 MHz) showed a broadened NH doublet at δ 6.65 for NH ($J_{10,NH}$ = 9 Hz), a doublet at 5.46 for H_9 ($J_{9,10}$ = 4 Hz) and a sextet at 4.67 for H_{10} ($J_{10,10a}$ = 9 Hz) (Figure 1). The nmr spectrum is consistent with the *cis* disposition of substituents.

When a chloroform solution of **2** was warmed at 75° for 10–20 min, formation of oxazoline **3** hydrochloride was noted by following the course of the reaction by observing the nmr spectrum of the reaction mixture (Figure 1). The nmr spectrum of **3** hydrochloride showed a doublet for H_9 at δ 6.18 ($J_{9,10}$ = 9 Hz) and a triplet for H_{10} at 4.52 ($J_{10,10a} \simeq$ 9 Hz), consistent with *cis*-oxazoline **3**. Cyclization of **2** was more readily accomplished in refluxing acetone in the presence of

(1) Public Health Service Predoctoral Fellowship 1-F1-GM-33,942, 1966–1969.

(2) (a) K. Kotera, M. Motomura, S. Miyazaki, T. Okada, and Y. Matsukawa, *Tetrahedron*, **24**, 1727 (1968); (b) K. Kotera, T. Okada, and S. Miyazaki, *ibid.*, **24**, 5677 (1968).

(3) N. B. Chapman and D. J. Triggle, *J. Chem. Soc.*, 1385 (1963).

(4) (a) N. J. Leonard, E. F. Kiefer, and L. E. Brady, *J. Org. Chem.*, **28**, 2850 (1963); (b) N. J. Leonard and K. Jann, *J. Amer. Chem. Soc.*, **84**, 4806 (1962).

(5) (a) H. W. Heine, *Angew. Chem. Intern. Ed. Engl.*, **1**, 528 (1962); (b) H. W. Heine and M. S. Kaplan, *J. Org. Chem.*, **32**, 3069 (1967), and references cited therein; (c) H. W. Heine, D. C. King, and L. A. Portland, *ibid.*, **31**, 2662 (1966).

(6) P. E. Fanta and E. N. Walsh, *ibid.*, **30**, 3574 (1965).

(7) We have chosen to designate the epoxides and aziridines in this system as *syn* or *anti* to indicate the relative geometry of the heterocyclic three-membered ring and the hydrogen atom at C-10a.

(8) All materials are racemic, although only a single isomer is drawn.

(9) The central ring is arbitrarily assigned the half-chair conformation where the equatorial (*e*) and axial (*a*) substituents at C-9 are in fact pseudo-equatorial and pseudoaxial, respectively.

(10) Elemental analysis does not distinguish between **2** and the hydrochloride salt of **3**.

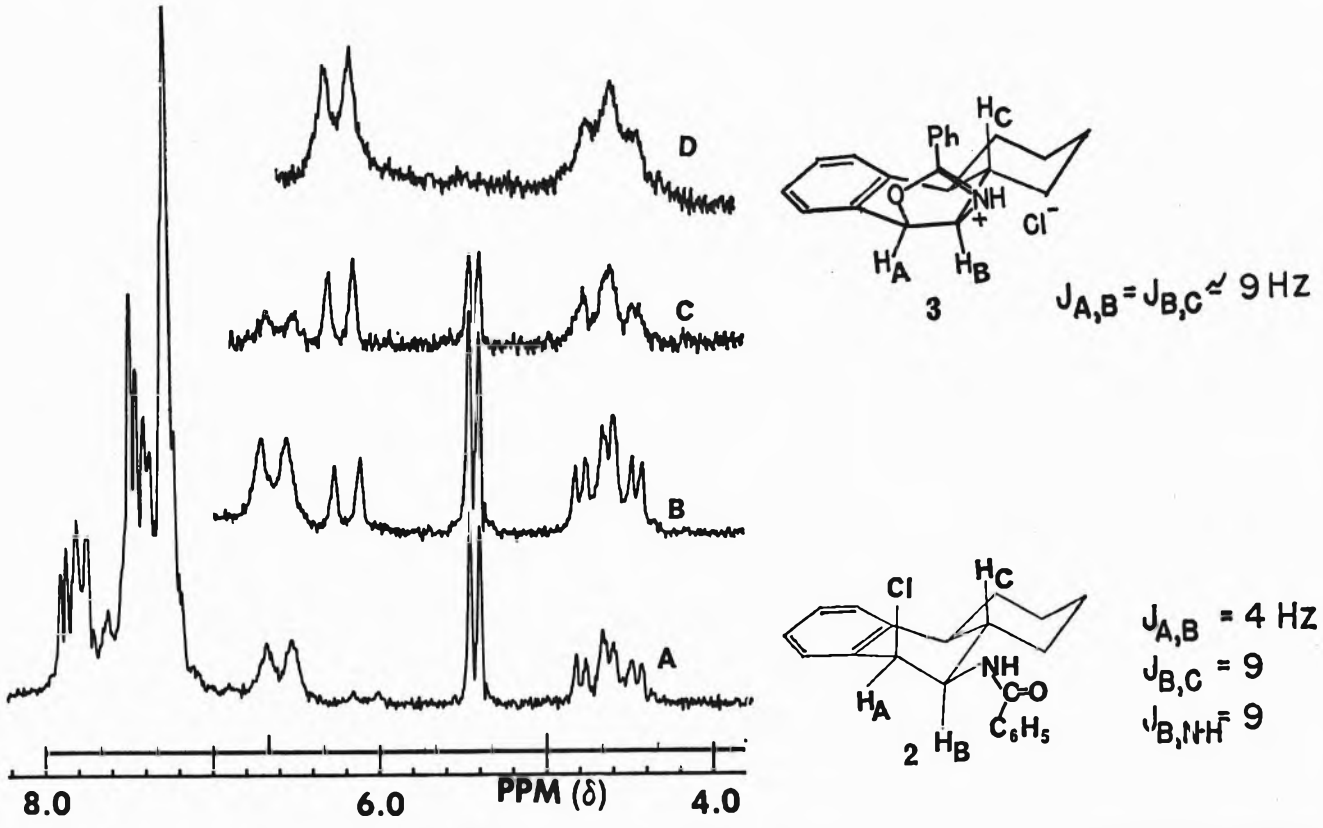


Figure 1.—(A) Nmr spectrum of 2; (B, C) nmr spectra of mixtures of 2 and 3 at 15 and 20 min, respectively; (D) nmr spectrum of oxazoline 3 hydrochloride.

sodium bicarbonate.[11] The nmr spectrum of the free oxazoline showed a doublet for H_9 and a triplet for H_{10} ($J_{9,10} \sim J_{10,10a} \sim 9.5$ Hz) at δ 5.49 and 4.12, respectively.

Amino alcohol 4[13] was converted into the oxazoline 3, utilizing ethyl benzimidate, as further evidence for structure 3. Carefully controlled hydrolysis of 3 also yields 4.

The assignment of *cis* stereochemistry to intermediate 2 is based primarily on the nmr spectral data, comparison of its spectrum with those of other 9(*a*),10(*e*)-disubstituted octahydrophenanthrenes,[14] and similar opening of aziridines and aziridinium ions.[2-4] Opening of other styryl aziridines, which can readily form benzylic carbonium ions, has been shown to occur through mixed SN1 and SN2 processes.[2] Opening of aziridinium ions (ethylene immonium ions) also gives products consistent with both mechanisms.[3,4,15]

In this system, the somewhat unexpected *cis* product probably arises because of some degree of carbonium ion character at the benzylic position in the transition state, which may then be attacked either from above or below the plane of the carbocyclic skeleton. Great differences in the relative degree of steric hindrance to attack are not obvious from Dreiding models. Both the *cis* stereochemistry and the direction of aziridine ring opening are most consistent with a carbonium ion or carbonium ion like intermediate followed by stereoselective addition of chloride. Formation of the oxazoline may similarly be envisioned to occur by solvolytic loss of the halide followed by ring closure.

Although finding products consistent with a double-displacement mechanism for the isomerization would have been academically more satisfactory, the isolation and characterization of an intermediate which readily undergoes the isomerization process lends considerable support to the mechanism of oxazoline formation from the N-acylaziridine which involves the intermediacy of a β-haloamide. The stereochemical configuration of the intermediate isolated in this study is probably a characteristic of this system and therefore not generally applicable to the chemical process of conversion of N-acylaziridines into oxazolines.

(11) Sodium bicarbonate is added to prevent the hydrolysis of the oxazoline hydrochloride to the corresponding β-aminobenzoate.[12]

(12) W. S. Johnson and E. N. Schubert, *J. Amer. Chem. Soc.*, **72**, 2187 (1950).

(13) G. Drefahl and D. Martin, *Chem. Ber.*, **93**, 2497 (1960).

(14) D. D. Miller and W. L. Nelson, unpublished results.

(15) Aqueous acid opening of 1 provides a mixture of 9(*e*)- and 9(*a*)-hydroxy-10(*e*)-amino-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (4), with the latter predominating.[14]

Experimental Section

Melting points were determined using a Thomas–Hoover Uni-Melt and are corrected. Microanalyses were conducted by Dr. G. B. Weiler and Dr. F. B. Strauss, Microanalytical Laboratory, Oxford, England. Ultraviolet spectra were recorded on a Cary 14 spectrometer. Infrared spectra were recorded on Beckman IR-5A, IR-8, and IR-20 spectrophotometers. Nmr spectra were obtained on the Varian A-60 and Varian T-60 instruments using tetramethylsilane as internal standard.

9(*a*)-Carbomethoxyamino-10(*a*)-iodo-1,2,3,4,4a,9,10,10a(*trans*-4a,10)-octahydrophenanthrene.—To a cold (−5 to −10°) solution of 3.9 g (0.02 mol) of 1,2,3,4,4a,10a-hexahydrophenanthrene in 200 ml of anhydrous ether was added 4.2 g (0.028 mol) of freshly prepared silver cyanate. To this slurry was added 5.04 g (0.021 mol) of solid iodine in one portion. The slurry was stirred for 2 hr in the cold and then at room temperature for an additional 6 hr. The inorganic salts were removed by filtration, the solution was diluted with 200 ml of anhydrous methanol, and the mixture was refluxed for 2 hr. The light brown precipitate was removed by filtration and washed with ether. The precipi-

tate was then recrystallized from methanol, giving 5.35 g (70%) of white needles: mp 138°; $\lambda_{max}^{95\% EtOH}$ 217 nm (ϵ 7000); ν_{max}^{KBr} 3280 (NH stretching), 3040 (aromatic CH stretching), 2950 and 2870 (aliphatic CH stretching), 1695 (very broad, C=O stretching), 1550, 1490, 1445, 1325, 1265, 1190, 1135, 1120, 1035, 1010, 760, 735, and 705 cm^{-1}; nmr (pyridine) δ 5.59 (quartet, $J_{9,10}$ = 2 Hz, $J_{9,NH}$ = 8 Hz, benzylic proton H_A), 4.84 (multiplet, $W_{1/2}$ = 4 Hz, H_{10} proton), and 2.70–0.7 (multiplet, methylene–methine envelope).

Anal. Calcd for $C_{16}H_{20}INO_2$: C, 49.88; H, 5.23; N, 3.64. Found: C, 49.97; H, 5.32; N, 4.01.

syn-9,10-Imino-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (1).—A mixture of 5.0 g (0.013 mol) of the iodocarbamate and 12.9 g of potassium hydroxide in 130 ml of absolute ethanol was refluxed for 3 hr. The ethanol was then removed *in vacuo* and the remaining solid was dissolved in 500 ml of ether and washed with cold water until the aqueous washings were neutral. The ether layer was dried (Na_2SO_4) and evaporated *in vacuo* to a volume of 50 ml, which was then placed in the refrigerator overnight. A total of 2.49 g (93.5%) of white needles, mp 128–129°, were collected. A small portion of the aziridine was recrystallized from ether for the analytical sample: mp 129–130°; ν_{max}^{KBr} 3200 (NH stretching), 3030 (aromatic CH stretching), and 2870 (aliphatic CH stretching), 1550, 1490, 1450, 1420, 1290, 1050, 910, 870, 850, 815, 794, 770, 745, and 735 cm^{-1}; nmr ($CDCl_3$) δ 7.55–6.90 (multiplet, aromatic protons), 2.79 (doublet, J_{AB} = 6 Hz, benzylic H_9 proton), and 2.70–0.70 (multiplet, methylene–methine envelope).

Anal. Calcd for $C_{14}H_{17}N$: C, 84.37; H, 8.60; N, 7.03. Found: C, 84.25; H, 8.56; N, 6.82.

9(*a*)-Chloro-10(*e*)-benzamido-1,2,3,4,4a,9,10,10a(*trans*-4a,10a)-octahydrophenanthrene (2).—Into 250 ml of anhydrous ether was placed 450 mg (2.25 mmol) of the aziridine 1 and 177 mg (2.25 mmol) of pyridine. To this mixture was added 315 mg (2.55 mmol) of benzoyl chloride in 20 ml of anhydrous ether. With an ice bath, the cloudy suspension was maintained below 10° at all times during the addition. The mixture was then allowed to warm to room temperature and stirred for an additional 30 min. The ether mixture was filtered, and the filtrate was evaporated *in vacuo* to a volume of 15 ml, with the water bath kept at room temperature, and placed in the refrigerator. The needlelike crystals that formed were removed by filtration, giving a total of 515 mg (68%) of the benzamide 2, mp 142–143°. The benzamide could not be recrystallized, since upon heating in solution it formed oxazoline hydrochloride 3: ν_{max}^{KBr} 3330 (NH stretching), 2900 and 2180 (aliphatic CH stretching), 1630 (C=O stretching), 1520, 1480, and 690 cm^{-1}; nmr ($CDCl_3$) δ 8.05–7.05 (multiplet, 9 aromatic protons), 6.65 (doublet, amide proton), 5.46 (doublet, J_{AB} = 4 Hz, benzylic proton H_9), 4.67 (sextet, J_{BC} = 9 Hz, proton H_B), and 3.00–0.90 (multiplet, methylene–methine envelope).

Anal. Calcd for $C_{21}H_{22}ClNO$: C, 74.21; H, 6.53; N, 4.12. Found: C, 74.22; H, 6.13; N, 4.27.

2-Phenyloxazoline of 9(*a*)-Hydroxy-10(*e*)-amino-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (3). A. Cyclization of 2.—A mixture of 300 mg (0.89 mmol of chlorobenzamide 2, 75 mg (0.90 mmol) of anhydrous sodium bicarbonate, and 200 ml of acetone was refluxed for 5 hr with stirring. The mixture was then evaporated *in vacuo* to dryness and to this was added 100 ml of water. The aqueous mixture was then extracted several times with ether. The ether layers were combined, dried (Na_2SO_4), and evaporated *in vacuo* to give 260 mg of solid material. The solid material was passed over a 30-g alumina column (Merck, reagent aluminum oxide) using benzene as an eluent. No material was isolated in the first 160 ml of benzene eluted from the column, but the next 360 ml of benzene solvent eluted afforded 230 mg (86%) of the oxazoline: mp 142–143°; ν_{max}^{KBr} 3050 (aromatic CH stretching), 2910 and 2860 (aliphatic CH stretching), 1640 (C=N stretching), 1575, 1490, 1445, 1080, 1060, 1025, 960, 950, 930, 780, 740, 725, and 685 cm^{-1}; nmr ($CDCl_3$) δ 8.15–7.10 (multiplet, aromatic protons), 5.49 (doublet, J_{AB} = 9.5 Hz, benzylic proton H_A), 4.12 (triplet, J_{BC} = 9.5 Hz, proton H_B), and 2.80–0.80 (multiplet, methylene–methine envelope).

Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.97; N, 4.61. Found: C, 83.56; H, 6.98; N, 4.82.

B. Oxazoline 3 Synthesis *via* Amino Alcohol 4.—A mixture of 100 mg (0.46 mmol) of amino alcohol 4,[13] 80 mg (0.46 mmol) of ethyl benzimidate prepared by the method of McCasland and Smith,[16] and 100 ml of anhydrous pyridine was refluxed for 5 hr. The pyridine was then removed *in vacuo*, affording 108 mg of an oil which was placed on an alumina column snd eluted with benzene. A total of 94 mg (69%) of the oxazoline (3), mp 141–142°, was isolated. The spectral properties were identical with those of the oxazoline prepared previously.

Acid Hydrolysis of Oxazoline 3.—Oxazoline 3, 300 mg (1.0 mmol), was dissolved in 150 ml of 10% aqueous hydrochloric acid and refluxed for 1 hr. The acidic solution was allowed to cool and extracted with ether to remove benzoic acid. The acidic solution was made alkaline with aqueous 10% NaOH solution and extracted with $CHCl_3$. The $CHCl_3$ was separated, dried (Na_2SO_4), and evaporated *in vacuo*, affording 148 mg (68%) of amino alcohol 4, mp 180°.

Registry No.—1, 23385-94-6; 2, 23385-95-7; 3, 23385-96-8; 3 hydrochloride, 23385-97-9; 9(*a*)-carbomethoxyamino-10(*a*)-iodo-1,2,3,4,4a,9,10,10a(*trans*-4a,-10)-octahydrophenanthrene, 23385-98-0.

(16) G. E. McCasland and D. A. Smith, *J. Amer. Chem. Soc.*, **72**, 2190 (1950).

The Rearrangement of 1-Acylaziridines to Oxazolinium Cations in Strong Acid Media[1]

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Received July 22, 1969

General interest in the ring-opening reactions of aziridine derivatives developed as a result of their biological[2,3] and industrial[3,4] significance. Many biological alkylating agents, such as cancer-inducing mitomycin,[3c] contain aziridine ring functions. The recent preparation[5] of 1-alkylaziridinium ions, 1-acylaziridinium ions, and O-protonated 1-acylaziridines prompts us to report our studies of 1-acylaziridines in strong acid media.

Heine[6] has reviewed the well-known isomerization reactions of 1-acylaziridines. Fanta[7] and Heine[8] have investigated extensively the pyrolytic and catalytic

(1) (a) Acid-Catalyzed Cyclization Reactions. VIII. For other papers in this series, see S. P. McManus, J. T. Carroll, P. M. Grohse, and C. U. Pittman, *Org. Prep. Proc.*, in press. (b) This work was supported in part by the University of Alabama Research Committee and at Huntsville in part by the Petroleum Research Fund (Grant 3501-B) administered by the American Chemical Society and by the National Aeronautics and Space Administration (Grant NGL-01-002-001).

(2) (a) B. Belleau, *Can. J. Biochem.*, **36**, 731 (1968); (b) W. C. J. Ross, "Biological Alkylating Agents," Butterworth and Co. Ltd., London, 1962; (c) D. A. Karnofsky and F. Bergel in "Chemotherapy in Cancer," P. L. Plattner, Ed., Elsevier Publishing Co., New York, N. Y., 1964, pp 3–18, 21–23.

(3) P. E. Fanta in "Heterocyclic Compounds—Three- and Four-Membered Heterocycles," Part I, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, and references cited therein.

(4) (a) A. G. Pittman and R. E. Lundin, *J. Polym. Sci., Part A*, **2**, 3803 (1964); (b) R. H. Quacchia, D. E. Johnson, and A. J. DiMilo, *Ind. Eng. Chem., Prod. Res. Develop.*, **6**, 268 (1967).

(5) G. Olah and P. J. Szilagyi, *J. Amer. Chem. Soc.*, **91**, 2949 (1969).

(6) H. W. Heine, *Angew. Chem., Int. Ed. Engl.*, **1**, 528 (1962).

(7) P. E. Fanta and E. N. Walsh, *J. Org. Chem.*, **31**, 59 (1966), and previous papers in the series.

(8) P. G. Mente, H. W. Heine, and G. R. Scharoubin, *ibid.*, **33**, 4547 (1968), and previous papers in the series. See also references cited therein for other pertinent work.

TABLE I
NMR ASSIGNMENTS OF OXAZOLINIUM CATIONS IN 90% H_2SO_4[a]

Ion	R_1[b]	NH[b]	Ring CH_2CH,[b] C-4/C-5	C-5 CH_3[b]	Yield of oxazoline on drowning, %
2a	CH_3, 2.91 (s)	9.30 (br)	4.62, J_{cis} = 9.9 5.53, J_{trans} = 9.9		61
2b	CH_3, 2.70 (s)	9.10 (br)	4.41 (m)[c] 5.82 (m)	2.02 (d), J = 6.8	53
2c	CH_3, 2.90 (s)	9.75 (br)	4.34 (s)	2.16 (s)	66
2d	C_6H_6, 7.81–8.40 (m)	10.10 (br)	4.48 (t), J_{cis} = 9.8 5.42 (t), J_{trans} = 9.8		68
2e	C_6H_6, 7.75–8.37 (m)	10.02 (br)	4.20 (t),[d] J_{cis} = 9.9 4.71 (t), J_{trans} = 9.8 5.92 (m)	2.01 (d), J = 7.0	71

[a] Positions given in parts per million downfield from TMS (internal capillary) at 33°. [b] Abbreviations: s, singlet; d, doublets; m, multiplet; br, broadened singlet; t, triplet. [c] The C-4 protons *cis* and *trans* to methyl at C-5 are not well resolved. [d] *cis* to methyl.

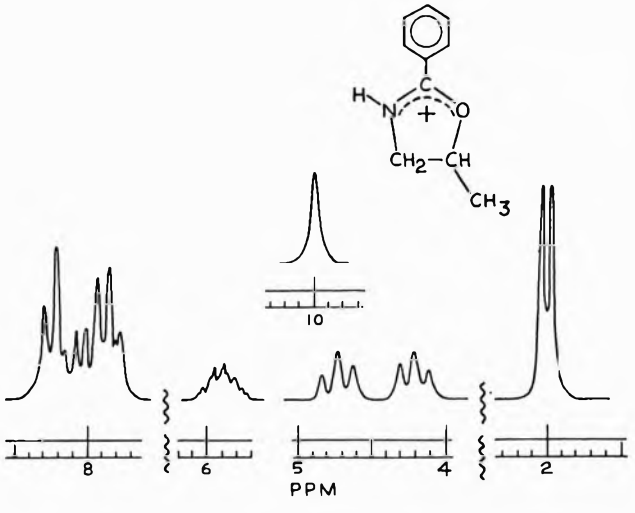
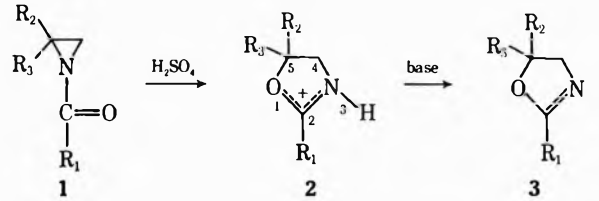


Figure 1.

SCHEME I



a, $R_1 = CH_3$; $R_2 = R_3 = H$
b, $R_1 = R_2 = CH_3$; $R_3 = H$
c, $R_1 = R_2 = R_3 = CH_3$
d, R_1 = Ph; $R_2 = R_3 = H$
e, R_1 = Ph; $R_2 = CH_3$; $R_3 = H$

isomerizations of 1-acylaziridines. 1-Acylaziridines undergo thermal rearrangements to 2-oxazolines, N-allylamides, and 2-benzamidobenzalacetophenones.[8] In the presence of various nucleophiles, 1-acylaziridines may isomerize to either a single 2-oxazoline or isomeric 2-oxazolines, depending on the substitution in the 2 and 3 position of the aziridine ring.[4b,8,9] Since Gabriel and Stelzner[10] observed that 1-aziridinethiocarboxanilide is converted into 2-anilino-2-thiazoline by concentrated hydrochloric acid, a few reports[6] of acid-catalyzed isomerizations have appeared. The most pertinent study to our work was that by Heine, Fetter, and Nicholson,[11] who reported the essentially quantitative conversion of 1-*p*-nitrobenzoyl-2,2-dimethylaziridine into 2-*p*-nitrophenyl-5,5-dimethyl-2-oxazoline in concentrated sulfuric acid. As part of our continuing probe into the mechanism of reactions involving carbonyl-group participation in carbonium ion reactions,[12] we decided to record the nmr spectra of some 1-acylaziridines in strong acid media to see whether oxazolinium ion formation, and intermediates leading to them, could be observed.

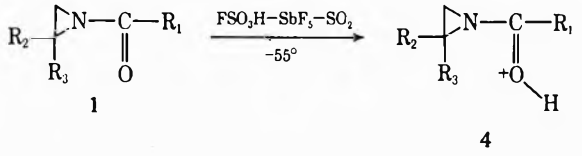
Quantitative rearrangement of 1-acetylaziridines **1a–1c** and 1-benzoylaziridines **1d** and **1e** to the corresponding 2-methyl- and 2-phenyloxazolinium cations **2a–2e**, respectively, occurred in 80–96% sulfuric acid (Scheme I). Careful drownings into base, in each case, liberated the expected 2-oxazolines **3a–3e**.

At 15°, no O- or N-protonated aziridine derivative or open-chain carbonium ion was observed. In each case immediate observation of the oxazolinium cation resulted. The oxazolinium ions were identified by (A) examination of their nmr spectra[13] at 33° (Table I), (B) isolation and subsequent identification of the 2-oxazolines, and (C) regeneration of the same oxazolinium ion from authentic samples of the 2-oxazolines. The nmr spectrum of ion **2e**, shown in Figure 1, is representative of the quality of the spectra obtained. The chemical shifts of the 2-methyl and 2-phenyl substituents in ions **2a–2e** were deshielded with respect to their positions in the spectra of their corresponding 2-oxazolines. The ring protons on C-5, adjacent to oxygen, were always found more than 0.7 ppm downfield from the protons at C-4. No long-range coupling involving the C-2 methyl protons was observed in the cations.[14] The proton on nitrogen appears as a broadened singlet owing to the nitrogen quadrapole,[15] which shortens the spin-lattice relaxation time to a value comparable with the reciprocal of the J_{HN} coupling constant. Observation of the proton on nitrogen rules out fast proton exchange with solvent. However, in 60%

(9) D. E. Johnson, R. H. Quacchia, and A. J. DiMilo, *Ind. Eng. Chem., Prod. Res. Develop.*, **6**, 273 (1967).
(10) S. Gabriel and R. Stelzner, *Chem. Ber.*, **28**, 2929 (1895).
(11) H. W. Heine, M. E. Fetter, and E. M. Nicholson, *J. Amer. Chem. Soc.*, **81**, 2202 (1959).
(12) (a) C. U. Pittman and S. P. McManus, *Chem. Commun.*, 1479 (1968); (b) C. U. Pittman and S. P. McManus, *Tetrahedron Lett.*, 339 (1969).
(13) The values of the chemical shift varied with acidity in H_2SO_4; in trifluoroacetic acid the downfield shifts were not so great as in H_2SO_4.
(14) In 2-oxazolines long-range coupling between the C-2 methyl protons and the C-4 protons are observed; *cf.* S. P. McManus, *Chem. Commun.*, 235 (1969).
(15) (a) J. D. Roberts, *J. Amer. Chem. Soc.*, **78**, 4495 (1956). (b) The broadening, due mainly to asymmetric fields near N, indicates the preserved sp^2 hybridization in cations **2a–2c** where the electric field symmetry is far lower than in ammonium ions.[16]
(16) A. D. Tiers and F. A. Bovey, *J. Phys. Chem.*, **63**, 302 (1959).

H_2SO_4 the nitrogen proton is not observed, indicating that, at this lower acidity, the rate of proton exchange with solvent is increased. The *cis* and *trans* vicinal coupling between the ring protons at C-4 and C-5 are equal, within experimental error, in ions **2a**, **2b**, **2d**, and **2e**. While this is an exception to the Karplus equation prediction, this phenomenon has been found in dihydrofuran ring systems[17] and five-membered-ring oxonium ions.[12] These couplings are large, with values of 9–10 Hz in each ion.

Since oxazolinium ions were the only cationic species which could be observed in sulfuric acid, stronger acids[18] were used at lower temperatures. In FSO_3H–SbF_5–SO_2 media at −55°, stable O-protonated 1-acylaziridines **4a–4c** were formed with nmr spectra



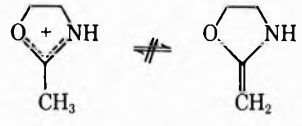
virtually identical with those recently reported by Olah and Szilagyi.[5] This conclusively demonstrates O protonation as opposed to N protonation. See Table II.

TABLE II
NMR ASSIGNMENTS OF PROTONATED 1-ACYLAZIRIDINES[a]

Ion	R_1	OH	Ring CH_2 (CH)	Ring CH_3
4a	CH_3, 2.98 (s)	9.12 (s)	5.10 (m)	
4b	CH_3, 2.89 (s)	9.40 (s)	4.89 (m)	1.86 (d)
			5.20 (m)	
4d	C_6H_6, 8.10[b]	10.60 (s)	4.90 (m)	

[a] s, singlet; d, doublet; m, multiplet; the positions are given in parts per million downfield from TMS. [b] Unlike most protonated aryl ketones, the *ortho*, *meta*, and *para* hydrogens of the ring are not well resolved.

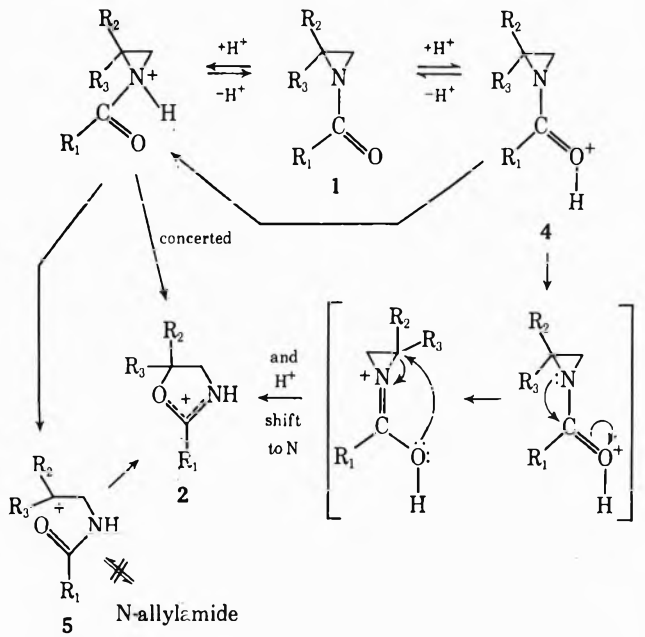
The resistance of oxazolinium ions **2a–2c** to H–D exchange is remarkable. When **1a–1c** rearrange in 96% D_2SO_4, other than at nitrogen, no H–D exchange occurs even after 14 hr at 120°. In 65% D_2SO_4, no H–D exchange has occurred after 10 min at 122°. Thus oxazolinium cations are similar to dioxolenium cations[12b] in their resistance to exchange but differ from 1-oxoniacyclopent-1-enyl cations[12a] in the H–D exchange propensity of the C-2 methyl group. Upon



heating **1a–1c** in 50% sulfuric acid, low molecular weight N-acylpolyethylenimine polymers are formed. Thus facile N-acylaziridine polymerization[4a,b,5,19,20] in the presence of proton acids appears to proceed by prior ring opening to oxazolinium ions.

Our results lead us to refine the Heine ring-opening mechanism[11] (Scheme II). O protonation of the

SCHEME II



acylaziridines[4] can be followed by concerted ring opening to an O-protonated oxazoline, which immediately converts into the observed oxazolinium ions (**2**). However, N-protonated acylaziridines could exist in equilibrium with O-protonated (**4**) or unprotonated (**1**) acylaziridines. The N-protonated species could rearrange directly by a concerted process to oxazolinium ions (**2**) or proceed through the short-lived carbonium ion **5**. The lack of H–D exchange during the rearrangement demonstrates that, if ion **5** has discrete existence, its lifetime is too short to permit equilibrium with the corresponding N-allylamides, which are known to cyclize to 2-oxazolines in acids.[21] N protonation is analogous to the proposed C protonation in acid-catalyzed ring opening of acylcyclopropanes.[22]

Experimental Section

Materials.—Aziridine and 2-methylaziridine were kindly donated by the Rohn and Haas Co. 2,2-Dimethylaziridine was prepared by the method of Fanta.[26] The 1-acetylaziridines were prepared by reaction of the appropriate aziridine with ketene,[24] and the 1-benzoylaziridines were prepared from the aziridines and benzoyl chloride as described by Stephens, *et al.*[25] Fluorosulfonic acid–antimony pentafluoride was purified as previously described.[26]

Nmr Spectra.—All spectra was recorded using a Varian HA-100 spectrometer with a variable-temperature probe. The chemical shifts are relative to tetramethylsilane as an internal standard (internal capillary).

Rearrangement of 1-Acylaziridines in Sulfuric Acid.—Carbon tetrachloride solutions containing *ca.* 10% of a 1-acylaziridine were added dropwise with rapid stirring to solutions of sulfuric acid at 15° or below. Sulfuric acid concentrations used were 80, 90, and 96%. In all cases portions of the solutions were quickly transferred to nmr tubes and the spectra were recorded. Spectral values at 33° of the oxazolinium ions produced in 90% sulfuric acid are compiled in Table I.

(17) L. M. Jackman, "Application of NMR Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p 87.

(18) (a) R. J. Gillespie, *Accounts Chem. Res.*, **1**, 202 (1968); (b) A. Commeyras and G. A. Olah, *J. Amer. Chem. Soc.*, **91**, 2929 (1959).

(19) J. W. Cornforth in "Heterocyclic Compounds," Vol. 5, C. R. Elderfield, Ed., John Wiley & Sons, Inc., New York, N Y., 1950, p 383.

(20) T. G. Basseri, A. Levy, and M. H. Litt [*Polymer Lett.* **5**, 871 (1967)] have reported polymerization of a wide variety of oxazolines to N-acylpolyethylenimines using a variety of Lewis and proton acids.

(21) R. H. Wiley and L. L. Bennett, *Chem. Rev.*, **44**, 447 (1949).

(22) C. U. Pittman and S. P. McManus, *J. Amer. Chem. Soc.*, **91**, 5915 (1969).

(23) P. E. Fanta, U. S. Patent 2,766,236 (Oct 9, 1956).

(24) P. E. Fanta and A. S. Deutsch, *J. Org. Chem.*, **23**, 72 (1958).

(25) W. D. Stephens, L. R. Moffett, H. W. Vaughn, W. E. Hill, and S. P. Brown, *J. Chem. Eng. Data*, **8**, 625 (1963).

(26) G. A. Olah, *J. Amer. Chem. Soc.*, **87**, 1103 (1965).

The oxazolines **3a–3e** were recovered in yields of 53–71% (Table I) by dropwise addition of the acid solution into excess, rapidly stirring aqueous sodium bicarbonate with continuous ether extraction.[1a] Each oxazoline was identified unequivocally by comparison with an authentic sample.[1a,24]

Proton Exchange Studies.—The exchange of the nitrogen proton of ions **2a–2e** in 65% sulfuric acid solution was determined by diluting solutions of the ions to the proper concentration and observing the disappearance of the previously observed nmr signal. The H–D exchange studies required monitoring of the nmr spectra and using peak integration as the measuring device.

Protonation of 1-Acylaziridine.—The aziridine derivatives **1a–1c** were each dissolved in sulfur dioxide and the resulting solutions were added to 1:1 fluorosulfonic acid–antimony pentafluoride at −70°. Their individual spectra were recorded at −55° (Table II).

Registry No.—**2a**, 23704-69-0; **2b**, 23704-70-3; **2c**, 23704-71-4; **2d**, 23704-72-5; **2e**, 23704-73-6; **4a**, 23402-58-6; **4b**, 23402-59-7; **4d**, 23402-60-0.

Acknowledgment.—The authors appreciate the assistance of Mr. J. T. Carroll in the preparation of some of the acylaziridines and thank Dr. C. O. Parker of the Rohm and Haas Co., Huntsville, Ala., for the gift of aziridine samples.

Nenitzescu Indole Synthesis with 2-Chloro-5-methylbenzoquinone

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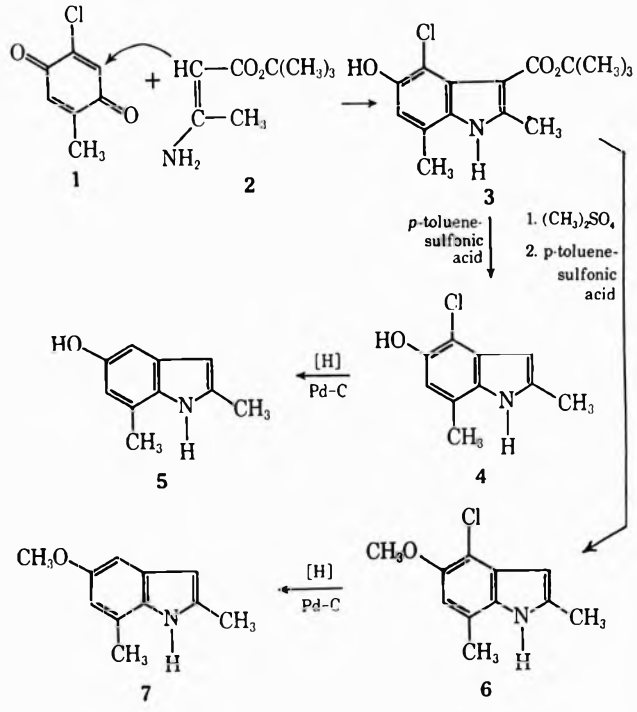
The reaction of aminocrotonate esters (*e.g.*, **2**) with *p*-quinones (*e.g.*, **1**) to form 5-hydroxy-3-carbalkoxyindoles (*e.g.*, **3**) proceeds *via* condensation of the terminal carbon of the enamine triad and one of the C=C carbons of the quinone system.[1,2] With unsymmetrically substituted quinones, the isomeric 5-hydroxyindole that is ultimately produced depends on which of the available double-bond carbons participates in this condensation. In the case of monosubstituted quinones, a 4-substituted 5-hydroxyindole product has been reported only with trifluoromethyl[3] and carbethoxy[4] qunone substituents. Such a product implies condensation of the enamine carbon at the *ortho* position in the quinone ring. With substituents such as alkyl,[1] halogen,[3] and alkoxy,[1] condensation occurs at the *para* or *meta* positions, and leads to 6-substituted and in some cases also 7-substituted 5-hydroxyindoles.

Since neither methyl nor chlorine leads to *ortho* condensation when substituted on the quinone ring, it was of some interest to investigate a Nenitzescu reaction with 2-chloro-5-methylbenzoquinone. In this case condensation would have to take place at an *ortho* position. From this condensation we have been able to detect only one isomer, the product of enamine condensation *ortho* to the chlorine substituent (namely, the 4-chloro-7-methyl isomer **3**), which was obtained in 51% yield. Proof of structure was provided by decarbalkoxylation and dechlorination (hydrogenolysis with Pd–C catalyst) to the known[1] 2,7-dimethyl-5-hydroxyindole (**5**). Although in this instance the dechlorination yield was low, a satisfactory yield (74%) was obtained with the 5-methoxy derivative **6** to give 2,7-dimethyl-5-methoxyindole (**7**). Thus, this procedure appears to offer a potentially useful synthetic method for the preparation of 2,7-dialkyl-5-oxyindoles.



Experimental Section[5]

***t*-Butyl 4-Chloro-5-hydroxy-2,7-dimethylindole-3-carboxylate (3).**—To a hot solution of 5-chloro-2-methyl-1,4-*p*-benzoquinone (**1**)[6] (3.12 g, 0.0199 mol) in glacial acetic acid (15 ml), *t*-butyl 3-aminocrotonate (**2**)[3] (3.14 g, 0.02 mol) was added. After 30 min without application of heat, the solution was cooled, and the resulting pink precipitate was filtered and washed with chilled acetic acid to give 2.99 g (51%) of **3**, mp 178–180° dec.

An analytical sample was obtained by elution from Florisil[7] (magnesia–silica gel adsorbent), followed by recrystallization from methylene chloride: mp 177–179°; λ_{max} 218, 248, 288 mμ (ε 27,300, 15,300, 885); ir 3.08, 6.0, 6.3, 7.05, 8.64, 8.9 μ; nmr, δ 1.53 [s, 9, C(CH$_3$)$_3$], 2.37 (s, 3, 7-CH$_3$), 2.47 (s, 3, 2-CH$_3$), 6.62 (broadened s, 1, 6-H), 8.97 (s, 1, OH), and 11.2 (broadened s, 1, NH) ppm.

Anal. Calcd for $C_{15}H_{18}ClNO_3$: C, 60.91; H, 6.13; Cl, 11.98; N, 4.73. Found: C, 61.14; H, 6.60; Cl, 11.78; N, 4.80.

4-Chloro-5-hydroxy-2,7-dimethylindole (4).—A magnetically stirred solution of *t*-butyl 4-chloro-5-hydroxy-2,7-dimethylindole-3-carboxylate (**3**) (2.99 g, 0.0101 mol) and *p*-toluenesulfonic acid (250 mg) in 250 ml of toluene was heated at reflux for 1 hr. The solution was cooled, filtered, and evaporated to dryness. The residue was dissolved in ethyl acetate and washed with dilute sodium bicarbonate solution and then with water. The organic

(1) G. R. Allen, Jr., C. Pidacks, and M. J. Weiss, *J. Amer. Chem. Soc.*, **88**, 2536 (1966).

(2) D. Raileanu and C. D. Nenitzescu, *Rev. Roum. Chem.*, **10**, 339 (1965); *Chem. Abstr.*, **63**, 9903 (1965).

(3) R. Littell and G. R. Allen, Jr., *J. Org. Chem.*, **33**, 2064 (1968).

(4) G. R. Allen, Jr., and M. J. Weiss, *ibid.*, **33**, 198 (1968).

(5) Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Ultraviolet spectra were determined in methanol solution with a Cary recording spectrophotometer, and infrared spectra were determined in potassium bromide disks with a Perkin-Elmer Model 21 spectrophotometer. The proton magnetic resonance spectrum was determined with a Varian A-60 spectrometer in dimethyl sulfoxide-*d*$_6$, using tetramethylsilane as an internal standard. Evaporations were done under reduced pressure.

(6) H. H. Hodgson and F. H. Moore, *J. Chem. Soc.*, 2036 (1926).

(7) Florisil is the trademark of the Floridin Co. for a magnesia–silica gel adsorbent.

phase was dried over magnesium sulfate and concentrated to a red oil. The oil was chromatographed on Celite[8] and the product, eluted with 10% ether–benzene, was recrystallized from ether–petroleum ether (bp 30–60°) to give 1.23 g (63%) of **4** as pink crystals: mp 111–113°; λ_{max} 218, 275 mμ (ε 22,500, 10,500); ir 2.9, 3.02, 6.5, 6.67, 8.15, 8.5 μ.

Anal. Calcd for $C_{10}H_{10}ClNO$: C, 61.34; H, 5.11; Cl, 18.14; N, 7.16. Found: C, 61.80; H, 5.46; Cl, 18.29; N, 7.34.

2,7-Dimethyl-5-hydroxyindole (5).—4-Chloro-5-hydroxy-2,7-dimethylindole (**4**) (392 mg, 2 mmol) and 40 ml of 0.1 *N* aqueous sodium hydroxide were shaken in a Parr low pressure hydrogenation apparatus with 500 mg of 10% palladium-on-charcoal catalyst, at an initial hydrogen pressure of 30 psi, until hydrogen uptake ceased. The reaction mixture was filtered, and the filtrate was acidified with dilute hydrochloric acid and then extracted with ethyl acetate. The combined extracts were dried over magnesium sulfate and concentrated to an oil, which was chromatographed on silica gel. The product was eluted with 5% ether–benzene. Recrystallization from methylene chloride–petroleum ether (bp 30–60°) gave near-white crystals, 58 mg (18%), mp 145–147°, undepressed on admixture of this substance with authentic **5**[1] and identical in ultraviolet and infrared spectrum.

***t*-Butyl 4-Chloro-2,7-dimethyl-5-methoxyindole-3-carboxylate.**—To a stirred solution of 15.5 g (0.0523 mol) of *t*-butyl 4-chloro-5-hydroxy-2,7-dimethylindole (**3**) in 96.3 ml of ethyl alcohol and 193 ml of 2 *N* sodium hydroxide solution was added dropwise over 1 hr 31.6 g (23.4 ml, 0.251 mol) of dimethyl sulfate. The mixture was heated at reflux temperature for 1.5 hr, cooled, diluted with water, and filtered, to give 13.1 g (80%) of product, mp 175–180°. A sample was recrystallized from ether to give crystals: mp 182–184° (gas evol); λ_{max} 221, 285 (shoulder), 285 mμ (ε 40,000, 17,100, 11,800); ir 3.05, 3.35, 6.00, 6.25, 6.85, 8.25, 8.6, 9.25 μ.

Anal. Calcd for $C_{16}H_{20}ClNO_3$: C, 62.03; H, 6.50; Cl, 11.47; N, 4.51. Found: C, 61.94; H, 6.65; Cl, 11.18; N, 4.32.

4-Chloro-2,7-dimethyl-5-methoxyindole (6).—A solution of 8.2 g (0.0266 mol) of *t*-butyl 4-chloro-2,7-dimethyl-5-methoxyindole-3-carboxylate and 600 mg of *p*-toluenesulfonic acid monohydrate in 900 ml of toluene was heated at reflux for 1 hr. The solution was cooled, filtered, and evaporated to dryness. The residue was chromatographed on silica gel, and elution of product with benzene gave 4.13 g (74.5%) of product melting at 132–136°. A sample was recrystallized from ether–petroleum ether (bp 30–60°) to give crystals: mp 139–140°; λ_{max} 221, 278 mμ (ε 28,800, 10,300); ir 2.9, 3.44, 6.26, 7.3 μ.

Anal. Calcd for $C_{11}H_{12}ClNO$: C, 62.99; H, 5.76; Cl, 16.92; N, 6.67. Found: C, 62.81; H, 5.64; Cl, 16.65; N, 6.98.

2,7-Dimethyl-5-methoxyindole (7).—4-Chloro-2,7-dimethyl-5-methoxyindole (**6**) (419.4 mg, 2 mmol), 392 mg (4 mmol) of potassium acetate and 480 mg of 10% palladium-on-charcoal in 50 ml of ethyl alcohol was shaken in a Parr low pressure hydrogenation apparatus at an initial hydrogen pressure of 30 psi until hydrogen uptake ceased. The reaction mixture was filtered and concentrated. The residue was partitioned between methylene chloride and water. The organic phase was separated, and washed several times with water, dried, and evaporated. The residue was crystallized from ether–petroleum ether (bp 30–60°) to give 257 mg (73.5%) of crystals, mp 73–75°, undepressed on admixture of this substance with authentic 2,7-dimethyl-5-methylindole (**7**), prepared as described below, and identical in ultraviolet and infrared spectrum.

2,7-Dimethyl-5-methoxyindole (7).—To a stirred solution of 26.4 g (0.163 mol) of 2,7-dimethyl-5-hydroxyindole (**5**),[1] 297 ml of ethanol and 595 ml of 2 *N* sodium hydroxide solution was added dropwise, under nitrogen, 73.3 ml of dimethyl sulfate (0.785 mol) over a period of 1 hr. The reaction mixture was then heated at reflux for 1 hr, cooled, diluted with water, and extracted with ethyl acetate. The combined extracts were washed with saline, dried over magnesium sulfate, and concentrated. The residue was dissolved in benzene and passed through a magnesia–silica column using benzene as the eluting solvent. The initial 1200 ml of eluate was evaporated to give 23 g (78%) of yellow oil, which crystallized on standing. A sample was recrystallized from ether–petroleum ether (30–60°) to give near white crystals: mp 76–77°; λ_{max} 215, 272 mμ (ε 19,200, 8570); ir 3.0, 3.45, 6.25, 6.73, 8.36, 9.55 μ.

(8) Celite is the trademark of the Johns-Manville Corp. for diatomaceous earth.

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.10; H, 7.31; N, 7.67.

Registry No.—**1**, 19832-87-2; **3**, 23386-23-4; **4**, 23386-24-5; **6**, 23386-25-6; **7**, 23386-26-7; *t*-butyl 4-chloro-2,7-dimethyl-5-methoxyindole-3-carboxylate, 23386-27-8.

Acknowledgment.—We are indebted to Mr. L. Brancone and his staff for the microanalyses and to Mr. W. Fulmor and his associates for the spectral data.

Reductive Cleavage of Ferrocene Derivatives

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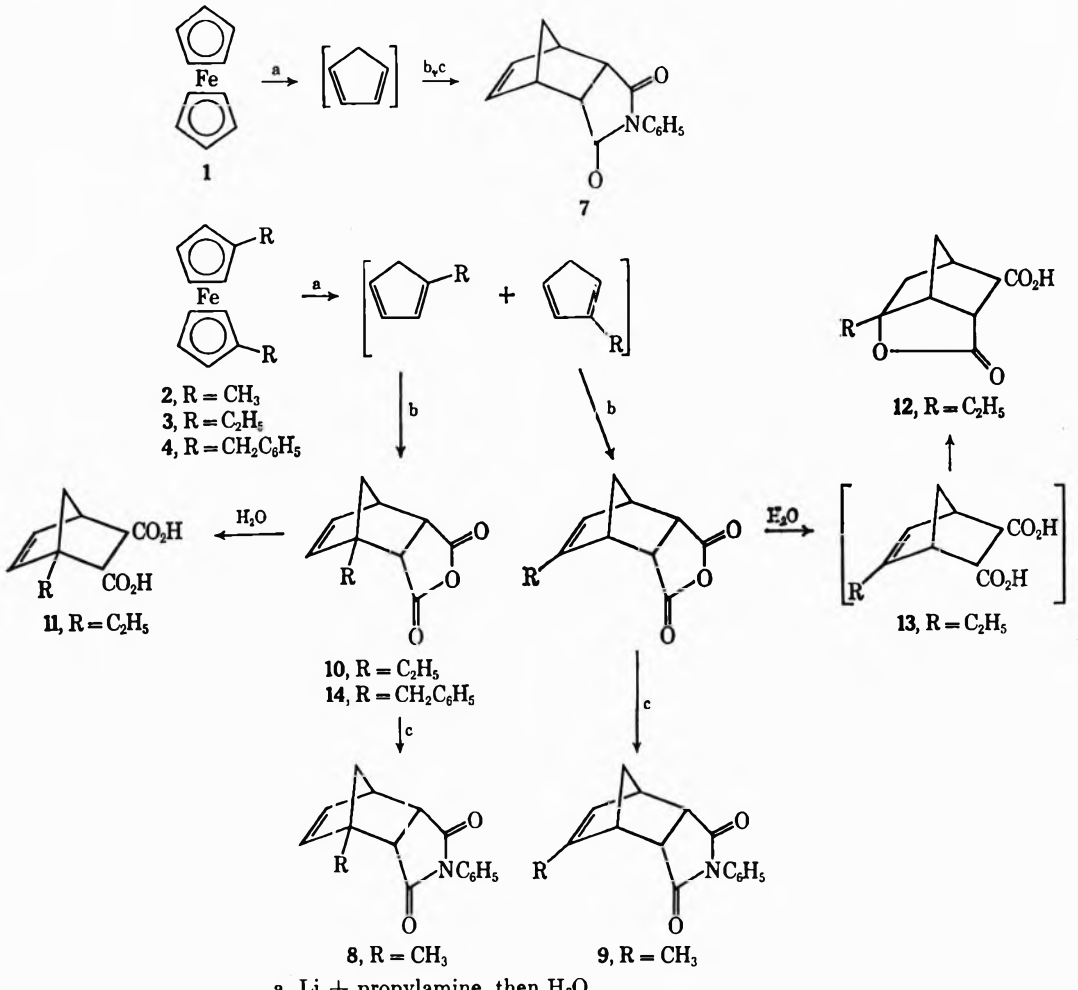
Received July 22, 1969

Ferrocene (**1**) and a number of ferrocene derivatives have been subjected to reduction by solutions of metals in amines.[1] As part of our research in ferrocene chemistry, we were interested in studying factors influencing the ease of reduction of substituted ferrocenes and in identifying the isomers of substituted cyclopentadienes obtainable by reductive cleavage of 1,1′-dialkylferrocenes. We subjected three symmetrically substituted dialkylferrocenes, 1,1′-dimethyl- (**2**), 1,1′-diethyl- (**3**), and 1,1′-dibenzylferrocene (**4**), and two ferrocenophanes, [3]ferrocenophane (**5**) and [3][3]-1,3-ferrocenophane (**6**), as well as **1**, to reduction by Li in propylamine (Scheme I). We assumed originally that reduction of each dialkyl compound would lead to three alkylcyclopentadienes and that these could be identified as 1-, 5-, or 7-substituted norbornene derivatives by preparing Diels–Alder adducts with maleic anhydride. However, we found no 7-substituted norbornenes and, in the case of 1,1′-dibenzylferrocene, only the 1-benzylnorbornene derivative, which arises from 2-benzylcyclopentadiene, was found. After reduction and quenching, **1** gave cyclopentadiene which was converted into N-phenyl-5-norbornene-2,3-dicarboximide (**7**) by treatment with maleic anhydride and then acetyl chloride, followed by aniline. Similarly, **2** gave a mixture of 2- and 3-methylcyclopentadienes which were characterized as 1- and 5-methyl-N-phenyl-5-norbornene-2,3-dicarboximides (**8** and **9**). The reduction of **3** and subsequent treatment of the reaction product with maleic anhydride led to 1-ethyl-5-norbornene-2,3-dicarboxylic anhydride (**10**), the corresponding dicarboxylic acid (**11**), and a lactonic acid, mp 157.5–158°, which proved to be 5-ethyl-5-hydroxynorbornane-2,3-dicarboxylic acid γ-lactone (**12**) indicating the formation of 2- and 3-ethylcyclopentadiene only. The preparation of 5-ethyl-5-norbornene-2,3-dicarboxylic acid (**13**), mp 156°, has been reported,[2] but, since its structure was not proved and since the

(1) (a) D. S. Trifan and L. Nichols, *J. Amer. Chem. Soc.*, **79**, 2746 (1957). (b) J. M. Osgerby and P. L. Pauson, *J. Chem. Soc.*, 4604 (1961). (c) A. N. Nesmeyanov, *et al.*, *Dokl. Akad. Nauk SSSR*, **160**, 137 (1965); **177**, 586 (1967). (d) G. W. Watt and L. J. Baye, *J. Inorg. Nucl. Chem.*, **26**, 2099 (1964). (e) D. W. Slocum and W. E. Jones, *J. Organometal. Chem.*, **15**, 262 (1968).

(2) K. Alder and H.-J. Ache, *Chem. Ber.*, **95**, 503 (1962).

SCHEME I



a, Li + propylamine, then H_2O
b, maleic anhydride
c, aniline, then acetic anhydride + potassium acetate

diacid obtained from 5-methyl-5-norbornene-2,3-dicarboxylic anhydride also undergoes spontaneous lactone formation,[3] we believe that the reported diacid **13**[2] was in fact the lactonic acid **12**.

When our reduction procedure was applied to **4**, only one product, 1-benzyl-5-norbornene-2,3-dicarboxylic anhydride (**14**), could be isolated after treatment with maleic anhydride, indicating that 2-benzylcyclopentadiene was the only isomer formed.

Yields of norbornene derivatives in the cases in which two isomers were formed were quite low since significant losses occurred in the difficult separation and purification steps. More important to us was the degree of degradation of the variously substituted ferrocenes and our experiments indicate that steric effects play a major role in the ease with which reduction occurs. Thus, **1** and **2** were degraded to the extent of 77 and 70% respectively, while **3** (34%) and **4** (45%) proved to be more resistant to reduction. The reduction of **5** was evidenced in the reaction mixture by evolution of heat and deposition of metallic iron, but no well-defined monomeric addition products with maleic anhydride, N-phenylmaleimide, or tetracyanoethylene could be isolated. Based on starting material recovered (67%), **5** is somewhat more resistant to reduction than any of the simple dialkylferrocenes studied. In contrast, no reaction was observed when the reduction was tried with **6**, similar to results reported by Schlögl[4] and Ellis,[5] and this compound was recovered quantitatively from the reaction mixture.

The failure of **6** to react could be due to the constricting effect[6] of the two bridging groups which tend to displace the rings from their equilibrium separation distance toward one another, effectively trapping the iron in a strained hydrocarbon cage. This results in a large reduction potential, probably associated with steric constriction of the transition state for such a process. We expect that [*m*][*n*]ferrocenophanes where *m* and *n* are greater than 3 should be more easily reduced and experiments are planned to explore this idea.

Experimental Section[7]

Ferrocene and Ferrocene Derivatives.—Ferrocene and 1,1′-dimethylferrocene were obtained from Arapahoe Chemical Co. and were purified by column chromatography or sublimation

(3) V. A. Mironov, E. V. Sololev, and A. N. Elizarova, *Tetrahedron*, **19**, 1939 (1963).

(4) Karl Schlögl, Annual Summary Report No. 3, March 1963, U. S. Air Force Contract No. 61 (052)-383, Air Force Materials Laboratory.

(5) A. F. Ellis, Ph.D. Dissertation, Part II, University of Illinois, Urbana, Ill., 1963.

(6) N. D. Jones, R. E. Marsh, and J. H. Richards, *Acta Crystallogr.*, **19**, 330 (1965).

(7) Melting points were taken on a Kofler hot stage and are uncorrected. Nmr spectra were determined in $CDCl_3$ on a Varian A-60 instrument with tetramethylsilane as an internal reference, and infrared spectra were recorded using a Beckman IR-4 spectrophotometer. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

prior to use. 1,1′-Diethyl-[8] and 1,1′-dibenzylferrocene,[8] [3]ferrocenophane,[9] and [3][3]-1,3-ferrocenophane[9] were prepared by reported procedures.

Reductive Cleavage Reactions.—The usual procedure was to stir 3–5 g of the ferrocene derivative in 30 ml of *n*-propylamine with 1.0–1.6 g of Li wire cut into two or three pieces. Except in the case of **6**, each reaction mixture darkened and boiled spontaneously after a few minutes. Stirring was continued for several hours at room temperature; then the mixtures were diluted with benzene and poured into ice–water. The aqueous layer was added slowly to ice–water containing excess HCl and extracted twice more with benzene. The combined benzene solutions were dried ($MgSO_4$), treated with maleic anhydride, and slowly distilled to dryness on a steam bath to give a mixture of the Diels–Alder adduct and starting material. Separation and purification were accomplished in two different ways as described in the following paragraphs.

N-Phenyl-5-norbornene-2,3-dicarboximide (7) from Ferrocene (1).—The crude product obtained from **1** (3.00 g, 16.1 mmol), 1.63 g of Li, and 2.7 g of maleic anhydride was taken up in acetyl chloride, refluxed for 1 hr, and evaporated; the residue was dissolved in a small volume of benzene and then treated with 2.6 ml of aniline. After 1 hr at room temperature, the mixture was evaporated and the residue was heated for 0.5 hr on the steam bath with 30 ml of acetic anhydride and 2.9 g of anhydrous sodium acetate. This suspension was diluted with benzene, washed thoroughly with water, dried ($MgSO_4$), concentrated, and chromatographed on silica gel. The first fraction eluted with benzene was rechromatographed on Al_2O_3 and gave 0.70 g of **1** (23.3%) and 2.43 g of **7**. Following fractions after rechromatographing (Al_2O_3) yielded 2.19 g of **7**; the total yield of **7** was 4.62 g (59.8%). Recrystallization from methylene chloride–hexane gave pure **7** as white needles: mp 142.5–144.5° (lit.[10] mp 144°); ir (mull) 5.63, 5.82 μ (C=O); nmr τ 8.67–8.21 (m, 2, CH_2), 6.69–6.42 (m, 4, CH), 3.83–3.61 (m, 2, CH=CH), 2.98–2.40 (m, 5, C_6H_5).

1- and 5-Methyl-N-phenyl-5-norbornene-2,3-dicarboximide (8 and 9) from 1,1′-Dimethylferrocene (2).—From **2** (3.46 g, 16.2 mmol), 1.55 g of Li, and 3.0 g of maleic anhydride by the procedure described for **1** was obtained 8.78 g of a thin red oil which was chromatographed on SiO_2. Elution with hexane yielded starting material (1.03 g, 29.7%), with 1:1 hexane–benzene, N-phenylmaleimide, and with benzene, a mixture of **8** and **9**, whose separation required rechromatographing (Al_2O_3) several times followed by recrystallization from methylene chloride–hexane or hexane alone before reasonably pure materials could be isolated. Isomer **8** was isolated: mp 168–180° (lit.[11] mp 179–180°); ir ($CHCl_3$) 5.54, 5.77 μ (C=O); nmr τ 8.38 (m, 5, CH_2 and CH_3), 6.95–6.33 (m, 3, CH), 4.03–3.60 (m, 2, CH=CH), 2.99–2.34 (m, 5, C_6H_5) (lit.[11] τ 8.40, 3.93). The 5-methyl isomer, **9**, was isolated in approximately the same purity: mp 116–122.5° (lit.[11] mp 128–129.5°); ir ($CHCl_3$) 5.54, 5.76 μ (C=O); nmr τ 8.67–8.06 (m, 5, CH_2 and CH_3), 6.76–6.40 (m, 4, CH), 4.22 (m, 1, C=CH), 3.00–2.33 (m, 5, C_6H_5) (lit.[11] τ 8.18, 4.24).

1-Ethyl-5-norborene-2,3-dicarboxylic Anhydride (10), 1-Ethyl-5-norbornene-2,3-dicarboxylic Acid (11), and 5-Ethyl-5-hydroxynorbornane-2,3-dicarboxylic Acid γ-Lactone (12) from 1,1′-Diethylferrocene (3).—Compound **3** (4.55 g, 18.8 mmol), 1.30 g of Li, and 3.0 g of maleic anhydride were allowed to react by the usual procedure to give the crude maleic anhydride adduct which was heated for 2 hr on the steam bath with 75 ml of 2 *N* Na_2CO_3 solution and then extracted three times with 100 ml of methylene chloride. From these extracts was recovered 3.01 g (66.2%) of starting material (chromatographed on Al_2O_3, eluted with hexane). After acidification with 4 *N* HCl, the clear aqueous solution was concentrated under vacuum and extracted three times with 100 ml of methylene chloride to give 5.01 g of crude products. These were separated by fractional crystallization from cyclohexane, cyclohexane–hexane, and methylene chloride–hexane into three components, **10**, **11**, and **12**. Characteristics of **10** follow: mp 64–66° (hexane) (lit.[12] mp 65–66°); ir ($CHCl_3$) 5.37, 5.61 μ (C=O); nmr τ 8.96 (t, 3, CH_3CH_2), 8.67–7.66 (m, 4, CH_3CH_2 and ring CH_2), 6.78–6.13 (m, 3, CH), 3.97–3.60 (m, 2, CH=CH). Those of **11** follow: mp 126–128.5° (methylene chloride–hexane or H_2O) (lit. mp 131–132°,[12] 136° [2]); ir ($CHCl_3$) 5.80 μ (C=O); nmr τ 9.25–7.90 (m, 7, CH_3CH_2 and ring CH_2; discernible are a triplet and quartet from the ethyl group, J = 7.3 Hz), 6.99–6.33 (m, 3, CH), 4.06–3.63 (m, 2, CH=CH), chemical shift variable with concentration (s, 2, OH); equiv wt (titration) 107, calcd 105. Those of **12** follow: mp 157.5–158°; ir (mull) 5.62 (C=O, lactone), 5.80 μ (C=O, acid); nmr (Na salt in D_2O) τ 9.07 (t, 3, CH_3CH_2), 8.65–7.93 (m, 6, CH_2), 7.60–6.84 (m, 4, CH).

Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71; mol wt, 210. Found: C, 62.48; H, 6.53; mol wt (titration), 205.

1-Benzyl-5-norbornene-2,3-dicarboxylic Anhydride (14) from 1,1′-Dibenzylferrocene (4).—Compound **4** (3.08 g, 8.4 mmol) and 0.92 g of Li wire were stirred for 7.5 hr in 30 ml of propylamine and subjected to the standard work-up. The resulting dried benzene solution containing benzylcyclopentadiene was treated with 1.5 g of maleic anhydride, concentrated on the steam bath, extracted five times with 50 ml of water (which yielded 0.57 g of maleic acid) and evaporated to dryness. The residue was heated 3.5 hr at 107° with 50 ml of 2 *N* Na_2CO_3 solution and the resulting suspension was extracted thoroughly with methylene chloride from which was recovered 1.63 g of **4** (52.9%). The alkaline solution was acidified with 2 *N* HCl and extracted with methylene chloride to give 2.14 g of crude acid (46.7%, calcd for benzylnorbornenedicarboxylic acid).

This acid was converted into its anhydride by refluxing for 1 hr with 25 ml of acetyl chloride. The solution was evaporated to dryness and the residue was extracted several times with hot hexane. The concentrated extracts, upon cooling, gave white crystals which were purified by recrystallization from ethyl acetate: mp 121–122.5° (lit.[13] mp 123°); ir ($CHCl_3$) 5.34, 5.58 μ (C=O); nmr τ 8.75–8.17 (m, 2, ring CH_2), 6.89–6.42 (m, 5, CH and benzyl CH_2), 3.88–3.60 (m, 2, CH=CH), 2.72 (s, 5, C_6H_5).

Attempted cleavage of [3]Ferrocenophane (5) and [3][3]-1,3-Ferrocenophane (6).—Attempted cleavage of **5** gave an intractable mixture whereas **6**, when subjected to similar reaction conditions, remained unchanged.

Registry No.—**1**, 102-54-5; **2**, 1291-47-0; **3**, 1273-97-8; **4**, 12114-61-3; **5**, 12402-44-7.

Acknowledgment.—We thank Mr. J. L. Pflug and Mrs. Antoinette Austin for assistance in taking spectra.

(8) K. Schlögl, A. Mohar, and M. Peterlik, *Monatsh. Chem.*, **92**, 921 (1961).

(9) K. L. Rinehart, Jr., D. E. Bublitz, and D. H. Gustafson, *J. Amer. Chem. Soc.*, **85**, 970 (1963).

(10) M. S. Morgan, R. S. Tipson, W. E. Baldwin, and A. Lowy, *ibid.*, **66**, 404 (1944).

(11) S. McLean and P. Haynes, *Tetrahedron*, **21**, 2313 (1965).

(12) R. Riemschneider, E. Reichelt, and E.-B. Grabitz, *Monatsh. Chem.*, **91**, 812 (1960).

(13) K. Alder and H. Holzrichter, *Justus Liebigs Ann. Chem.*, **524**, 145 (1936).

Quantitative Deuteration of a Grignard Reagent. The Preparation of 2-Butene 2-d_1

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Received August 1, 1969

In connection with a recent study of a photocycloaddition reaction,[1] a sample of 2-butene-2-d_1 was desired in which the label was introduced not only specifically but quantitatively. Quenching of the appropriate Grignard reagent appeared a good method of preparation; however, in our hands other prepartions had given less than quantitative introduction of label.[2] Also, Pocker and Exner,[3] in a careful study, had noted that phenyl- and benzyllithium and magnesium com-

(1) R. A. Caldwell, *J. Amer. Chem. Soc.*, in press.

(2) R. A. Caldwell and G. W. Sovocool, unpublished work.

(3) Y. Pocker and J. H. Exner, *J. Amer. Chem. Soc.*, **90**, 6764 (1968).

pounds gave 75–95% deuteration when quenched with D_2O, depending on conditions. This note describes the preparation of the title compound in almost quantitative isotopic purity.

It has long been known[4] that there is some intermediate in the formation of Grignard reagents from halides that behaves like a free radical. Thus, coupling and disproportionation products arise in appropriate cases (eq 2 and 3). I suggest that the reaction of eq 4,

$$RX + Mg(s) \longrightarrow R\cdot \quad (1)$$

$$2R\cdot \longrightarrow R_2 \quad (2)$$

$$2RCH_2CH_2\cdot \longrightarrow RCH{=}CH_2 + RCH_2CH_3 \quad (3)$$

$$R\cdot + (CH_3CH_2)_2O \longrightarrow RH + CH_3\dot{C}HOCH_2CH_3 \quad (4)$$

abstraction of a hydrogen from ether, is the reaction that is primarily responsible for incomplete label introduction. I believe that in any event the isotopic contamination occurs prior to quenching, as implied by Pocker and Exner.[3] A simple solution to the problem then appeared: *the separation of the RH species from the Grignard reagent after formation but before quenching.*

The preparation of 2-butenylmagnesium bromide in tetrahydrofuran was effected by standard procedures. The reaction mixture was then heated until a few milliliters of the solvent had distilled out, and with it any 2-butene that had been formed. Quenching of the reaction mixture then gave evolution of 2-butene-2-d_1 as a mixture of 90% *trans* and 10% *cis*, which could be trapped at −80°. It was analyzed by nmr as 100 ± 2% monodeuterated in the vinyl position (relative to 6 H in the methyls) and as 99.03% d_1, 0.81% d_0, and 0.16% d_2 by mass spectrometry at low voltage. Since the D_2O used was 99.82 at. % deuterated, and a small isotope effect on quenching can be expected,[3] only about 0.5% adventitious unlabeled material was present.

The present preparation suggests that development of separation procedures will enable quantitative deuteration of liquids and solids as well. The separation is, however, particularly simple for gaseous products.

Experimental Section

Bromine (40 g) in methylene chloride (75 ml) was stirred at 0° and gaseous *cis*-2-butene (Matheson CP, 99% *cis*, 1% *trans*) was added until decolorization occurred. The solvent was removed on a rotary evaporator and the crude dibromobutane was added to 100 ml of ethylene glycol containing the theoretical amount of 85% KOH (16.5 g). The solution was heated in a round-bottom flask to which a small Vigreux column was attached. Reaction occurred, and a mixture of the desired 2-bromo-2-butene and water distilled over. The material boiling below 95° was dried over anhydrous potassium carbonate and redistilled. A center cut, bp 82–86° (lit.[5] bp 85.55° for *trans*-2-bromo-2-butene), weighed 16.3 g (48%) and was used immediately in the next step.

Tetrahydrofuran (50 ml) was distilled from ethylmagnesium bromide directly into a dropping funnel and a three-necked flask. Formation of the Grignard reagent from the 2-bromo-2-butene under nitrogen in the standard manner required some heating until initiation occurred. At the end of the reaction, the mixture was again brought to reflux and several milliliters of the reaction mixture distilled out. The vessel was then fitted with a series of two dewar condensers, the first filled with an ice water bath and the second with Dry Ice–acetone. Deuterium oxide was added, and the condensate from the second dripped into a receiver cooled with Dry Ice–acetone. Removal from residual solvent by bulb-to-bulb distillation from Dry Ice–acetone to liquid nitrogen on a vacuum line afforded 2-butene (about 7 ml of liquid at 0°, 65%) that was free of any impurity detectable by nmr. It was analyzed by vpc on a 10% $AgNO_3$–15% benzyl cyanide column as 90% *trans*–10% *cis*.

Registry No.—2-Butene-2-d_1, 23042-68-4.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work through Grant 3031-A4.

(4) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," New York, N. Y., Prentice-Hall, Inc., 1954, pp 7, 59 ff.

(5) M. Lepingle, *Bull. Soc. Chim. Fr.*, **39**, 741 (1926).

Reaction of *p*-Tolylsulfonylmethylmagnesium Bromide with Ethyl Cinnamate

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Received July 16, 1969

In a previous paper from this laboratory, it was shown that *p*-tolylsulfonylmethylmagnesium bromide (I) added 1,2 but not 1,4 to a variety of α,β-unsaturated aldehydes and ketones.[1] To test the generality of 1,2 addition of sulfonyl Grignard reagents, the reaction of I and ethyl cinnamate (II) was studied. Some reactions of I with the methyl ester of cinnamic acid were also carried out and the results were similar.

Kohler and coworkers extensively studied the reactions of methyl and ethyl cinnamate with phenylmagnesium bromide.[2] The products were predominantly (>80%) those from 1,4 addition, along with small amounts of ketone.

$$C_6H_5CH{=}CHCO_2R + C_6H_5MgBr \longrightarrow (C_6H_5)_2CHCH_2CO_2R + (C_6H_5)_2CHCH_2COC_6H_5 \quad (1)$$
$$R = CH_3 \text{ or } C_2H_5$$

The addition of phenylmagnesium bromide to other esters has also been shown to give 1,4-addition products.[3,4] Methylmagnesium iodide, however, gave 1,2 addition to methyl cinnamate, affording the unsaturated tertiary alcohol.[2]

Allyl Grignard reagents have been reported to give low yields of tertiary alcohols arising from 1,2 addition.[5] Apparently other products were not isolated. The esters used were of the acrylate and crotonate types. Vinyl Grignard reagents were found to react with ethyl cinnamate giving ketone from 1,2 addition, followed by 1,4 addition of a second molecule of organometallic.[6] The reported yields were low.

$$C_6H_5CH{=}CHCO_2C_2H_5 + CH_3CH{=}CHMgBr \longrightarrow C_6H_5CH{=}CHC(=O)CH_2CH(CH_3)CH{=}CH_2 \quad (2)$$

(1) J. W. McFarland and D. N. Buchanan, *J. Org. Chem.*, **30**, 2003 (1965).

(2) E. P. Kohler and G. Heritage, *Amer. Chem. J.*, **33**, 21 (1905).

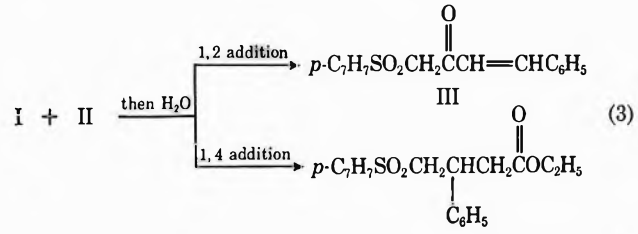
(3) E. P. Kohler and G. Heritage, *ibid.*, **34**, 568 (1906).

(4) G. P. Reynolds, *ibid.*, **46**, 198 (1911).

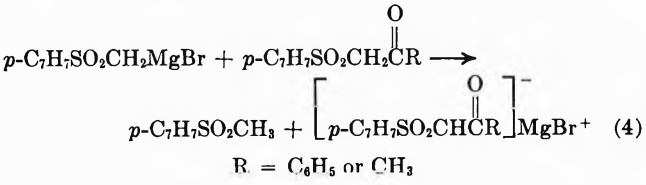
(5) I. N. Nazarov and A. I. Kakhniashvili, *Sb. Statei Obshch. Khim.*, **2**, 919 (1954); *Chem. Abstr.*, **49**, 6848*b* (1955).

(6) C. Lumbroso and P. Maitte, *Bull. Soc. Chim. Fr.*, **2**, 315 (1965).

Two distinct products would be possible from the reaction of I and II, one from a 1,2-addition reaction and the other from 1,4 addition. It was not expected that ketone III would add a molecule of I in the conventional sense because Field and coworkers[7] had shown that the following reaction takes place.



(3)



(4)

In this paper we shown that the product from the reaction of I and II is always III. There was no evidence for 1,4 addition over a I/II ratio of 3:1 to 1:2 and a temperature range of 0–80°. Consistent with Field's results, the yield of III was less than the possible 50% when a 1:1 ratio of Grignard reagent and ester was used. Furthermore, one-half of the methyl *p*-tolyl sulfone and one-half of the ethyl cinnamate should be recovered. Our results approximated those predictions. The low yields of III in some cases may have been due to difficulty in the separation of mixtures. Fractional crystallization was found better for separating III from sulfone and unreacted II than was chromatography on alumina.

In conclusion, sulfonyl Grignard reagents undergo only 1,2 additions to cinnamate esters. This behavior is analogous to the reactions of I with α,β-unsaturated aldehydes and ketones. The sulfonyl Grignard reagent resembles vinyl Grignard reagents more than it does phenylmagnesium bromide in its reactions with cinnamate esters. The possible reasons for exclusive 1,2 addition have already been discussed.[1]

Experimental Section

Reaction of *p*-Tolylsulfonylmethylmagnesium Bromide (I) with Ethyl Cinnamate (II).—The *p*-tolylsulfonylmethylmagnesium bromide (I) was prepared from 12.75 g (0.075 mol) of methyl *p*-tolyl sulfone[8] by the procedure used previously.[1] To the slurry of I in ether–benzene was added during 20 min at room temperature 13.47 g (0.077 mol) of II in 80 ml of dry benzene. After the mixture was stirred an additional 4 hr at room temperature, hydrolysis was effected with 100 ml of cold 1 *N* HCl solution. Removal of solvent *in vacuo* gave 22.7 g of greasy solid, mp 70–80°. Recrystallization from benzene–petroleum ether afforded 6.4 g (28.4%) of white needles, mp 115–119°. Further recrystallization gave 1-(*p*-tolylsulfonyl)-4-phenyl-3-buten-2-one (III) with constant mp 127–128°. Ir and nmr spectroscopy confirmed the structure of III.

Anal. Calcd for $C_{17}H_{16}O_3S$: C, 68.00; H, 5.33; S, 10.67. Found: C, 67.86; H, 5.21; S, 10.82.

The addition of 2 vol. of petroleum ether to the filtrate gave 6.60 g (51.8%) of recovered methyl *p*-tolyl sulfone, mp 73–78°. Recrystallization from ethanol–water gave pure sulfone, mp 85–86°, which did not depress the melting point of an authentic sample.

Removal of solvent and distillation of the residue afforded 9.28 g (68.5% recovery) of unreacted ethyl cinnamate (II), bp 66–69° (0.10 mm). The ir spectrum was identical with that of starting material.

In other reactions at various temperatures and I/II ratios, the maximum yield of III (86.6%) was obtained at room temperature with a I/II ratio of 2:1.

Registry No.—I, 3048-28-0; II, 103-36-6; III, 23042-70-8.

Acknowledgment.—The authors wish to thank the donors of the Petroleum Research Fund for the PRF Grant No. 2571-B which partially supported this investigation.

(7) L. Field, J. E. Lawson, and J. W. McFarland, *J. Amer. Chem. Soc.*, **78**, 4389 (1956).

(8) R. Otto, *Ber.*, **18**, 161 (1885).

Ring Inversion of Perfluoro-1,4-dithiane[1]

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Received September 2, 1969

Interconversion of chair conformations of six-membered rings containing two identical heteroatoms has been much studied by the nmr method,[3] with the exception of the 1,4-dithiane system. The results so far obtained for 1,2- and 1,3-dithianes in comparison with those of dioxanes and the corresponding diaza systems suggest that this barrier should be readily measureable by the nmr method. We are concerned here with the ring inversion of octafluoro-1,4-dithiane (1).

The ^{19}F nmr spectrum of 1, kindly supplied by Dr. B. C. McKusick of the Central Research Department of E. I. du Pont de Nemours and Co., in 2:1 (v/v) acetone–chloroform at 70° is a single line of half band width of *ca.* 1.8 Hz, 71.8 ppm downfield from internal hexafluorobenzene. At −90°, the spectrum appears as an AB quartet, each line of which shows small additional splittings, centered 70.0 ppm downfield from internal hexafluorobenzene. The chemical-shift difference between the A and B parts is 15.02 ppm and J_{AB} is 230 Hz. The quartet coalesces to a broad singlet at −32°. To gain information about the barrier to inversion, spectra were recorded at 23 temperatures between −62 and 17°.

A series of spectra, calculated as a function of τ, the average lifetime spent in either chair confirmation, was generated by standard procedures[4] and compared with the experimental spectra to obtain a value of τ for each temperature. The variation of the rate constant k_{inv} $(= 1/\tau)$ for interconversion of chair conformations with temperature gave the free energy of activation ($\Delta G^{\ddagger}$) as 10.05 ± 0.10 kcal/mol at −32°, the enthalpy of activation ($\Delta H^{\ddagger}$) as 9.74 ± 0.20 kcal/mol, and the entropy of activation ($\Delta S^{\ddagger}$) as −1.2 ± 1 eu.

(1) Supported by the National Science Foundation.

(2) Harkness Fellow of the Commonwealth Fund of New York, 1966–1968. Chemistry Department, University College, Gower Street, London, W.C. 1.

(3) G. Binsch in "Topics in Stereochemistry," Vol. 3, E. L. Eliel and N. L. Allinger, Ed., Interscience Publishers, Inc., New York, N. Y., 1968, p 97, provides an excellent review.

(4) J. T. Gerig and J. D. Roberts, *J. Amer. Chem. Soc.*, **88**, 2791 (1966).

The barrier to ring inversion for **1** is slightly smaller than those of 1,2-dithiane, 11.6 kcal/mol,[5] and 1,3-dithiane, 10.4 kcal/mol,[6] although it would hardly be tenable to draw very detailed conclusions concerning dithiane itself from the results for **1**. On the basis of the fluorine chemical-shift differences at −90°, which compare reasonably well with those for noninverting (or slowly inverting) *gem*-fluorocyclohexanes,[7] we have assumed that the preferred conformation of **1** is a chair—possibly strongly puckered as for 1,4-dithiane.[8]

Registry No.—**1**, 710-65-6.

Acknowledgment.—We are grateful to Mr. J. E. Leininger for assistance with the computing.

(5) C. Claesen, G. M. Androes, and M. Calvin, *J. Amer. Chem. Soc.*, **82**, 4428 (1960).

(6) H. Friebolin, S. Kabuss, W. Maier, and A. Luttringhaus, *Org. Magnetic Resonance*, **1**, 67 (1969).

(7) Cf. G. A. Yousif and J. D. Roberts, *ibid.*, **90**, 6428 (1968), and references cited therein.

(8) J. B. Lambert, *J. Amer. Chem. Soc.*, **89**, 1836 (1967); J. B. Lambert, R. E. Carhart, and P. W. R. Corfield, *ibid.*, **91**, 3567 (1969).

Observations Related to the Preparation of 2-Phenyliodoniobenzoate

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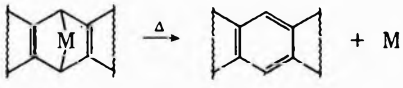
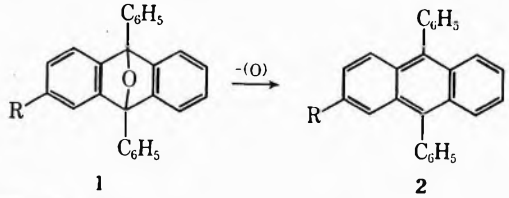
Received September 15, 1969

Several M-bridged polycyclic systems are known to undergo thermally induced extrusion of the bridging elements with concomitant formation of an aromatic system. When this operation is conducted in the



presence of a reagent to trap M, it frequently constitutes a synthetically useful process.[1] With this notion in mind, we investigated the thermolysis of 9,10-epoxy-9,10-diphenyl-9,10-dihydroanthracene (**1**, R = H), a compound previously reported to undergo thermal decay, ostensibly in accord with the above-mentioned principle, to produce 9,10-diphenylanthracene (**2**, R = H), although the fate of the oxygen bridge was not established.[2]



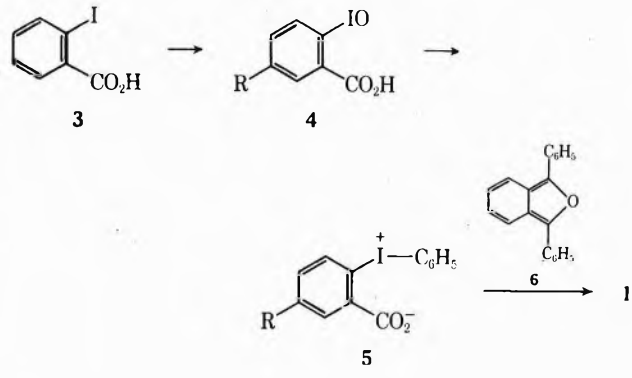
1 **2**

(1) *Inter alia*, diimide (M = HNNH), E. J. Corey and W. L. Mock, *J. Amer. Chem. Soc.*, **84**, 685 (1962); dimethylsilylene [M = $Si(CH_3)_2$], H. Gilman, S. S. Cottis, and W. H. Atwell, *ibid.*, **86**, 1596 (1964); singlet oxgen, H. H. Wasserman, and J. R. Scheffer, *ibid.*, **89**, 3073 (1967); tetramethyldisilene, G. J. D. Peddle, D. N. Roark, A. M. Good, and S. G. McGeachin, *ibid.*, **91**, 2807 (1969). For a survey of other examples, see B. P. Stark and A. J. Duke, "Extrusion Reactions," Pergamon Press, New York, N. Y., 1967.

(2) F. M. Beringer and S. J. Huang, *J. Org. Chem.*, **29**, 445 (1964).

We reproduced the procedure (Scheme I) for the synthesis of **1** (R = H) from 2-phenyliodoniobenzoate (**5**) and 1,3-diphenylisobenzofuran (**6**), which involved:[2] oxidation (fuming nitric–sulfuric acid mixture) of *o*-iodobenzoic acid (**3**) to an *o*-iodosobenzoic acid (**4**); sulfuric acid-catalyzed condensation of **4** with benzene to produce betaine **5**, followed by thermal decomposition of the benzyne precursor **5** in the presence of **6**.

SCHEME I



3 **4** **5** **1**

The physical properties of compounds **4**, **5**, and **1** obtained by this route were in accord with those reported[2] for **4** (R = H), **5** (R = H), and **1** (R = H). However, **1** was recovered (91% yield) after being heated at reflux in triglyme solution.[3]

In view of the well-documented analogy between various thermolysis and electronolysis reactions,[4] the mass spectrum of **1** was investigated for an M − 16 ion. Although such fragmentation was not observed to be appreciable, the appearance of the molecular ion at *m/e* 391, consistent with the formulation $C_{26}H_{17}NO_3$, *requires reconstitution of* **1** (*R* = *H*), *prepared by this route, as* **1** (*R* = NO_2). Correspondingly, materials synthesized by this procedure are reassigned structures **4** (R = NO_2) and **5** (R = NO_2). All revised assignments are supported by correct compositional analyses, as well as corroborative ultraviolet, infrared, proton magnetic resonance, and mass spectroscopic evidence (*cf.* Experimental Section). Apparently the conditions selected for oxidation (ArI → ArIO) were adequate to effect electrophilic aromatic nitration as well.[5]

An authentic sample of **5** (R = H) was obtained by successively treating a mixture of **3** in concentrated sulfuric acid with potassium persulfate, benzene, then base, according to the method of LeGoff[6] and Fieser.[7] Compounds **5**-H and **5**-NO_2 were thereby readily distinguished; compounds **1**-H and **1**-NO_2 were also spectroscopically differentiated. Compound **1**-H was recovered (92% yield) after being heated at reflux in triglyme solution (2.5 hr),[3] and in 90% yield after a 2.25-hr reflux period in a diglyme solution containing cyclohexene.

Compound **5**-NO_2 serves as an effective "4-nitrobenzyne" precursor. Thermolysis of **5**-NO_2 in the

(3) Although this result differs from previous observations,[2] we cannot account for the discrepancy.

(4) A. Maccoll in "Modern Aspects of Mass Spectroscopy," R. I. Reed, Ed., Plenum Press, New York, N. Y., 1968, pp 143–168.

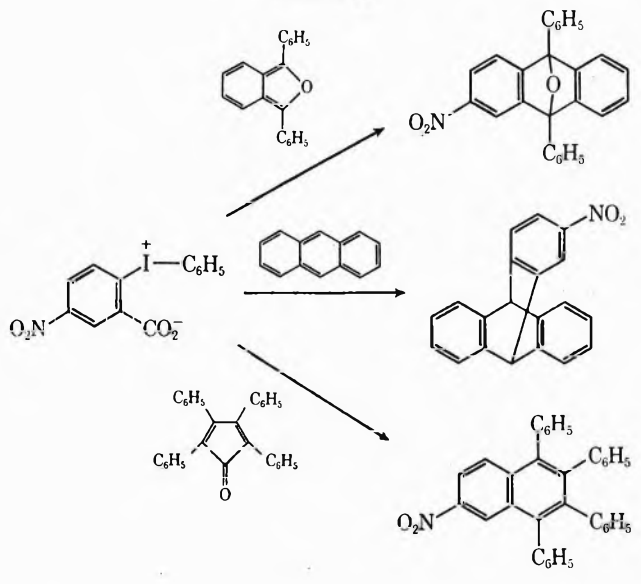
(5) This result is in accord with the observations of H. Goldstein and A. V Grampoloff, *Helv. Chim. Acta*, **13**, 310 (1930).

(6) E. LeGoff, *J. Amer. Chem. Soc.*, **84**, 3786 (1962).

(7) L. F. Fieser, "Organic Experiments," D. C. Heath and Co., Boston, Mass., 1964, pp 311–313; L. F. Fieser and M. J. Haddadin, *Org. Syn.*, **46**, 107 (1966).

presence of tetraphenylcyclopentadienone, anthracene, and 1,3-diphenylisobenzofuran, respectively (Scheme

SCHEME II



II), produced the corresponding adducts in isolated yields of 86, 43,[8] and 54%.

Experimental Section[9]

5-Nitro-2-iodosobenzoic Acid (4, R = NO_2) and 3-Nitro-2-iodobenzoic Acid.—2-Iodobenzoic acid (4.96 g; 20 mmol) was heated at 100° for 1 hr in a mixture of concentrated sulfuric acid (6.7 ml) and fuming nitric acid[2] (3.3 ml). After cooling, the mixture was poured into ice–water and the resultant precipitate was filtered, washed with water, and dried to give pale yellow crystals (5.28 g). Fractional crystallization from water afforded two components, the first of which was 5-nitro-2-iodosobenzoic acid (3.32 g) as colorless crystals: mp 229–229.5° dec; 54% yield; uv max (H_2O) 207 mμ (ε 23,400), 272 (7080); ir (Nujol) 1616 (C=O of a 2-iodosobenzoic acid),[10] 1523 and 1348 cm^{-1} (NO_2); nmr (DMSO-d_6) AMX system, τ 1.24, 1.38, and 1.85, J_{MX} = 0.5 Hz, J_{AX} = 9 Hz, and J_{AM} = 2.5 Hz; mass spectrum *m/e* (rel intensity) 309 (1), 293 (100), 248 (39), 83 (47), 71 (53), 69 (62) 57 (94), 55 (75), 43 (87), 41 (58).

Anal. Calcd for $C_7H_4NIO_5$: C, 27.18; H, 1.30; N, 4.53; I, 41.08. Found: C, 27.11; H, 1.31; N, 4.37; I, 41.38.

The molecular weight was determined by the iodometric titration method of Twiss and Heinzelmann[11] as 311.6 (calcd for $C_7H_4NIO_5$: 309.0).

The second crop of crystals was identified as 3-nitro-2-iodobenzoic acid and was obtained as pale yellow crystals (0.90 g), mp 174–207° dec (lit.[12] 204–205.5°), in 15% yield: ir (Nujol) 1710 (C=O of acid), 1540 and 1374 cm^{-1} (NO_2); nmr (DMSO-d_6) AMX system, τ 2.09, 2.19, and 2.35, J_{AM} = 2 Hz, J_{AX} = 7 Hz, and J_{MX} = 8 Hz; ir and nmr spectra were essentially identical with those of a sample independently synthesized by a known procedure.[12]

Anal. Calcd for $C_7H_4NIO_4$: C, 28.69; H, 1.37; N, 4.77; I, 43.31. Found: C, 28.67; H, 1.55; N, 4.69; I, 43.43.

5-Nitro-2-Phenyliodoniobenzoate (5, R = NO_2).—5-Nitro-2-iodosobenzoic acid (3.32 g; 10.7 mmol) was dissolved in concentrated sulfuric acid (10 ml) at 0–5° and successively processed with benzene (10 ml), saturated potassium iodide solution (4 ml), and 10 ml of 5 *N* sodium hydroxide solution,[2] to afford a tan precipitate. This was filtered, washed with water, dried, and recrystallized (chloroform–methanol; 30:70 by volume), to afford colorless crystals: mp 220–221° dec; 68% yield; uv max (H_2O) 205 mμ (log ε 4.24), 266 (log ε 4.02); ir (KBr) 3100 (w), 3050 (w), 1625 (s), 1522 (s), 1400 (m), 1342 (s), 1338 (s), 1005 (m), 990 (m), 817 (m), 735 (s), 721 (s), and 685 cm^{-1} (m); nmr (DMSO-d_6) fine structure for ring hydrogens from τ 1.34 to 3.06; mass spectrum *m/e* 369 (0.2), 205 (7), 204 (100), 78 (5), 77 (84), 76 (6), 75 (6), 74 (7), 51 (29) [lit.[2] uv max (H_2O) 205 mμ (log ε 4.43), 266 (log ε 4.02); ir (KBr) 3005 (w) 1630 (s), 1524 (s), 1400 (m), 1335 (s), 1005 (w), 995 (w), 817 (m), 738 (s), 720 (s) and 685 cm^{-1} (m); nmr fine structure for ring hydrogens from τ 1.46 to 3.28].

Anal. Calcd for $C_{13}H_8NIO_4$: C, 42.29; H, 2.18; N, 3.80; I, 34.37. Found: C, 42.39; H, 2.22; N, 3.76; I, 34.24.

2-Nitro-9,10-epoxy-9,10-diphenyl-9,10-dihydroanthracene (1, R = NO_2).—To a solution of 1,3-diphenylisobenzofuran (1.35 g; 5 mmol) in refluxing triglyme (38 ml) under nitrogen, was added 5-nitro-2-phenyliodoniobenzoate (3.16 g; 9 mmol) in small portions. After the addition (*ca.* 12 min) the mixture was maintained at reflux for a further 3 min. The majority of the solvent was then removed under reduced pressure (1 mm). Addition of water caused precipitation of a solid (2.80 g), which was chromatographed over Florisil using petroleum ether as eluant to give 2-nitro-9,10-epoxy-9,10-diphenyl-9,10-dihydroanthracene. Recrystallization (benzene–methanol) afforded very pale yellow crystals: mp 189–190°; 54% yield; uv max (95% EtOH) 216 mμ (ε 22,900), 244 (9300), 290 (4170); ir (Nujol) 1522 and 1340 cm^{-1} (NO_2); nmr τ 1.94 (d, 1, *J* = 2 Hz), 2.15 (m, 5), 2.60 (m, 9), 3.03 (m, 2); mass spectrum *m/e* 391 (80), 375 (8), 374 (27), 344 (20), 315 (12), 314 (13), 313 (16), 267 (12), 239 (24), 105 (100), 77 (47).

Anal. Calcd for $C_{26}H_{17}NO_3$: C, 79.78; H, 4.38; N, 3.58. Found: C, 79.99; H, 4.34; N, 3.70.

6-Nitro-1,2,3,4-tetraphenylnaphthalene was prepared in 86% yield from 2,3,4,5-tetraphenylcyclopentadienone and 5-nitro-2-phenyliodoniobenzoate by a method analogous to that of Fieser.[7] Recrystallization (chloroform–methanol) yielded yellow crystals: mp 275–277°; uv max (95% EtOH) 208 mμ (ε 53,500), 231 (38,000), 279 (29,500); ir (Nujol) 1522 and 1339 cm^{-1} (NO_2); nmr τ 1.35 (d of d, 1, *J* = 0.5, 2.5 Hz), 1.87 (d of d, 1, *J* = 2.5, 8.5 Hz), 2.22 (d of d, 1, *J* = 0.5, 8.5 Hz), 2.75 (m, 10), 3.13 (m, 10); mass spectrum *m/e* 477 (30), 447 (7), 78 (100), 77 (16), 52 (17), 51 (16), 50 (13).

Anal. Calcd for $C_{34}H_{23}NO_2$: C, 85.51; H, 4.85; N, 2.93. Found: C, 85.34; H, 5.10; N, 2.80.

2-Nitrotriptycene.—5-Nitro-2-phenyliodoniobenzoate (1.85 g, 5 mmol) was added to a refluxing solution of anthracene (0.89 g, 5 mmol) in triglyme (10 ml). After 3 min, excess anthracene was removed by addition of maleic anhydride (0.49 g, 5 mmol), refluxing for 5 min, and then adding ethanolic potassium hydroxide. The crystals which appeared upon cooling in an ice bath were filtered, washed with aqueous methanol, and dried to give 2-nitrotriptycene: 43% yield; mp 277–279° (methylene chloride–methanol) (lit.[8] mp 270–271°); ir (Nujol) 1517 and 1340 cm^{-1} (NO_2); nmr τ 1.80 (d, 1, *J* = 2.5 Hz), 2.08 (d of d, 1, *J* = 2.5, 8.5 Hz), 2.57 (m, 5), 2.92 (m, 4), 4.48 (s, 2); mass spectrum *m/e* 299 (100), 282 (18), 254 (11), 253 (60), 252 (100), 251 (17), 250 (27), 127 (12), 126 (24), 124 (16), 113 (13).

Anal. Calcd for $C_{20}H_{13}NO_2$: C, 80.25; H, 4.38; N, 4.68. Found: C, 80.04; H, 4.32; N, 4.93.

2-Phenyliodoniobenzoate (5, R = H).—2-Iodobenzoic acid (10.0 g; 40 mmol) was converted into 2-phenyliodoniobenzoate by the method of Fieser and Haddadin.[7] The betaine was obtained as colorless crystals: mp 226–227° dec (lit.[7] mp 219–220° dec); 78% yield; uv max (H_2O) 207 mμ (ε 24,000), 226 (shoulder); ir (KBr) 1610 and 1347 cm^{-1} (C=O of carboxylate anion); nmr (DMSO-d_6) τ 1.86 (m, 3), 2.46 (m, 5), 3.32 (m, 1).

(8) A synthesis of 2-nitrotriptycene (6.5% yield) *via* a 4-nitrobenzyne-route utilizing the reaction of anthracene and diazotized 4-nitroanthranilic acid, has been previously recorded: C. J. Paget and A. Burger, *J. Org. Chem.*, **30**, 1329 (1965).

(9) Melting points were determined with a Fisher-Johns apparatus and are uncorrected. Infrared spectra were measured on a Perkin-Elmer grating spectrophotometer Model 421. Ultraviolet spectra were recorded using a Perkin-Elmer ultraviolet-visible spectrophotometer Model 202. Nmr spectra were obtained with a Varian A-60 or HR-100 spectrometer. Mass spectra were measured with an AEI MS9 mass spectrometer at an ionizing energy of 70 eV. The microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, University of Alberta, Alberta, Canada, and by Galbraith Laboratories, Inc., Knoxville, Tenn.

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Anal. Calcd for $C_{13}H_{11}IO_3$: C, 45.61; H, 3.21; I, 37.13. Found: C, 45.37; H, 3.12; I, 37.12.

9,10-Epoxy-9,10-diphenyl-9,10-dihydroanthracene (1, R = H).—1,3-Diphenylisobenzofuran (4.0 g, 15 mmol) was reacted with 2-phenyliodoniobenzoate (5.5 g, 16 mmol) according to the method of Fieser.[7] 9,10-Epoxy-9,10-diphenyl-9,10-dihydroanthracene was obtained as colorless crystals: mp 190–192° (lit.[13] mp 188–188.5°); 87% yield. Recrystallization (benzene–ether–methanol) caused no change in melting point: uv max (petroleum ether) 220 mμ (ε 38,000); nmr τ 2.02 (m, 4), 2.54 (m, 10), 3.01 (m, 4); mass spectrum *m/e* 346 (35), 330 (4), 269 (15), 268 (15), 241 (20), 239 (24), 134 (11), 119 (10), 106 (12), 105 (100), 77 (49), 51 (13).

Anal. Calcd for $C_{26}H_{18}O$: C, 90.14; H, 5.24. Found: C, 90.25; H, 5.11.

A portion of the product was reduced by refluxing with zinc dust in glacial acetic acid for 20 min.[13] 9,10-Diphenylanthracene was obtained as pale yellow crystals, mp 246–249° (lit.[2] mp 246–247°), in 68% yield, and exhibited an infrared spectrum identical with that of an authentic sample.

Thermal Behavior of 9,10-Epoxy-9,10-diphenyl-9,10-dihydroanthracene (1, R = H).—The epoxy compound (200 mg) was dissolved in triglyme (5 ml). The solution was heated at reflux (*ca.* 225°) for 2.5 hr under nitrogen, then cooled to 90°, and ethanol (3 ml) was added. The solution was reheated to boiling and water was added dropwise until a faint, permanent precipitate was formed. On cooling, there was obtained 186 mg of colorless crystals, mp 190–192°. The absence of 9,10-diphenylanthracene was confirmed (tlc), and the product was recrystallized (cyclohexane) to give colorless crystals, mp 191–192°.

Anal. Calcd for $C_{26}H_{18}O$: C, 90.14; H, 5.24. Found: C, 89.86; H, 5.33.

Thermal Behavior of 2-Nitro-9,10-Epoxy-9,10-Diphenyl-9,10-Dihydroanthracene (1, R = NO_2).—The nitroepoxy compound (200 mg) was treated as described above for the unnitrated derivative. Pale yellow crystals, mp 187–189° (182 mg), were recovered and recrystallized (benzene–methanol, 1:2 by volume) to give starting material, mp 190–190.5°.

Anal. Calcd for $C_{26}H_{17}NO_3$: C, 79.78; H, 4.38; N, 3.58. Found: C, 79.88; H, 4.45; N, 3.46.

Thermal Behavior of 9,10-Epoxy-9,10-diphenyl-9,10-dihydroanthracene (1, R = H) in Presence of Cyclohexene.—Cyclohexene (0.82 g; 10 mmol) and diglyme (10 ml) were placed in a 50-ml 3-necked flask, fitted with a gas inlet tube and condenser; the latter was connected to a cold finger filled with Dry Ice–acetone. Nitrogen was bubbled through the solution prior to and for a few minutes after the addition of 9,10-epoxy-9,10-diphenyl-9,10-dihydroanthracene (0.35 g, 1 mmol). The mixture was then heated to reflux (146°) under nitrogen for 2.25 hr.

Analysis by glpc (10% Squalane, 100°) showed almost complete recovery of cyclohexene (>98%) and no other visible volatile products.

The clear, colorless solution was distilled to *ca.* half volume and then ethanol (5 ml) was added. The solution was reheated to boiling and water added dropwise until a faint, permanent precipitate was formed. The solution was cooled to afford colorless crystals, mp 188–190° (0.315 g). The product was recrystallized (cyclohexane) to give colorless crystals, mp 191–192°.

Anal. Calcd for $C_{26}H_{18}O$: C, 90.14; H, 5.24. Found: C, 90.02; H, 5.23.

Registry No.—**1**, R = NO_2, 23367-37-5; **1**, R = H, 19061-38-2; **4**, R = NO_2, 23330-00-9; **5**, R = NO_2, 23330-01-0; **5**, R = H, 1488-42-2; 6-nitro-1,2,3,4-tetraphenylnaphthalene, 23330-03-2; 2-nitrotriptycene, 4628-55-1.

Acknowledgment.—We wish to thank the National Research Council of Canada for financial support of this work and the University of Alberta for an Intersession Bursay (G. F. M.).

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Synthesis of Esters of Acid-Unstable Alcohols by Means of *n*-Butyllithium[1]

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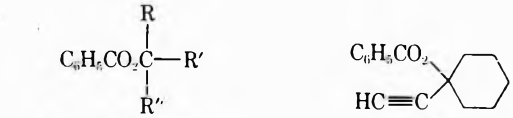
Received July 24, 1969

Esters are most conveniently prepared by the action of acid chlorides on alcohols. However, the by-product in such reactions, hydrogen chloride, usually precludes substantial ester formation when the alcohol can form relatively stable carbonium ions. For example, the reaction of phenylacetyl chloride with *t*-butyl alcohol affords predominately phenylacetic acid and isobutylene rather than the desired *t*-butyl phenylacetate. Esters of tertiary alcohols can be prepared, though, in the presence of tertiary amines like pyridine and N,N-dimethylaniline,[3] or magnesium metal[4] where such bases react with the hydrogen chloride as it is formed.

This report describes a convenient synthesis of esters derived from tertiary alcohols, and from other alcohols which readily undergo acid-catalyzed rearrangements. The synthesis simply involves conversion of alcohols into their lithium alkoxide salts by means of *n*-butyllithium in tetrahydrofuran (THF)–hexane, followed by the addition of an equivalent of an appropriate acid halide, and heating for 1 hr (eq 1).

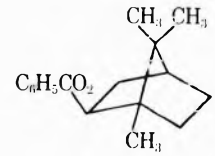
$$\mathrm{ROH} \xrightarrow[\text{THF–hexane}]{n\text{-}C_4H_9Li} \mathrm{ROLi} \xrightarrow[1\ \mathrm{hr}]{\mathrm{R'COCl}} \mathrm{R'COOR} + \mathrm{LiCl} \qquad (1)$$

The results are summarized in Table I. This Table shows that benzoate esters **1a–e** and **2–5**, pivalate esters **6a** and **6b**, cinnamate ester **7**, and hydrocinnamate



1a, R = R′ = R″ = CH_3
b, R = CH_3; R′ = R″ = C_2H_5
c, R = R′ = R″ = C_2H_5
d, R = H; R′ = CH_3; R″ = *t*-C_4H_9
e, R = R′ = H; R″ = *t*-C_4H_9

2



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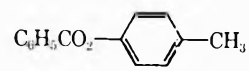

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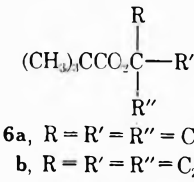
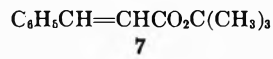


6a, R = R′ = R″ = CH_3
b, R = R′ = R″ = C_2H_5



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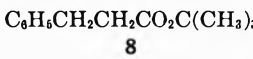

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(1) Supported by the Petroleum Research Fund, administered by the American Chemical Society, on Grant 959-G.

(2) Undergraduate research participant.

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TABLE I

SUMMARY OF ESTERS PREPARED FROM LITHIUM ALKOXIDES AND ACID CHLORIDES

Ester	Yield, %	Bp (mm) or mp, °C	Lit bp (mm) or mp, °C	Nmr, δ
1a	89	88–90 (3)	96 (2)[a]	7.06 (m, 5, ArH), 0.93 (s, 9, CH_3)
1b	87	106–108 (3)	89 (1.5)[b]	7.16 (m, 5, ArH), 1.1 (q, 4, CH_2), 0.48 (t, 6, CH_3), 0.375 (s, 3, CH_3)
1c	94	95–97 (2.5)		7.2 (m, 5, ArH), 2.5 (q, 6, CH_2), 0.4 (t, 9, CH_3)
1d	76	98–100 (3)	105–106 (5)[c]	7.16 (m, 5, ArH), 4.42 (q, 1, OCH), 0.65 (d, 3, $HCCH_3$), 0.38 (s, 9, CH_3)
1e	78	73–75 (1.2)	110 (10)[d]	7.46 (m, 5, ArH), 3.65 (s, 2, CH_2), 0.65 (s, 9, CH_3)
2	70	54–55	54–55[e]	7.65 (m, 5, ArH), 2.43 (s, 1, ≡CH), 2.1, 1.5 (m, 10, CH_2)
3	69	152 (2.5)	25.5[f]	7.72 (m, 5, ArH), 5.0 (m, 1, OCH), 1.7 (m, 16, CH_2CH_3)
4	91	98.5–100 (7.5)		7.8 (m, 5, ArH), 4.2 (d, 2, CH_2), 0.9 (m, 5, Δ)
5	94	71–72	71–72[g]	7.73 (m, 9, ArH), 2.35 (s, 3, CH_3)
6a	64	78–80 (105)	134–5 (760)[h]	1.21 (s, 9, CH_3), 0.91 (s, 9, CH_3)
6b	75	32 (0.5)		1.88 (q, 6, CH_2), 1.16 (s, 9, CH_3), 0.8 (t, 9, CH_3)
7	88	75–77 (0.3)	144 (3)[i]	7.3 (m, 5, ArH), 6.83 (q, 2, C=CH), 1.47 (s, 9, CH_3)
8	72	120–122 (7)	119–121 (10)[j]	7.0 (s, 5, ArH), 2.5 (m, 4, CH_2), 1.23 (s, 9, CH_3)

[a] Reference 3. [b] British Patent 932,773 (July 31, 1963); *Chem. Abstr.*, **59**, 11167*f* (1965). [c] P. G. Stevens, *J. Amer. Chem. Soc.*, **55**, 4237 (1933). [d] Tissier, *Ann. Chim. Phys.*, **29**, 371; Beilstein, **9**, 113 (1926). [e] I. N. Nazarov, R. I. Kruglikova, and G. M. Nikolaev, *Zh. Obshch. Khim*, **29**, 1859 (1959). [f] M. A. Haller, *Comp. Rend.*, **109**, 31 (1889). [g] A. Behal and E. Choary, *Bull. Soc. Chim Fr.*, **11**, 603 (1894). [h] A. Butlerow, *Justus Liehigs Ann. Chem.*, **173**, 372 (1874). [i] B. Abramovitch, J. C. Shivers, B. E. Hudson, and C. R. Hauser, *J. Amer. Chem. Soc.*, **65**, 986 (1943). [j] W. von E. Doering and R. M. Haines, *ibid.*, **76**, 1859 (1959).

TABLE II

INFRARED AND ANALYTICAL DATA FOR NEW ESTERS

Ester	Ir, μ	Calcd, % C	Calcd, % H	Found, % C	Found, % H
1c	5.89, 7.82, 8.95, 9.7, 11.1, 14.0	76.36	9.09	76.13	9.16
4	6.05, 7.1, 7.6, 7.8, 8.0, 9.1, 9.9, 14.1	75.56	6.67	75.23	6.62
6b	5.7, 6.0, 7.0, 7.9, 8.6, 9.0, 11.0, 11.6, 13.0	72.00	12.00	71.89	12.13

ester **8** were prepared from appropriate lithium alkoxides and the respective acid chlorides in yields of 64–94%.

The structures of the esters were supported by comparison of their physical properties with literature values, and by nmr spectroscopy (Table I). Elemental analyses and infrared spectra were also obtained for esters **1c**, **4**, and **6b**, which appear to be new (Table II).

Incidentally, certain steroidal alcohols have been similarly esterified by means of their bromomagnesium salts. However, a wide range of yields below 70% were realized in these reactions and the corresponding lithium and sodium alkoxides were reported not to be so effective as magnesium.[5] Also, it has recently been shown that thallium salts of phenols react nearly quantitatively with certain acid halides but this metallic cation has apparently not yet been utilized in the synthesis of esters derived from tertiary alcohols.[6]

The current method seems to be applicable to any alcohol, but it may be limited to acid chlorides without labile α hydrogens, or at least to those halides whose corresponding ketenes are not volatile or do not dimerize readily.

(5) D. D. Evans, D. E. Evans, G. S. Lewis, P. J. Palmer, and D. J. Weyell, *J. Chem. Soc.*, 3578 (1963).

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Experimental Section[7]

General Preparation of Esters by Means of *n*-Butyllithium.—To a solution of 0.05 mol of the appropriate alcohol (Table I) in 75 ml of anhydrous THF, was added under nitrogen during several minutes, 35.0 ml (0.055 mol) of 1.6 *M* *n*-butyllithium in hexane.[8] After 30 min, the resulting solution was treated during 5 min by the dropwise addition of a solution of 0.055 mol of the acid chloride (Table I) in 50 ml of THF. The resulting solution was brought to reflux for 1 hr, cooled to 0° by an ice bath, and hydrolyzed by the addition of 100 ml of water. The aqueous phase was extracted with three 50-ml portions of ethyl ether, and the combined organic phases were dried ($CaSO_4$ or $MgSO_4$), and concentrated. The crude product was purified by vacuum distillation or by recrystallization (Table I). Infrared and nmr spectra were determined for each ester and were in agreement with the assigned structures.

Registry No.—*n*-Butyllithium, 109-72-8; **1a**, 774-65-2; **1b**, 23293-73-4; **1c**, 23293-74-5; **1d**, 23293-75-6; **1e**, 23581-70-2; **2**, 23293-77-8; **3**, 20279-54-3; **4**, 23293-79-0; **5**, 614-34-6; **6a**, 16474-43-4; **6b**, 23293-82-5; **7**, 14990-09-1; **8**, 16537-10-3.

(7) Boiling points and melting points are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 137 spectrometer either neat or as Nujol mulls. Nmr spectra were determined on a Varian Associates A-60 spectrometer. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(8) Supplied by the Foote Mineral Co., Exton, Pa.

Models for the Study of Macrocyclic Ring–Chain Tautomerism

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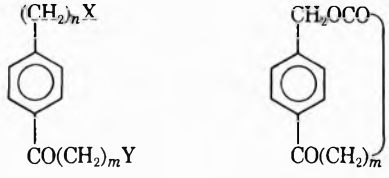
Received July 8, 1969

The phenomenon of ring–chain tautomerism[2] is well known in both natural and synthetic organic compounds, where the ring is five or six membered. Yet it has never been observed experimentally in any system involving a large ring (16 membered or higher), in spite of the fact that such large rings, once formed, are stable. The stability of macrocycles is illustrated by the increasingly large number of naturally occurring many-membered ring compounds being investigated. In particular, the macrolides,[3] macrocyclic keto lactones (containing other functional groups as well), bear a structural resemblance to smaller ring tautomers such as phthalaldehydic acid,[4] the alkaloid lycorenine,[5] and the sugars.

As a means of probing for the existence of macrocyclic ring–chain tautomerism, we have synthesized a number of new compounds (**1–12**), which are described in Table I. These were chosen for study because the corresponding ring tautomers would possess the *ansa* structure, which is known to be stable provided the ring is large.[6] It has already been pointed out[7a] that the keto lactone **13a**[7b] is a good model compound for such *ansa* ring tautomers derived from **2–10**.

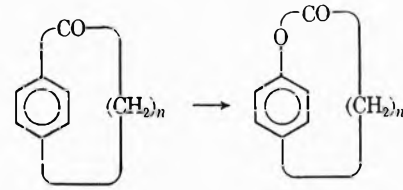


1–10
$n = 0, 1$
$m = 8, 10$

13a, $m = 8$
b, $m = 10$

It was expected that cyclization of the bromo acid **2** would afford the homologous, strain-free lactone **13b**, by analogy to the previously reported synthesis of **13a**. Because this ring formation could not be effected cleanly under a variety of conditions, **2** was reduced to **11**, which was subsequently brominated with NBS. The product was a statistical mixture of two monobromo acids which were not amenable to separation, however; so this route to a macrocyclic lactone was not pursued further.

Entrance into a second series of model ring–chain compounds derived from phenolic acids was eventually achieved by a totally different route. Although all attempts to cyclize the phenolic acids **10** and **12** by acid catalysis or by way of the acid chlorides failed, the macrocyclic *ansa* lactone **15b** could be obtained indirectly. The successful route to its synthesis (eq 1) was the Baeyer–Villiger oxidation of the *ansa* ketone **14b**, which could be obtained by Huisgen's intramolecular, high-dilution Friedel–Crafts acylation.[8] It is striking that the ring expansion occurred smoothly with the 16-membered ketone **14b** but failed for the lower homolog **14a**. In the latter case, where the product **15a** would still contain a strained ring, the oxidation led to nonaromatic degradation products.

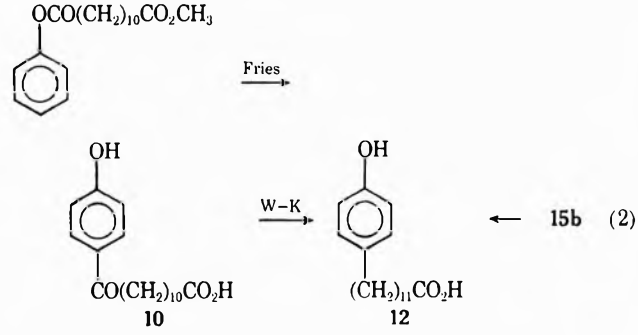


(1)

14a, $n = 9$
b, $n = 11$

15a, $n = 9$
b, $n = 11$

The distinctive nmr shielding effect on the bridge methylenes, evident in **14** and **15b**, varied somewhat with ring size. The structure of **15b** was confirmed by saponifying it to the phenolic acid **12** which was synthesized independently, as indicated in eq 2.



(2)

10 **12**

As shown by their infrared, ultraviolet, and nmr spectra, compounds **2–10** and **12** exist at ambient temperatures solely as chain tautomers, within the limits of detection (5–10%). The most important criterion for the presence of ring tautomer was considered to be the appearance in the nmr spectrum of high-field protons caused by aromatic shielding of some of the bridge methylene hydrogens.[7b] Any chemical conversions led to new chain tautomers exclusively. Examples are provided in eq 3 and 4.

(1) (a) Part of this work was initiated during the tenure of a National Science Foundation Science Faculty Fellowship at the Max Planck Institut für experimentelle Medizin, Göttingen, Germany, 1964–1965; (b) taken in part from Ph.D. theses submitted by M. D. S. (1968) and R. J. P. (1967) to the University of New Hampshire; (c) National Science Foundation Summer Fellow, 1967; (d) National Defense Education Act Fellow, 1963–1966.

(2) P. R. Jones, *Chem. Rev.*, **63**, 461 (1963).

(3) (a) M. W. Miller, "The Pfizer Handbook of Microbial Metabolites," McGraw-Hill Book Co., Inc., New York, N. Y., 1961, Chapter 7; (b) M. Berry, *Quart. Rev.*, (London), **17**, 343 (1963); (c) H. Griesbach and W. Hofheinz, *J. Roy. Inst. Chem.*, **88**, 332 (1964).

(4) J. Kagan, *J. Org. Chem.*, **32**, 4060 (1967), and references cited therein.

(5) T. Kitagawa, W. I. Taylor, S. Uyeo, and H. Yajima, *J. Chem. Soc.*, 1066 (1955).

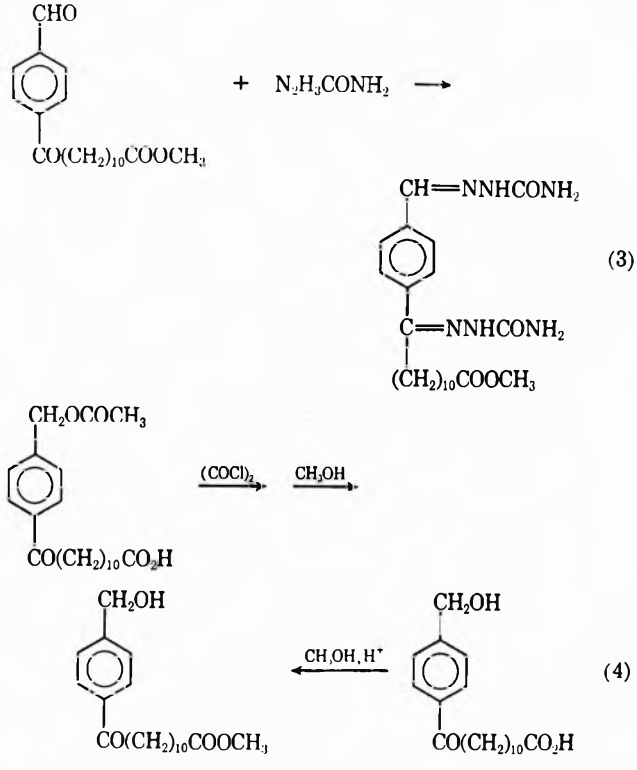
(6) A. Lüttringhaus, *Justus Liebigs Ann. Chem.*, **528**, 181 (1937); D. J. Cram, *Rec. Chem. Progr.*, **20**, 71 (1959).

(7) (a) P. R. Jones, M. D. Saltzman, and R. J. Panicci, Abstracts, 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, No. ORGN 100; (b) P. R. Jones, R. J. Panicci, R. M. Stimson, and L. Port, *J. Org. Chem.*, **31**, 4277 (1966).

(8) R. Huisgen, W. Rapp, I. Ugi, H. Walz, and I. Clogger, *Justus Liebigs Ann. Chem.*, **586**, 52 (1954).

TABLE I
MODEL CHAIN COMPOUNDS

Compd	X	n	m	Y	Mp, °C	Molecular formula	Calcd, % C	Calcd, % H	Calcd, % Other	Found, % C	Found, % H	Found, % Other
A. $X(CH_2)_nC_6H_4CO(CH_2)_mY$												
1	H	1	10	CO_2H	86–88	$C_{19}H_{28}O_3$	74.96	9.27	...	75.11	9.45	...
1 semicarbazone	H	1	10	CO_2H	156–158	$C_{20}H_{31}N_3O_3$	66.45	8.64	11.62 (N)	66.32	8.59	11.60 (N)
2	Br	1	10	CO_2H	113–115	$C_{19}H_{27}BrO_3$	59.51	7.11	20.85 (Br)	59.27	7.06	20.86 (Br)
3	AcO	1	10	CO_2H	94–96	$C_{21}H_{30}O_5$	65.59	8.34	...	65.51	8.20	..
4	TsO	1	10	CO_2H	108–110	$C_{26}H_{34}O_6S$	65.80	7.22	...	65.96	7.22	...
5	HO	1	10	CO_2H	83–84	$C_{19}H_{28}O_4$	71.22	8.81	...	70.99	8.61	...
6	HO	1	8	CO_2CH_3	70–70.5	$C_{18}H_{26}O_4$	70.56	8.55	...	70.38	8.43	...
7	HO	1	10	CO_2CH_3	76–78	$C_{20}H_{30}O_4$	71.82	9.04	...	71.73	9.02	...
8	AcO	1	8	CHO	110–112	$C_{19}H_{26}O_4$	71.67	8.23	...	71.46	8.05	...
9	CHO	0	10	CO_2CH_3	161 dec	$C_{20}H_{28}O_4$	72.26	8.49	...	71.80	8.45	...
9 bissemicarbazone	CHO	0	10	CO_2CH_3	208–210	$C_{22}H_{34}N_6O_4$	59.17	7.67	18.82 (N)	59.45	7.76	18.54 (N)
10	HO	0	10	CO_2H	92–94	$C_{18}H_{26}O_4$	70.56	8.55	...	70.39	8.85	...
B. $X(CH_2)_nC_6H_4(CH_2)_mY$												
11	H	1	11	CO_2H	57–59	$C_{19}H_{30}O_2$	78.57	10.41	...	78.44	10.09	...
12	HO	0	11	CO_2H	103–105	$C_{18}H_{28}O_3$	73.93	9.65	...	73.74	9.77	...



Failure of any of the acyclic *p*-phenylene bridged compounds 2–12 to undergo spontaneous ring tautomerization may reflect the high entropy requirement for such a process. The unfavorable geometry of X and Y in 1–12, where these groups are part of flexible chains emerging from diametrically opposing points on the aromatic ring, probably mitigates against bridging to an *ansa* structure.

Experimental Section[9]

11-(*p*-Toluyl)undecanoic Acid (1).—To a stirred solution of 48.8 g (0.2 mol) of 11-carbomethoxyundecanoic acid,[10] bp 170° (10 mm), in 200 ml of dry ether was added batchwise 60 g (0.4 mol) of thionyl chloride. The mixture was stirred at room temperature for 8 hr and then the solvent and excess thionyl chloride were removed *in vacuo*. The residual yellow oil (52.6 g, 0.2 mol), ν_{CO} 1800 cm^{-1}, was used without further purification. To a solution of the crude acid chloride in 250 ml of dry toluene was added 54 g (0.4 mol) of anhydrous aluminum chloride portionwise so as to maintain the temperature below 10°. Heated overnight on the steam bath, the mixture was decomposed in ice–6 *N* HCl; the organic layer, combined with ether washings of the aqueous phase, was washed repeatedly with saturated solutions of $NaHCO_3$ and NaCl, dried, and freed of solvent by rotary evaporation. Vacuum distillation effected removal of dimethyl dodecanedioate and then of the methyl ester of 1. The latter was saponified in refluxing methanolic KOH for 3 hr. The alkaline solution was acidified with 6 *N* HCl and the product 1 was collected, dried, and recrystallized from ether–ligroin (bp 30–60°): yield 30 g (50%); ir (CCl_4) 1720 (acid) and 1690 cm^{-1} (ketone); nmr (acetone) 7.5 (q), 2.8 (t), 2.3 (t), and 1–1.8 ppm (m).

11-(*p*-Bromomethylbenzoyl)undecanoic Acid (2).—The bromination of 15.2 g (0.05 mol) of 1 with NBS was carried out as described previously for a lower homolog.[7] After crystallization from THF–ligroin, there was obtained 11 g (57%) of the acid. The nmr spectrum (dioxane) contained a characteristic singlet at 4.5 ppm (CH_2Br).

11-(*p*-Acetoxymethylbenzoyl)undecanoic Acid (3).—A mixture of 5.8 g (0.015 mol) of 2, 1.6 g (0.02 mol) of sodium acetate, and 100 ml of glacial acetic acid was heated at reflux for 10 hr. The mixture was decomposed in ice–water and the solid was collected by filtration, washed repeatedly with water, dried, and recrystallized from chloroform–hexane: yield 2.3 g (44%); ir ($CHCl_3$) 1750 (ester), 1720 (acid), and 1690 cm^{-1} (ketone); nmr ($CDCl_3$) 5.17 ppm (s, CH_2OAc).

11-[*p*(*p*-Toluenesulfonylmethyl)benzoyl]undecanoic Acid (4).—A mixture of 5.7 g (0.015 mol) of bromo acid 2, 4.5 g (0.015 mol) of silver *p*-toluenesulfonate,[11] and 100 ml of acetonitrile was stirred in the dark for a period of 48 hr. The reaction mixture was added to water and the product was extracted with two 100-ml portions of ethyl ether. The ethereal extract was washed several times with saturated NaCl and dried, and the solvent was removed *in vacuo*. The residual solid, a mixture of bromo acid and tosylate, was subjected to the above treatment again. The tosylate was finally obtained in 10% yield after recrystallization from ether–hexane, nmr ($CDCl_3$) 5.08 ppm (s, CH_2OTs).

11-(*p*-Hydroxymethylbenzoyl)undecanoic Acid (5). A.—A mixture of 1.5 g of the bromo acid 2, 5.6 g of KOH, and 100 ml of THF was heated at reflux ovenight. It was acidified, concentrated, and extracted with ether several times. The ether solution was washed repeatedly with saturated NaCl, dried ($MgSO_4$), and freed of solvent by rotary evaporation. The solid was re-

(9) Nmr chemical shifts are given in parts per million downfield from TMS.

(10) L. J. Durham, D. J. McLeod, and J. Cason, "Organic Syntheses," Coll. Vol. IV, John Wiley & Sons, Inc., New York, N. Y., 1963, p 635.

(11) N. Kornblum, W. J. Jones, and G. J. Anderson, *J. Amer. Chem. Soc.*, **81**, 4113 (1959).

crystallized repeatedly from benzene–pentane: ir ($CHCl_3$) 3500 cm^{-1} (broad) (OH); nmr ($CHCl_3$) 4.78 ppm (s, CH_2OH). The hydroxy acid reacted instantaneously with chromic acid.[12]

B.—Saponification of 10.8 g (0.03 mol) of **3** with methanolic KOH led to a solid, which was identical in every way with that from A, yield 7.5 g (79%).

Methyl 9-(*p*-Hydroxymethylbenzoyl)nonanoate (6).—The following is typical of the Fischer esterifications carried out with several acids. A solution of 2.6 g (0.01 mol) of 9-(*p*-hydroxymethylbenzoyl)nonanoic acid in saturated methanolic hydrogen chloride was heated at reflux for 2–14 hr. The mixture was poured into ice–water; the ether layer, combined with ether washings of the water layer, was extracted with $NaHCO_3$ and water, dried ($MgSO_4$), and then concentrated. The ester was separated from the residual oil by thick layer chromatography on silica gel (5% MeOH in $CHCl_3$): uv max (methanol) 250 mμ (ε 54,000); ir (double mull) 3400 (OH), 1750 (ester), and 1690 cm^{-1} (ketone); nmr ($CDCl_3$) 4.76 (s, CH_2OH), 3.57 (s, CO_2CH_3), 2.3 (t, $COCH_2$), 2.9 (t, $CH_2CO_2CH_3$), and 1–2 ppm (m, CH_2). The same ester was obtained by Fischer esterification of 9-(*p*-acetoxymethylbenzoyl)nonanoic acid.

Methyl 11-*p*-(Hydroxymethylbenzoyl)undecanoate (7). A.—Fischer esterification of either the hydroxy acid **5** or acetoxy acid **3** led to the methyl ester, which was recrystallized from chloroform–hexane: ir ($CHCl_3$) 1735 (ester) and 1690 cm^{-1} (ketone); nmr ($CDCl_3$) 4.75 (s) and 3.67 (s).

B.—A mixture of 2 g (0.0055 mol) of 11-(*p*-acetoxymethylbenzoyl)undecanoic acid (**3**), 1.3 g (0.01 mol) of oxalyl chloride, and 50 ml of anhydrous ethyl ether was stirred at room temperature for 12 hr. After the solvent and excess oxalyl chloride had been removed *in vacuo*, excess methanol was added and the mixture was stirred for 2 hr and decomposed with water. The organic product was taken up in ether, washed with saturated NaCl, $NaHCO_3$, and again with NaCl, and dried ($MgSO_4$). The product obtained by removal of the solvent and recrystallization as above was identical with the ester from A.

9-(*p*-Acetoxymethylbenzoyl)nonanal (8).—A solution of acid chloride, prepared from 10 g (0.03 mol) of *p*-(acetoxymethylbenzoyl)nonanoic acid and oxalyl chloride, in 50 ml of dry diglyme was cooled to Dry Ice–acetone temperature. To this was added 7.6 g (0.03 mol) of lithium aluminum tri-*t*-butoxyhydride in 50 ml of dry diglyme over a period of 1 hr, with stirring. After removal of the bath, the solution was stirred for an additional 2 hr and then decomposed in ice–dilute HCl. The combined ether extracts were washed with dilute NaOH and water, dried ($MgSO_4$), and concentrated. The residual yellow, waxy solid was recrystallized six times from ether–hexane: ir (double mull) 1760 (ester), 1720 sh (aldehyde), and 1690 cm^{-1} (ketone); nmr ($CHCl_3$) 2.13 (s, $OCOCH_3$), 5.18 (s, CH_2OCO–), and 9.88 ppm (s, CHO).

The yield of aldehyde was greatly increased by use of THF instead of diglyme as solvent.

10-(*p*-Hydroxymethylphenyl)-1,10-decanediol.—To a magnetically stirred suspension of 1.6 g of lithium aluminum hydride in 70 ml of anhydrous ether was added, over a 2-hr period, 2 g of 9-(*p*-acetoxymethylbenzoyl)nonanoic acid. Then refluxing was maintained for 4 hr and the mixture was decomposed by dropwise addition first of water and then of dilute HCl. The ether layer and ether extracts of the aqueous layer were combined, washed with $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated. The triol, after recrystallization from ether–hexane, amounted to 1.67 g (98%): mp 88–90°; ir (double mull) 3200 cm^{-1} (broad, OH); mass spectrum *m/e* 280 (molecular ion).

Anal. Calcd for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06. Found: C, 72.8; H, 10.3.

All attempts to oxidize the triol selectively with MnO_2 or $KMnO_4$ failed.

Methyl 11-(*p*-Formylbenzoyl)undecanoate (9).—To a solution of 0.01 mol of **1** in 50 ml each of glacial acetic acid and acetic anhydride, cooled in an ice–salt bath, was added first 3 ml of concentrated H_2SO_4 and then 0.04 mol of chromium trioxide such that the temperature never exceeded 5°. Stirring was continued for 10 min, and then the solution was poured into ice–water. The crude *gem*-diacetate was collected, washed with water repeatedly to remove chromium salts, and air-dried. It was heated at reflux with 10 ml of ethanol, 10 ml of water, and 1 ml of concentrated H_2SO_4 for 30–40 min. The hot mixture was filtered and the filtrate was cooled to give solid, which was recrystallized from ether–ligroin: nmr ($CDCl_3$) 2.91 and 2.33 (t, $-CH_2CO$), 8.05 (d, ArH), 3.63 (s, $COOCH_3$), 10.01 (s, CHO), and 1–1.8 ppm (m, $-CH_2-$).

The bissemicarbazone was recrystallized twice from ethanol–water.

11-(*p*-Hydroxybenzoyl)undecanoic Acid (10).—A solution of 78 g of polyphosphate ester,[13] 12.2 g (0.13 mol) of phenol, and 31.7 g (0.13 mol) of 11-carbomethoxyundecanoic acid[10] was heated at reflux for 1 hr and then added to ice–water. The organic phase, combined with chloroform washings of the aqueous layer, was washed with 7.5% KOH and saturated NaCl and dried ($MgSO_4$). After removal of the solvent, there remained 35.5 g (83%) of pale yellow, liquid phenyl methyl dodecanedioate, ir (neat) 1765 and 1750 cm^{-1} (ester CO). The Fries rearrangement was carried out by mixing, in the cold, 16 g (0.05 mol) of ester, 26.8 g (0.20 mol) of anhydrous aluminum chloride, and 100 ml of nitrobenzene and allowing the mixture to stand at room temperature for 2 days. It was decomposed in ice–water and extracted twice with ether. The ether solution was extracted with 10% NaOH and the basic solution was acidified with 6 *N* HCl. The solid product was taken up in ether and washed with saturated NaCl, and the solution was dried ($MgSO_4$) and concentrated. After recrystallization of the residue from benzene–hexane, it amounted to 3.8 g (25%): ir (double mull) 3300–3500 (ArOH), 1720 (COOH), and 1690 cm^{-1} (ketone).

12-(*p*-Tolyl)dodecanoic Acid (11).—Wolff–Kishner reduction of 30.4 g of methyl 11-(*p*-toluyl)undecanoate in 300 ml of diethylene glycol with 25 ml of 85% hydrazine hydrate gave, after recrystallization from ligroin, 17 g (61%) of acid: nmr ($CDCl_3$) 2.30 (s, $ArCH_3$) and 7.08 (s, ArH).

12-(*p*-Hydroxyphenyl)dodecanoic Acid (12).—Wolff–Kishner reduction in diethylene glycol of 3.5 g (0.012 mol) of **10** furnished 1.1 g (31%) of **12** after two recrystallizations from ether–ligroin: ir ($CHCl_3$) 3350 (broad, ArOH) and 1715 cm^{-1} (COOH); nmr ($CDCl_3$) 6.87 ppm (q, ArH).

Intramolecular, High-Dilution, Friedel–Crafts Acylations.—The *cnsa* ketones **14a** and **14b** were prepared according to Huisgen, *et al.*,[8] from the corresponding ω-phenylalkanoic acids. Data for **14a** follow: mp 87–89° (aqueous ethanol) (lit.[8] mp 92–93°); nmr ($CDCl_3$) 7.4 (q, 4, ArH), 2.75 (q, 4, $ArCH_2$, $-CH_2CO$), 1–1.8 [m, 6, $-(CH_2)_n-$], and 0.5–1.0 ppm [m, 8, $-(CH_2)_n-$]. The semicarbazone of **14a** was prepared, mp 200–202° (methanol) (lit.[8] mp 207–208°). Data for **14b** follow: mp 74–76° (methanol) (lit.[8] mp 78–78.5°); nmr (CS_2) 7.4 (q, 4, ArH), 2.75 (m, 4, $ArCH_2$, $-CH_2CO$), 1–2 (m, 6, $-(CH_2)_n-$), and 0.5–1.0 ppm [m, 12, $-(CH_2)_n-$]. The 2,4-dinitrophenylhydrazone of **14b** was prepared, mp 150–152° (lit.[8] mp 154°).

Baeyer–Villiger Oxidation of 14b.—To a mechanically stirred mixture of 2 g (0.008 mol) of **14b** in 75 ml of methylene chloride containing 6.2 g (0.04 mol) of disodium hydrogen phosphate was added, at room temperature over a period of 30 min, a solution containing 0.016 mol of freshly prepared trifluoroperoxyacetic acid dissolved in 25 ml of methylene chloride. Refluxing was maintained for 18 hr; the mixture was filtered and the filtrate was washed successively with water, 10% $NaHCO_3$, and water and dried ($MgSO_4$). An infrared spectrum of the crude product remaining after removal of solvent indicated both ketone and lactone. After the entire oxidation process had been repeated and the product had been purified by thick layer chromatography on silica gel (75% chloroform, 25% benzene), **15b** was in the form of an oil: nmr ($CDCl_3$) 7.08 (q, 4, ArH), 2.4 (broad m, 4, $ArCH_2$, $-CH_2COO-$), 1–1.9 [m, 7, $-(CH_2)_n-$], and 0.5–1.0 ppm [m, 11, $-(CH_2)_n-$].

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.58; H, 9.45.

Saponification of 15b.—A solution of 0.2 g of KOH and 0.1 g of **15b** in 25 ml of methanol was heated at reflux for 2 hr. It was added to dilute HCl and the mixture was extracted twice with ether. The ether solution was washed several times with saturated NaCl and dried ($MgSO_4$), and the solvent was removed to give, after recrystallization from chloroform–ligroin (bp 40–60°), 0.07 g (68%) of **12**, mp 104–106°. A mixture melting point with **12** prepared above was undepressed, and their ir spectra were identical.

Registry No.—**1**, 23334-73-8; **1** semicarbazone, 23293-58-5; **2**, 23293-59-6; **3**, 23293-60-9; **4**, 23293-

(12) F. G. Bordwell and K. M. Wellman, *J. Chem. Educ.*, **39**, 308 (1962).

(13) Y. Kanaoka, O. Yonemitsu, K. Tanizawa, K. Matsuzaki, and Y. Ban, *Chem. Ind.* (London), 2102 (1964).

61-0; **5**, 23293-62-1; **6**, 23293-63-2; **7**, 23293-64-3; **8**, 23293-65-4; **9**, 2334-74-9; **9** bissemicarbazone, 23293-66-5; **10**, 23293-67-6; **11**, 23293-68-7; **12**, 23293-69-8; **15b**, 23293-71-2; 10-(*p*-hydroxymethylphenyl)-1,10-decanediol, 23293-70-1.

Substituent Constants of Difluoraminoalkyl and *gem*-Bis(difluoramino)alkyl Groups[1]

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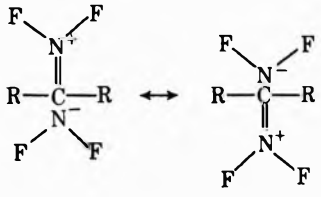
Received June 25, 1969

Although the difluoramino group of simple difluoramino alkanes has an electron-withdrawing inductive effect,[2] the difluoramino group is also capable of supplying electrons mesomerically to support simple cations such as NF_2O^+ and $NF_2{=}NF^+$,[3,4] as well as difluoraminocarbonium ions.[5,6] The operation of this effect in *gem*-bisdifluoramino compounds could reduce the additive inductive effects by resonance structures such as the following. The aliphatic substituent constant,



σ^*, would therefore show a "saturation" effect[7] relative to that of compounds with single difluoramino groups.

3-Difluoraminopropionic acid,[5] 4,4-bis(difluoramino)-pentanoic acid,[8] and 5,5-bis(difluoramino)hexanoic acid[8] were prepared as described previously. 4-Difluoramino-4-methylpentanoic acid was obtained by the alkaline hydrolysis of methyl 4-difluoramino-4-methylpentanoate, which in turn was obtained by the reaction of methyl 4-methyl-4-nitropentanoate[9] with difluoramine in the presence of fuming sulfuric acid. Although replacement of nitro groups by difluoramine under these conditions has been used extensively with α-halo derivatives,[10] the synthesis of a tertiary alkyl difluoramino compound in this way has not been reported previously.

$$(CH_3)_2C(NO_2)CH_2CH_2CO_2CH_3 \xrightarrow[H_2SO_4,\ SO_3]{HNF_2} (CH_3)_2C(NF_2)CH_2CH_2CO_2CH_3 \xrightarrow[2.\ H^+]{1.\ NaOH,\ H_2O} (CH_3)_2C(NF_2)CH_2CH_2COOH$$

(1) This work was supported by the Office of Naval Research.

(2) The electronegativity of the difluoramino group has been reported to be 3.25: R. Ettinger, *J. Phys. Chem.*, **67**, 1558 (1963).

(3) W. B. Fox, *et al.*, *J. Amer. Chem. Soc.*, **88**, 2604 (1966).

(4) A. R. Young and D. Moy, *Inorg. Chem.*, **6**, 178 (1967).

(5) K. Baum, *J. Amer. Chem. Soc.*, **90**, 7083 (1968).

(6) K. Baum, *ibid.*, 7089 (1968).

(7) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, Chapter 13.

(8) K. Baum, *J. Org. Chem.*, **34**, 3377 (1969).

(9) M. C. Kloetzel, *J. Amer. Chem. Soc.*, **70**, 3571 (1948).

(10) K. Baum, *J. Org. Chem.*, **34**, 2049 (1969).

TABLE I
IONIZATION CONSTANTS

Compd	pK at 25°	σ^*	$\sigma^*_{NF_2}$
$NF_2CH_2CH_2COOH$	3.74	0.528	4.13
$(CH_3)_2C(NF_2)CH_2CH_2COOH$	4.35	0.174	4.84
$CH_3C(NF_2)_2CH_2CH_2COOH$	4.01	0.372	4.33
$CH_3C(NF_2)_2CH_2CH_2CH_2COOH$	4.62	...	...
$CH_3C(NF_2)_2CH_2CH_2C(NO_2)_2H$	3.87	0.381	4.42

The ionization constants of the carboxylic acids, determined by potentiometric titration,[11] and the corresponding σ^* values of R in RCOOH are shown in Table I. The ionization constant of 5,5-bis(difluoramino)hexanoic acid was within experimental error of that of the reference, acetic acid[7]; it was not informative as to the effect of the difluoramino groups because of the distance between functional centers.

The ionization constant of 5,5-dinitro-2,2-bis(difluoramino)pentane[8] was obtained by the spectroscopic method. The σ^* value of 0.381 was calculated using the ρ^* for 1,1-dinitro alkane ionization reported by Sitzmann, Adolph, and Kamlet.[12] The σ^* values for $CH_3C(NF_2)_2CH_2CH_2-$ derived from the dinitro alkane and the carboxylic acid ionization constants are within experimental error.

The σ^* value of the difluoramino group was calculated using the normal quenching factor of 2.8 for intervening methylene groups and the value of σ^* for hydrogen, 0.49, to convert methyl groups into hydrogens.[7] The value of $\sigma^*_{NF_2}$ derived from 3-difluoraminopropionic acid is considered the most reliable because only two correction factors were required.

Within the combined calculation uncertainties, the σ^* values for two difluoramino groups are additive and therefore do not present evidence for unusual resonance effects. The difluoramino group is seen to be strongly electron-withdrawing, comparable with the nitro group. The reported pK for 4,4-dinitropentanoic acid[13] is, in fact, almost identical with that of the corresponding difluoramino acid.

Experimental Section

Because difluoramine and many difluoramino compounds are sensitive explosives, the safety precautions described previously[5] were followed. Ionization constants of the carboxylic acids were determined with a Metrohm E336 potentiograph at expanded scale by standard methods.[11]

The reduction of 5,5,5-trinitro-2,2-bis(difluoramino)pentane with alkaline hydrogen peroxide was carried out using $^1/_{20}$ of the previously described quantities.[8] The salt solution was diluted to 10 ml with water, and 1-ml aliquots were diluted with base, acid, and buffers as described by Sitzmann, Adolph, and Kamlet.[12] The log ϵ value of the 0.1 N sodium hydroxide solution was 4.11 at λ_{max} 375 mμ.

Methyl 4-Difluoramino-4-methylpentanoate.—The previously described[5] difluoramine generation procedure was followed. Methyl 4-methyl-4-nitropentanoate[9] (5.0 g, 0.0286 mol) was added dropwise with stirring to 9 g of refluxing difluoramine and 8 ml of 20% fuming sulfuric acid. The mixture was quenched with 100 ml of ice 15 min after the addition was completed. The product was extracted with three 10-ml portions of methylene chloride, dried over sodium sulfate, and distilled through a 25-cm Holzmann column to give 1.30 g (25.1% conversion, 40.5%

(11) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley & Sons, Inc., New York, N. Y., 1966, Chapter 2.

(12) M. E. Sitzmann, H. G. Adolph, and M. J. Kamlet, *J. Amer. Chem. Soc.*, **90**, 2815 (1968).

(13) M. I. Fauth, A. C. Richardson, and G. W. Nauflett, *Anal. Chem.*, **38**, 1947 (1966).

yield) of methyl 4-difluoramino-4-methylpentanoate, bp 56° (1.5 mm), and 1.9 g of recovered starting material.

Anal. Calcd for $C_7H_{13}NF_2O_2$: C, 46.43; H, 7.19; N, 7.74. Found: C, 46.60; H, 7.15; N, 7.43.

The proton nmr spectrum ($CDCl_3$ solution) consisted of a singlet at δ 3.80 for OCH_3, a triplet (J = 1.8 cps) at δ 1.32 for $(CH_3)_2CNF_2^-$, and a multiplet at δ 1.7–2.9 for CH_2. The infrared spectrum showed a carbonyl band at 5.75 μ and bands in the NF region at 10.50 (m), 10.71 (m), and 11.65 μ (s).

4-Difluoramino-4-methylpentanoic Acid.—A mixture of 1.20 g (0.00663 mol) of methyl 4-difluoramino-4-methylpentanoate and 10 ml of 2.5 *N* sodium hydroxide was heated intermittently in a 50° bath and agitated with a vortex mixer for 10 min to give a clear solution. Acidification with sulfuric acid, extraction with two 5-ml portions of ether, and distillation gave 0.79 g (71.3% yield) of 4-difluoramino-4-methylpentanoic acid, bp 72–73° (0.05 mm).

Anal. Calcd for $C_6H_{11}NF_2O_2$: C, 43.11; H, 6.60; N, 8.39. Found: C, 42.84; H, 6.41; N, 7.95.

The proton nmr spectrum ($CDCl_3$ solution) consisted of a singlet at δ 11.02 for COOH, a triplet (J = 2 cps) at δ 1.30 for CH_3, and a multiplet at δ 1.8–2.9 for CH_2.

Registry No.—Methyl 4-difluoramino-4-methylpentanoate, 22427-05-0; 4-difluoramino-4-methylpentanoic acid, 22427-06-1.

Acknowledgment.—The author is grateful to Mrs. Yoshie Kadota for the pK determinations of the carboxylic acids, to Mr. K. Inouye for elemental analysis, and to Dr. W. Woolfenden for nmr spectra.

Studies on Enamines. II. The Effect of the Amino Group on the Stabilities of Isomeric Vinyl Anions[1,2]

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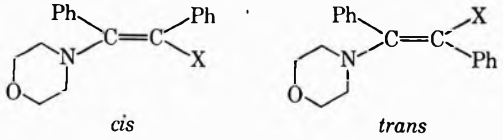
Received July 24, 1969

Earlier we reported the synthesis and *cis–trans* isomerization of 1-bromo- and 1-chloro-2-(4-morpholino)-1,2-diphenylethene (I and II).[1] In the same article we also reported the easy heterolytic cleavage of the carbon–halogen bond to give a vinyl cation. We have now studied the reactions of I and II with phenyllithium and triphenylphosphine. In both cases the halo enamines were reduced to give 1-(4-morpholino)-1,2-diphenylethene (III) through a vinyl anion intermediate.

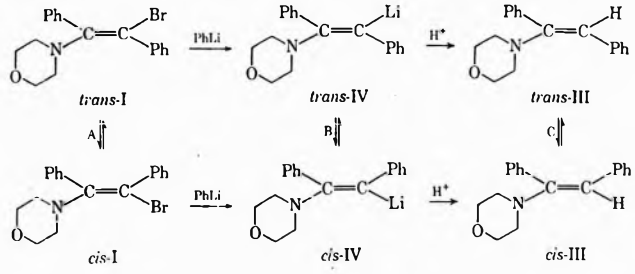


cis *trans*

I, X = Br
II, X = Cl
III, X = H

Reaction with Phenyllithium.—When treated with an equimolar amount of phenyllithium in benzene at room temperature, both I and II were converted into the enamine III (51% and 45%, respectively). A *cis–trans* 1:1 equilibrium mixture of I was converted quantitatively into III after reaction with twice the equimolar amount of phenyllithium. In all cases the enamine III formed was the pure *cis* form, as determined by nmr. Possible routes for converting *trans*-I into *cis*-III are shown in Scheme I.

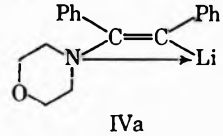
SCHEME I



According to Munk and Kim, the equilibrium mixture for enamine III is *cis–trans* (88:12).[4] Since we detected no *trans*-III and since the conditions necessary for the *cis*-III–*trans*-III isomerization are much more severe than those employed in our studies, we feel that the isomerization of products, route C, can be considered to be rather unlikely.

It is generally accepted that protonation of vinyllithium reagents occurs with retention of configuration.[4–7] There are then two remaining possible routes for the conversion of *trans*-I into *cis*-IV. In route A, *cis*-I reacts faster than *trans*-I with phenyllithium, and consequently the equilibrium *cis*-I–*trans*-I is shifted toward *cis*-I. Our study showed that the *cis*-I–*trans*-I isomerization reaches equilibrium after several hours in benzene at room temperature, showing that route A is possible. Alternatively, both *cis*-I and *trans*-I may react with phenyllithium at similar rates to give *cis*-IV and *trans*-IV, respectively, and a fast conversion of *trans*-IV into *cis*-IV may occur (route B). Since diarylvinyllithium and triarylvinyllithium are known to undergo *cis–trans* isomerization at rather fast rates,[5–7] it is reasonable to assume that *trans*-IV also isomerizes to *cis*-IV at a rather fast rate. Detailed kinetic studies will be necessary to estimate the relative importance of route A and of route B. However, attempts to study such kinetics have been frustrated, as *trans*-I can not be obtained in pure form; also the reaction rate of I with phenyllithium is too fast to be measured in an easy way.

The fact that only *cis*-III is formed in the above reactions (our nmr measurements are estimated to be accurate to ±2%) suggests that *cis*-IV is much more stable than *trans*-IV. We feel that intramolecular coordination of the nonbonded electrons of the morpholino nitrogen to the lithium metal probably is responsible for the relatively high stability of the *cis* form of IV, which may be more accurately represented as IVa rather than *cis*-IV. Such intramolecular coordination is not possible in the *trans* form of IV.



IVa

(1) Part I: S. J. Huang and M. V. Lessard, *J. Amer. Chem. Soc.*, **90**, 2432 (1968).

(2) Abstracted from the Ph.D. dissertation of M. V. Lessard, University of Connecticut, 1969.

(3) University of Connecticut Predoctoral Fellow, 1966–1969.

(4) M. E. Munk and Y. K. Kim, *J. Org. Chem.*, **30**, 3705 (1965).

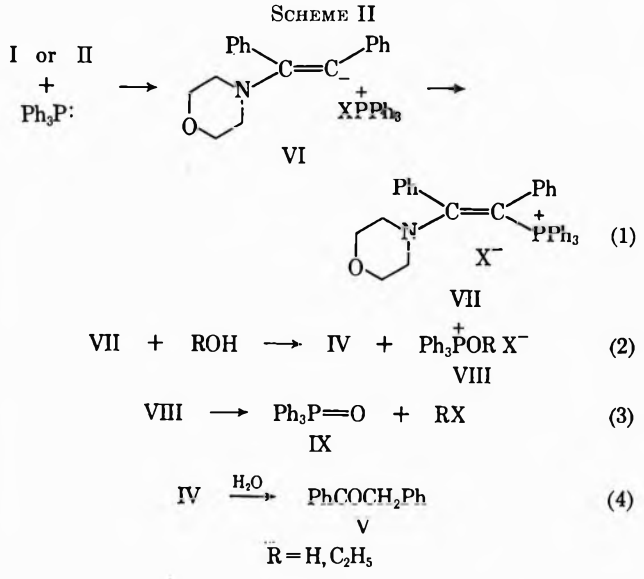
(5) A. N. Nesmeyanov and A. E. Borisov, *Tetrahedron*, **1**, 158 (1957).

(6) D. Y. Curtin and J. W. Crump, *J. Amer. Chem. Soc.*, **80**, 1922 (1958).

(7) D. Y. Curtin and W. J. Koehl, Jr., *ibid.*, **84**, 1967 (1962).

Reaction with Triphenylphosphine.—Reaction of a mixture of the *cis* and *trans* forms of bromo enamine I with triphenylphosphine in benzene at room temperature yielded 37% of *cis*-III, 27% of deoxybenzoin (V, hydrolysis product of III), and a white, hygroscopic solid believed to be the triphenylphosphonium salt of the enamine. Reaction of a mixture of the *cis* and *trans* forms of the chloro enamine II with triphenylphosphine under the same conditions yielded 29% deoxybenzoin. A possible mechanism for the reaction is shown in Scheme II. A nucleophilic displacement of triphenylphosphine on halogen yields the phosphonium salt VI, which may rearrange to give phosphonium salt VII (eq 1). Hydrolysis of the phosphonium salt VII by water present in the reaction system would yield enamine III [which may undergo further hydrolysis to give deoxybenzoin (V), eq 4] and phosphonium salt VIII (eq 2). Decomposition of VIII could then yield triphenylphosphine oxide (IX).[8] Support for this mechanism was provided by treating bromo enamine I with triphenylphosphine in benzene under anhydrous conditions, followed by addition of ethanol. The reaction yielded 86% *cis*-III, 9% deoxybenzoin (V), 92% triphenylphosphine oxide (IX), and 50% ethyl bromide. The fact that the bromo enamine I underwent a faster and more complete reaction than the chloro enamine II supported the postulated nucleophilic attack on halogen rather than on carbon.[8-14] Indeed, very similar mechanisms have been suggested by several workers on the reduction of halo ketones by triphenylphosphine.[8-12]

SCHEME II



An alternative mechanism for formation of the phosphonium salt VII may involve addition of triphenylphosphine to the olefin followed by elimination of a halide ion. This mechanism may be ruled out by two considerations: (1) steric hindrance probably makes the addition of the large triphenylphsophine molecule to the olefin very difficult; and (2) in an addition–elimination reaction one would expect that the chloro enamine II would react as easy as or more easily than the bromo enamine I. This was not the observed case.

Again, the fact that only *cis*-III was obtained suggests that internal coordination between the morpholino nitrogen and the cationic phosphorus makes the *cis* forms of VI and VII more stable than the *trans* forms.

(8) S. Trippett, *J. Chem. Soc.*, 2337 (1962).
(9) P. A. Chopard, R. F. Hudson, and G. Klopman, *ibid.*, 1379 (1965).
(10) I. J. Borowitz and L. I. Grossman, *Tetrahedron Lett.*, **11**, 741 (1962).
(11) K. Pilgram and H. Ohse, *J. Org. Chem.*, **54**, 1592 (1969).
(12) I. J. Borowitz, P. E. Rusek, and A. Virkhaus, *ibid.*, **34**, 1595 (1969).
(13) A. J. Speziale and L. J. Taylor, *J. Org. Chem.*, **31**, 2450 (1966); A. J. Speziale and L. R. Smith, *J. Amer. Chem. Soc.*, **84**, 1868 (1962).
(14) For recent reviews on nucleophilic attack on halogen, see H. Hoffman and H. J. Diehr, *Angew. Chem., Int. Ed. Engl.*, **3**, 737 (1964); B. Miller in "Topics in Phosphorus Chemistry," Vol. 2, M. Grayson and E. J. Griffith, Ed., Interscience Publishers, Inc., New York, N. Y., 1965, pp 133–199.

Experimental Section

All melting points were uncorrected and were taken on a Thomas–Hoover apparatus. Infrared spectra were recorded on a Perkin-Elmer Model 137B Infracord. Nuclear magnetic resonance spectra were determined using a Varian A-60 spectrometer and carbon tetrachloride solution containing tetramethylsilane was used as internal standard. Mass spectra were obtained on an AEI MS-12 mass spectrometer. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and Baron Consulting Co., Orange, Conn. Thin layer chromatography (tlc) was performed on 0.25-mm layers using silica gel GF 254 or PF 254 (Merck), Darmtadt, Germany. The silica gel used for column chromatography was obtained from Gerbrüder Hermann, Köln, Germany.

All solvents and reagents were purified according to standard procedures before use. All products were identified by melting point and spectroscopic methods.

1-Bromo-2-(4-morpholino)-1,2-diphenylethene (I).—To a solution of 15.0 g (57 mmol) of *cis*-1-(4-morpholino)-1,2-diphenylethene (III)[4] in 250 ml of dry benzene stirred under nitrogen was added 10.2 g (57 mmol) of N-bromosuccinimide in small portions. After completion of the addition of NBS (30 min) the mixture was stirred for 1.5 hr; after this time tlc showed that all of III had reacted. Filtration of the succinimide formed in a vacuum system followed by evaporation of solvent *in vacuo* resulted in a yellow-brown oil. The oil was crystallized from dry methanol to give 15.5 g (79%) of a *cis–trans* (3.4:1) mixture of I. Two more recrystallizations from methanol yield the pure *cis* isomer, mp 109–110°. The infrared spectrum showed the following peaks: 3030, 2940, 1590, 1140, 950, 740, 710, and 705 cm^{-1}. The nmr spectrum was reported elsewhere.[1]

Anal. Calcd for $C_{18}H_{18}BrNO$: C, 62.79; H, 5.28; N, 4.07. Found: C, 63.06; H, 5.23; N, 4.03.

Attempts to isolate the pure *trans* form failed.

1-Chloro-2-(4-morpholino)-1,2-diphenylethene (II).—The enamine II was prepared in 70% yield from *cis*-III and N-chlorosuccinimide in a similar manner. The pure *cis*-II was obtained by recrystallization, mp 79–80°. The infrared spectrum showed the following peaks 3030, 2940, 1590, 1575, 1110, 940, 745, and 700 cm^{-1}. The nmr spectrum was reported elsewhere.[1]

Anal. Calcd for $C_{18}H_{18}ClNO$: C, 72.11; H, 6.03; N, 4.67. Found: C, 71.94; H, 6.08; N, 4.53.

Attempts to isolate the pure *trans* form failed.

Reaction with Phenyllithium.—Reactions were run on a 5-mmol scale. Phenyllithium (Alfa Inorganics) in benzene–ether was added to a stirred solution of an equilibrium mixture of I or II in dry benzene under nitrogen at room temperature. The reaction was instantaneous and the organometallic intermediate was hydrolyzed 1 hr later by addition of isopropyl alcohol (acid hydrolysis was not employed in order to avoid hydrolysis of enamine III). Removal of solid by filtration and evaporation of the solvent *in vacuo* gave a yellow oil. The nmr spectrum of the oil in carbon tetrachloride solution revealed the presence of only unreacted halo enamine and *cis*-III. Preparative tlc and column chromatography gave deoxybenzoin (hydrolysis product of III) and α-halodeoxybenzoin (hydrolysis product of I or II). The result are listed in Table I.

TABLE I
REACTION OF THE α-HALO ENAMINES WITH PHENYLLITHIUM

Reactants (ratio)	Yield of product, % *cis*-III	Yield of product, % *trans*-III
I and PhLi (1:1)	51	0
I and PhLi (1:2)	100	0
II and PhLi (1:1)	45	0

Reaction of I with Triphenylphosphine. A.—To a solution of 2.28 g (8.7 mmol) of triphenylphosphine (Carlisle Chemical Co.) in 100 ml of benzene stirred under nitrogen was added a solution of 3.00 g (8.7 mmol) of the bromoenamine I in 20 ml of benzene. After 1 hr of stirring at room temperature, tlc showed the absence of unreacted I. A white, hygroscopic precipitate, mp 128–130°, was filtered from the reaction mixture. An oil was obtained from the filtrate after removal of solvent. Hydrolysis of the oil with undried methanol gave 0.86 g (37%) of enamine III and 0.56 g (27%) of deoxybenzoin after fractional recrystallization from methanol. The white precipitate could not be purified, as it hydrolyzed rapidly in air to give enamine III, deoxybenzoin, and triphenylphosphine oxide.

B.—The same reaction was carried out in a carefully dried system. Instead of filtration of the precipitate, a different work-up procedure was employed. A mild exothermic reaction took place with the dissolution of the original precipitate when 1.8 times the equimolar amount of absolute ethanol was added to the reaction mixture. After having been stirred overnight, the mixture was fractionally distilled. Comparison of the nmr spectra of the distillate fractions with that of authentic ethyl bromide showed a 50% yield of ethyl bromide. An 85% yield of *cis*-III, a 9% yield of deoxybenzoin, and a 92% yield of triphenylphosphine oxide were obtained from the residue by fractional recrystallization from methanol.

Reaction of II with Triphenylphosphine.—The reaction was carried out in a manner similar to A above. After 24 hr of stirring tlc showed the presence of unreacted II. Column chromatography yielded 70% unreacted triphenylphosphine and 29% deoxybenzoin.

Registry No.—*cis*-I, 20735-65-3; *trans*-I, 20735-66-4; *cis*-II, 20735-67-5; *trans*-II, 20735-68-6; phenyllithium, 591-51-5; triphenylphosphine, 603-35-0.

Acknowledgments.—Financial support from the Petroleum Research Fund, administered by the American Chemical Society, and the University of Connecticut Research Foundation are gratefully acknowledged.

The Coupling of Nitrophenyl Radicals and Anions To Form Anion Radicals

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Received August 12, 1969

Dimerization, disproportionation, and atom abstraction are among frequently reported reaction pathways for organic free radicals.[1] Evidence has been presented recently which shows that still another reaction pathway, the coupling of a radical with an anion, predominates for nitrobenzyl radicals in the presence of certain anions.[2] Similarly, the coupling of a phenyl radical with an anion has been suggested to rationalize the formation of biphenyl in the photolysis of a phenyllithium in ether solution.[3]

In the course of some of our earlier work we reported that the presence of iodide ion markedly altered the rate of halogenated nitrobenzene anion radical decomposition.[4] That observation suggested that further studies should be made into the reactions of phenyl radicals in the presence of anions. The results of such a study are reported herein.[5]

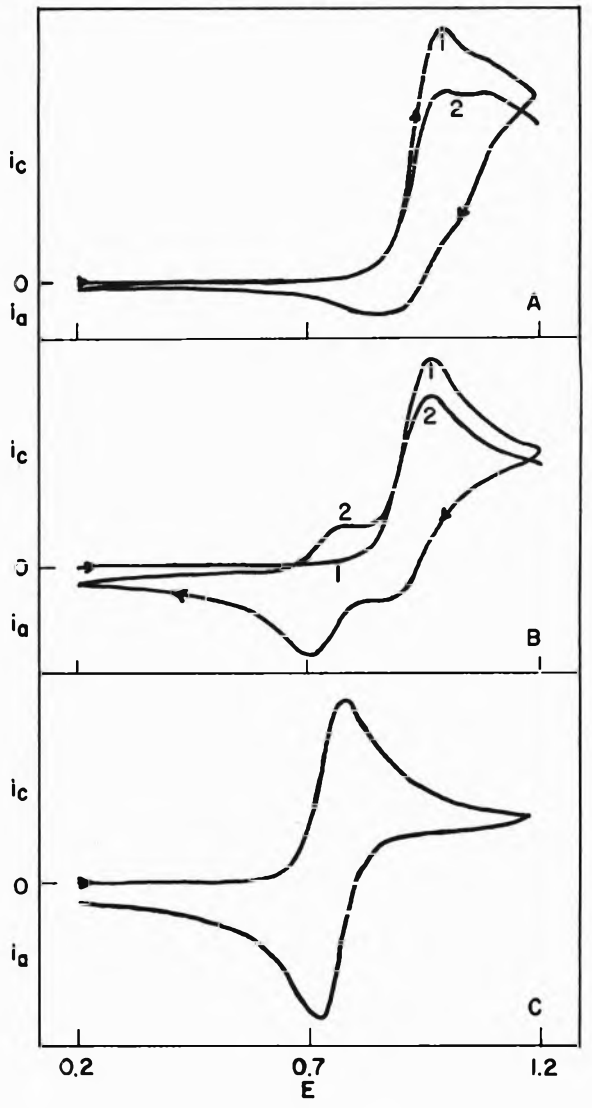


Figure 1.—Cyclic voltammograms in 0.1 *M* TEAP–DMSO at a scan rate of 80.6 mV/sec: (a) 7.32×10^{-3} *M* *p*-iodonitrobenzene; (b) 7.32×10^{-3} *M* *p*-iodonitrobenzene and 0.1 *M* NaCN; (c) 5.82×10^{-3} *M* *p*-nitrobenzonitrile. Numbers 1 and 2 represent cycles 1 and 2, respectively.

Evidence for a phenyl radical–anion reaction is shown in Figure 1. In the absence of a reactive anion, such as cyanide (Figure 1a), the nitrophenyl radical formed by the electrochemical reduction of *p*-iodonitrobenzene (cathodic peak near −1.0 V) abstracts a hydrogen atom from the solvent to form nitrobenzene. The nitrobenzene is then reduced in a one-electron process at slightly more negative potential (cathodic peak near −1.09 V) to its anion radical.[6] The absence of appreciable anodic current on the reverse, anodic sweep is the result of a solution oxidation–reduction reaction involving nitrobenzene anion radical and *p*-iodonitrobenzene.[4]

Hydrogen atom abstraction is virtually eliminated as a reaction pathway in dimethyl sulfoxide (DMSO)

(1) W. A. Pryor, "Free Radicals," McGraw-Hill Book Co., Inc., New York, N. Y., 1966.

(2) G. A. Russell and W. C. Danen, *J. Amer. Chem. Soc.*, **88**, 5663 (1966); **90**, 347 (1968); N. Kornblum, R. E. Michel, and R. C. Kerber, *ibid.*, **88**, 5660 (1966).

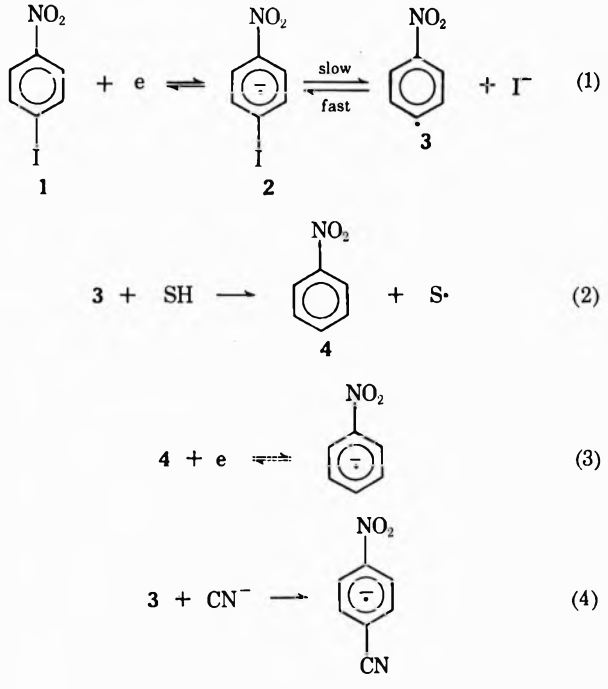
(3) E. E. van Tamelen, J. I. Brauman, and L. E. Ellis, *ibid.*, **87**, 4964 (1965).

(4) J. G. Lawless and M. D. Hawley, *J. Electroanal. Chem.*, **21**, 365 (1969).

(5) Since the completion of this work, the coupling of phenyl radical and nitrite ion was observed by esr spectroscopy in aqueous solution: A. L. J. Beckwith and R. O. C. Norman, *J. Chem. Soc., B*, 403 (1969).

(6) For additional applications of cyclic voltammetry to organic systems, see, *e.g.*, R. N. Adams, "Electrochemistry at Solid Electrodes," Marcel Dekker, New York, N. Y., 1969.

when cyanide ion is present. In the presence of cyanide ion (Figure 1b), only the reduction wave owing to the one-electron reduction of *p*-iodonitrobenzene to its anion radical is readily discernible on the first cathodic sweep. After reversal of the potential scan at −1.2 V, an anodic wave not seen in Figure 1a is observed at −0.72 V. Subsequent cathodic sweeps show an additional reduction process at −0.78 V. A comparison of the cyclic voltammograms of authentic *p*-nitrobenzonitrile (Figure 1c) and the present system clearly shows that the new redox couple is due to *p*-nitrobenzonitrile-*p*-nitrobenzonitrile anion radical. The absence of a reduction wave at −0.78 V on the first cathodic scan shows unequivocally that the anion radical of *p*-nitrobenzonitrile cannot result unless the reduction of *p*-iodonitrobenzene is first made to occur. A reaction scheme consistent with this interpretation is shown by eq 1–4.



Confirmation of *p*-nitrobenzonitrile anion radical formation was obtained by esr spectroscopy. The esr spectrum of the anion radical obtained in this manner was identical with the spectrum of the anion radical of an authentic sample of *p*-nitrobenzonitrile. As expected, the hyperfine splitting constants ($a^{N}_{NO_2}$ = 7.15, a^{H}_{O} = 3.06, and a^{H}_{M} = a^{N}_{CN} = 0.76 G) differ only slightly from those reported previously for the anion radical in acetonitrile.[7]

Formation of *o*-nitro- and *m*-nitrobenzonitrile anion radicals from the corresponding nitrophenyl radicals and cyanide ion is observed similarly by cyclic voltammetry. In the presence of 0.1 *M* sodium cyanide in DMSO, thin-layer coulometry[8] results (Table I) show that the yields of the nitrobenzonitrile anion radicals are greater than 90% from each of the nitrophenyl radicals.

As expected, increasing the ease with which a hydrogen atom can be abstracted from the solvent decreases the amount of coupling with cyanide ion. Thus, as the solvent is varied from DMSO to AN (acetonitrile) to DMF (dimethylformamide), nitrobenzene formation is observed qualitatively to increase in the order DMSO < AN < DMF.[9] Since ion-pair formation is probably extensive (but unknown) in these solvents, a quantitative study of the relative rates in the several solvents was not attempted.

Coupling of phenyl radicals with nitrite ion was also observed. Phenyl radical, prepared by the thermal decomposition of phenylazotriphenylmethane in DMSO in the presence of 0.1 *M* $NaNO_2$, yielded a product which upon electroreduction gave a strong esr spectrum of nitrobenzene anion radical; glpc showed the presence of approximately 5% nitrobenzene and 75% benzene. Coupling of electrochemically generated *p*-nitrophenyl radical with nitrite ion nearly eliminates hydrogen atom abstraction as a reaction pathway, as evidenced by the absence of a nitrobenzene reduction wave (Figure 2). The pair of reduction waves near −0.59 and −0.73 V arises from the stepwise reduction of the coupled reaction product, dinitrobenzene, to its dianion. The anodic peak remaining at −0.90 V represents the reoxidation of unreacted *p*-iodonitrobenzene anion radical.

Attempts to prepare other anion radicals by coupling a nitrophenyl radical with an anion were not successful. As observed previously by Parker and coworkers,[10] thiophenoxide reacts rapidly with *p*-iodonitrobenzene to form *p*-nitrophenylthiophenyl ether prior to the electrochemical reduction. A similar reaction occurred between thiophenoxide and *m*-iodonitrobenzene.[11] Coupling of either *m*- or *p*-nitrophenyl radical with either chloride or bromide ion to form the corresponding halonitrobenzene anion radical was not observed. Although coupling of a nitrophenyl radical with iodide ion has been reported previously,[4] the resulting anion radical (as used in the present study) readily dissociates to regenerate the nitrophenyl radical.

TABLE I

COULOMETRIC REDUCTION OF IODONITROBENZENES IN DMSO[a]

Nitrobenzene substituent	Anion added	$-E_{applied}$	*n* value[b]
4-Iodo-		1.2	1.93
4-Iodo-	CN^-	1.2	1.04
3-Iodo-		1.2	1.93
3-Iodo-	CN^-	1.2	0.92
2-Iodo-		1.4	1.89
2-Iodo-	CN^-	1.2	0.96

[a] Supporting electrolyte is 0.1 *M* tetraethylammonium perchlorate. When cyanide ion is indicated to be present, its concentration is 0.1 *M*. [b] The theoretical number of electrons (*n* value) for the reduction of an iodonitrobenzene to nitrobenzene anion radical and iodide ion is 2.0; see eq 1–3 for a description of the electrochemical and chemical process. The formation of a nitrobenzonitrile anion radical corresponds to a one-electron process; see eq 1, 2, and 4 for a description of these processes. Relative average deviation is less than 5% of an *n* value.

(7) A. H. Maki and D. H. Geske, *J. Amer. Chem. Soc.*, **83**, 1852 (1961).

(8) A. T. Hubbard, R. A. Osteryoung, and F. C. Anson, *Anal. Chem.*, **38**, 692 (1966).

(9) The ease of hydrogen atom abstraction by phenyl radical decreases in the order DMF > AN > DMSO. See R. F. Bridger and G. A. Russell, *J. Amer. Chem. Soc.*, **85**, 3754 (1963); J. D. Hunt, Ph.D. Thesis, Iowa State University, Ames, Iowa, 1966.

(10) B. O. Coniglio, D. E. Giles, W. R. McDonald, and A. J. Parker, *J. Chem. Soc., B*, 152 (1966).

(11) This substitution reaction may also proceed by a free-radical chain process with coupling of the nitrophenyl radical with thiophenoxide to form an anion radical intermediate. See ref 2 for a complete discussion of this mechanism with nitrobenzyl halides.

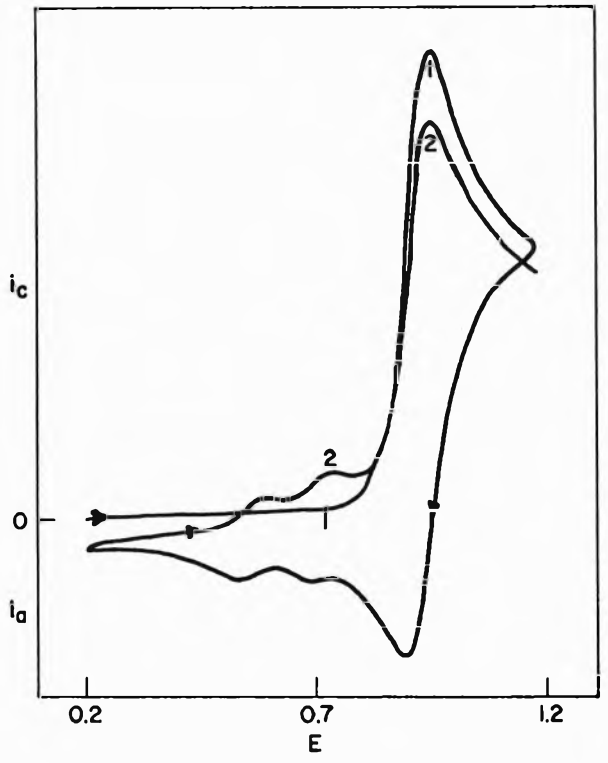


Figure 2.—Cyclic voltammogram of 5.52×10^{-3} *M* *p*-iodonitrobenzene and 0.1 *M* $NaNO_2$ in 0.1 *M* TEAP–DMSO at a scan rate of 80.6 mV/sec.

This work illustrates the facile nature of the coupling process of an organic free radical and anion. In contrast to the earlier reported work utilizing relatively stable benzyl free radicals,[2] the results reported herein illustrate that reactive phenyl radicals can be effectively scavenged by various anions even in the presence of reasonably good hydrogen-donating solvents. Such a low-energy reaction pathway available to free radicals is understandable, since only bond-formation and no bond-cleavage processes are involved.

Experimental Section

Instrumentation.—The cyclic voltammetric and thin-layer coulometric studies were performed on a transistorized, three-electrode potentiostat–galvanostat described previously.[4] The techniques suggested by Brown, Smith, and Booman[12] for stabilization of the potentiostat with 100% *iR* compensation were incorporated into this instrument.

Electron spin resonance spectra were obtained on a Varian V-4502 spectrometer. The anion radicals were produced *in situ* by the electrochemical reduction of the required iodonitrobenzene in the presence of the reacting anion.

The gas chromatograph was a Hewlett–Packard Model 700 equipped with flame ionization detection.

Cells and Electrodes.—The working electrode in the cyclic voltammetric experiments was a planar platinum button (Beckman No. 39273) with a geometric area of *ca.* 0.23 cm^2. The auxiliary electrode, a platinum foil, and the reference electrode, a saturated calomel electrode (sce), were isolated from the working electrode compartment by means of porous vycor glass (Corning No. 7930) and a bridge containing the solvent and 0.1 *M* supporting electrolyte.

A thin-layer electrode similar to the one described by McClure and Maricle[13] was used for the rapid determination of *n* values. The working electrode was a 3-mm length of 0.25-cm-diameter platinum rod attached to a stainless steel spindle (L. S. Starrett Co.) by means of electrically conducting epoxy. The sides of the spindle and the platinum rod were covered with a thin layer of epoxy cement (Devcon WR-2) in order to render them electroinactive. While the electrode functioned well in solutions of DMSO and AN, degradation of the epoxy covering occurred within several hours after placement in DMF solutions.

In the thin-layer experiments the potential of the working electrode was set sufficiently cathodic so as to reduce iodonitrobenzene and nitrobenzene (the product of hydrogen atom abstraction), but not so cathodic as to further reduce the product of the coupling reaction with cyanide ion. The method is not applicable in the case of nitrite ion, since the product of the coupling reaction, a dinitrobenzene anion radical, is further reduced at the applied potential to the corresponding dianion.

Chemicals.—All organic compounds were commercially available samples. The purity of each was checked by gas chromatography, cyclic voltammetry, and melting point; impure samples were recrystallized repeatedly until at least 99% purity was obtained.

Tetraethylammonium perchlorate was prepared according to the method of Kolthoff and Coetzee;[14] the method of Pocker and Kevill[15] was used for the preparation of tetraethylammonium nitrite. All supporting electrolytes were stored in a vacuum desiccator prior to their use. In a typical experiment, data were obtained first for the particular electrochemical system with 0.1 *M* tetraethylammonium perchlorate as the supporting electrolyte. The experiment was then repeated with the sodium salt of the desire anion added (0.1 *M*). Because of the insolubility of sodium nitrite in AN, tetraethylammonium nitrite was used as the anion source in this solvent.

DMF, AN, and DMSO were purified by previously described procedures[4] and stored over Linde Type 4A molecular sieves. All electrochemical experiments were performed in a glovebag under a nitrogen atmosphere. The solutions were deaerated with purified nitrogen for at least 20 min prior to the electrochemical measurements. All work was conducted at room temperature (22.5 ± 0.5°).

In the thermal generation of phenyl radicals, phenylazotriphenylmethane (0.005 *M*) was decomposed at 60.0 ± 0.1° with DMSO containing 0.10 *M* $NaNO_2$. Gas phase chromatography analysis showed formation of both benzene and nitrobenzene.

Registry No.—**1**, 636-98-6; **3**, 2395-99-5; *p*-nitrobenzonitrile anion radical, 12402-47-0; 3-iodonitrobenzene, 645-00-1; *m*-nitrophenyl radical, 3522-58-5; *m*-nitrobenzonitrile anion radical, 12402-46-9; 2-iodonitrobenzene, 609-73-4; *o*-nitrophenyl radical, 23209-57-6; *o*-nitrobenzonitrile anion radical, 12402-45-8.

Acknowledgments.—Acknowledgment is made to the Kansas State Bureau of General Research for partial support of this work and to the donors of the Petroleum Research Fund, administered by the American Chemical Society (Grant PRF 1123-G1).

(12) E. R. Brown, D. E. Smith, and G. L. Booman, *Anal. Chem.*, **40**, 1411 (1968).
(13) J. E. McClure and D. L. Maricle, *ibid.*, **39**, 236 (1967).
(14) I. M. Kolthoff and J. F. Coetzee, *J. Amer. Chem. Soc.*, **79**, 870 (1957).
(15) Y. Pocker and D. N. Kevill, *ibid.*, **87**, 4760 (1965).

The Reaction of Benzyne with 1,3-Cyclohexadiene

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Received March 13, 1969

The recent report by Grisdale, *et al.*,[2] describing the synthesis and characterization of the series of phenyl-

(1) J. R. Geigy A. G., 1061.419 Grundlagenforschung, 4000, Basel 21, Switzerland.
(2) P. J. Grisdale, T. H. Regan, J. C. Doty, J. Figueras, and J. L. R. Williams, *J. Org. Chem.*, **33**, 1116 (1968).

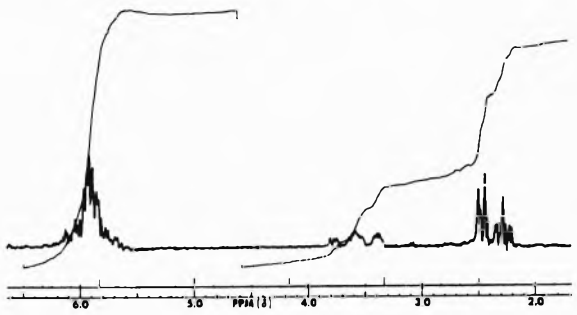


Figure 1.—Nmr spectrum of 5-phenyl-1,3-cyclohexadiene (3).

been adequately characterized by Grisdale, *et al.*[2] The integration of the nmr spectra of both 2 and 3 gave identical group integral ratios: five aromatic, four olefinic, one benzylic, and two allylic protons. As would be expected of an asymmetric structure, the signals for the olefinic protons of 3 are very complicated multiplets. Signals for the benzylic and allylic protons of 3 appeared at appreciably higher field, δ 3.60 and 2.38, respectively, than those of 2 (*cf.* Figure 1 and ref 2). This is consistent with the assigned structures, since the protons in question are monoallylic in 3 and bisallylic in 2. The uv spectrum of 3 showed a broad absorption at 259 nm (ϵ 5100) in contrast to the absorption bands of 2, which were found similar to those reported by Grisdale, *et al.*[2]

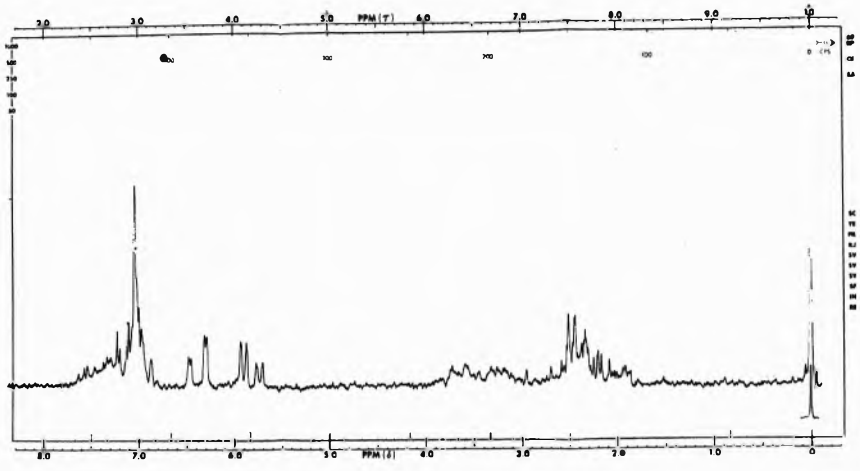


Figure 2.—Nmr spectrum of 4,5-benzobicyclo[4.2.0]octa-2,4-diene (5).

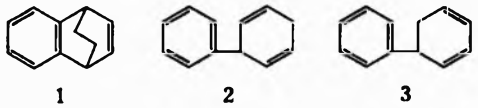
cyclohexadienes prompts us to report information concerning the reaction of benzyne with 1,3-cyclohexadiene.

This reaction has been reported by Simmons[3a] and further investigated by Huisgen and Knorr.[3b] The principal product, 5,6-benzobicyclo[2.2.2]octa-2,5-diene (1), has been identified by ir and nmr spectroscopy. In addition, Simmons isolated a mixture of isomers and suggested that the nmr spectrum of the mixture is consistent with the presence of a benzocyclobutene ring system.[3a]

Besides 1, Huisgen and Knorr isolated three other products and tentatively assigned structures 2 and 3 for two of them.

Via Simmons' procedure and preparative vapor chromatography using a 39 ft × 0.75 in. o.d. stainless steel column, packed with 25% Carbowax 20M on 30–60 Chromosorb W, with a column temperature of 150° and an injector temperature of 180°, triphenylene, 1, 2, 3, and another isomer were isolated. The structural assignments were based upon nmr and uv spectroscopy of the analytical pure products.

5,6-Benzobicyclo[2.2.2]octa-2,5-diene (1) was identified by comparing the nmr data with those published by Tori, *et al.*[4,5] 3-Phenyl-1,4-cyclohexadiene (2), has



1 2 3

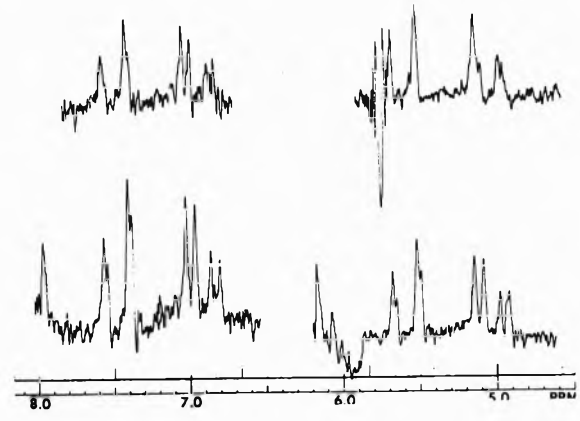


Figure 3.—Double-resonance experiments with 4,5-benzobicyclo[4.2.0]octa-2,4-diene: left, no decoupling by irradiating at δ 3.6; right, decoupling by irradiating at δ 3.2.

Because most of the benzyne reactions with dienes are known to yield 1,2 as well as 1,4 addition, we considered structure 4 for the fifth product, which appeared in a yield of 3%. However, the ultraviolet spectrum shows a maximum at 248 nm (ϵ 8600),[6] typical of styrene derivatives.[7] The nmr spectrum (Figure 2) shows four aromatic and two olefinic protons and two and four protons at δ 3.2. and 2.4, respectively. In double-resonance measurements, the frequencies as-

(3) (a) H. E. Simmons, *J. Amer. Chem. Soc.*, **83**, 1657 (1961); (b) R. Huisgen and R. Knorr, *Tetrahedron Lett.*, 1017 (1963).

(4) K. Tori, Y. Takano, and K. Kitahonoki, *Chem. Ber.*, **97**, 2798 (1964).

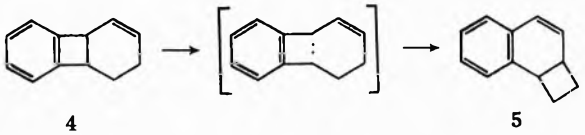
(5) K. Tori, Y. Hata, R. Muneyuki, Y. Takano, T. Tsuji, and H Tanida, *Can. J. Chem.*, **42**, 926 (1964).

(6) This compound is very sensitive to air; the ϵ value might be too low.

(7) R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley & Sons, Inc., New York, N. Y., 1951.

signed to olefinic protons (δ 6.35 and 5.84) were saturated without noticeable effect on the methylene signals. However, decoupling by saturation of the frequency of one of the bridgehead protons (δ 3.2, *cf.* Figures 2 and 3) led to simplification of the signals in the olefinic region. The combined results point strongly to **5** as the structure of the new product.

We speculate that 4,5-benzobicyclo[4.2.0]octa-2,4-diene (**5**) is produced by thermal rearrangement from **4**, which may be unstable under the conditions of vapor chromatographic work-up.



4 5

Registry No.—**3**, 21473-05-2; **5**, 21367-71-5; benzyne, 462-80-6; 1,3-cyclohexadiene, 592-57-4.

Acknowledgment.—This work was supported by a grant from the National Science Foundation. I am grateful to Professor George S. Hammond for his sponsorship of the work and for helpful discussion of the results, and to Dr. Christian Tanzer for his help in the double-resonance experiments.

A New Electrochemical Method for the Selective Reduction of Aliphatic Amides to Aldehydes or Alcohols

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Received July 23, 1969

Although the reduction of aliphatic amides to alcohols and aldehydes has been reported, the reaction has been limited to rather specific compounds. Thus aldehydes were obtained from amides using sodium in liquid ammonia,[1] but reaction occurred only with compounds possessing a phenyl group attached either to the nitrogen atom or to the carbonyl carbon.

The reduction of amides has also been accomplished electrolytically, but, here again, the substrates were quite specific, *e.g.*, N-aryl amides,[2] amides of isonicotinic acid,[3] and 2-carboxythiazole.[4] It was our purpose to develop a general and selective method, if possible, for the electrolytic reduction of primary, secondary, and tertiary amides to either the corresponding alcohol or aldehyde.

The reductions were carried out in an undivided electrolytic cell[5] consisting simply of a three-neck, round-bottom flask fitted with a Dry Ice condenser and two platinum electrodes. Lithium chloride dissolved in monomethylamine was used as electrolyte.

As can be seen (Table I), alcohols were obtained as major product when the reductions were carried out in the absence of an added proton source like ethanol. Further, it can be seen that the yield of alcohol product was generally good and not adversely affected by the length of the carbon chain of the starting amide or by substitution of one or two alkyl groups on the amide nitrogen.

TABLE I[a]

ELECTROREDUCTION OF VARIOUS ALIPHATIC AMIDES TO THE CORRESPONDING ALDEHYDE OR ALCOHOL

Entry	Amide[b]	Alcohol, %	Aldehyde, %	Coulombs
1	$CH_3(CH_2)_4CONH_2$ (0.05, 700)	58[c]	...	50,400
2	$CH_3(CH_2)_6CONH_2$ (0.01, 350)[d]	...	22	14,400
3	$CH_3(CH_2)_8CONH_2$ (0.05, 700)	59[c]	...	50,400
4	$CH_3(CH_2)_8CONH_2$ (0.005, 350)[e]	...	28	14,400
5	$CH_3(CH_2)_{12}CONH_2$ (0.02, 450)	92	...	50,400
6	$CH_3(CH_2)_{14}CONH_2$ (0.01, 450)	86	...	50,400
7	$CH_3(CH_2)_{16}CONH_2$ (0.01, 450)	79	...	50,400
8	$CH_3(CH_2)_4CONHCH_3$ (0.05, 600)[e]	4	50	12,960
9	$CH_3(CH_2)_4CONHCH_3$ (0.05, 600)	51	...	50,400
10	$CH_3(CH_2)_8CONHCH_3$ (0.02, 300)	81	...	46,800
11	$CH_3(CH_2)_8CONHCH_3$ (0.01, 300)[e]	24	58	14,400
12	$CH_3(CH_2)_8CON(CH_3)_2$ (0.008, 350)	93	...	14,400
13	$CH_3(CH_2)_8CON(CH_3)_2$ (0.01, 350)[e]	...	45	14,400
14	$CH_3(CH_2)_{14}CON(CH_3)_2$ (0.02, 450)	97	...	50,400
15	$CH_3(CH_2)_8CONH_2$ (0.005, 350)[e]	50	4	57,600

[a] The products reported in this table were identified by a combination of physical (ir and nmr spectra) and chemical methods (*e.g.*, melting points of compounds and derivatives such as 2,4-dinitrophenylhydrazones of aldehydes and 3,5-dinitrobenzoates of alcohols. [b] The first value in parentheses represents the number of moles of amide used; the second value represents the number of milliliters of methylamine employed as solvent. [c] A minor product observed in this case was the N-methylimine of the corresponding aldehyde. [d] Seven grams of ethanol present during reduction. [e] Five grams of ethanol present during reduction.

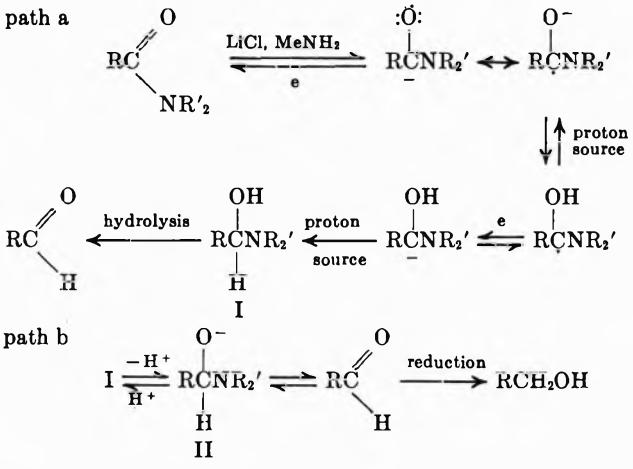
Reduction to aldehydes was achieved in the same cell and under the same reaction conditions as were used to produce alcohols, except that absolute ethanol was added to serve as a proton source. The yield of aldehydes (Table I) was not affected by the length of the carbon chain of the starting amide, but was influenced by alkyl substitution on the amide nitrogen. Reduction of secondary and tertiary amides resulted in better yields of aldehydes than reduction of primary amides.

The mechanistic scheme shown in Scheme I has been proposed[1] to explain such reaction products.

When electrolysis is conducted in the absence of ethanol, the equilibrium between I and II (path b)

(1) A. J. Birch, J. C. Craig, and M. Slaytor, *Aust. J. Chem.*, **8**, 512 (1955).
(2) L. Horner and H. Neuman, *Chem. Ber.*, **98**, 3462 (1965).
(3) H. Lund, *Acta Chem. Scand.*, **17**, 2325 (1963).
(4) P. Iversen and H. Lund, *ibid.*, **21**, 389 (1967).
(5) R. A. Benkeser and E. M. Kaiser, *J. Amer. Chem. Soc.*, **85**, 2858 (1963).

SCHEME I



would likely favor II because of the relative acid–base strengths involved. Hence the alcohol products observed would arise from II *via* path b as shown. It is necessary to assume that the aldehyde formed by path b undergoes rapid reduction to alcohol in the immediate vicinity of the cathode; otherwise it may well have sufficient opportunity to react with solvent to form the N-methylimine, which upon further reduction would yield amine.[6] The fact that amines were not obtained as reaction products excludes the formation of such N-methylimines, since we have shown that imines are converted into amines under the reaction conditions employed.

Electrolysis in the presence of a proton donor such as ethanol causes the reaction to proceed by path a, the equilibrium between I and II now favoring I. Since in the presence of ethanol the yields of alcohols were greatly reduced and amine products were not observed, one might conjecture that intermediate I effectively resists further reduction. Hydrolysis of I with aqueous acid yields the corresponding aldehyde.

To determine the effect of increased reaction times, a fiftyfold excess of current was passed through a solution of decanamide containing ethanol. It was found (entry 15, Table I) that decanol was the major product, with the yield of aldehyde being significantly decreased. This would be the predicted result if intermediates I and II were in equilibrium as depicted in Scheme I. Longer reaction times would increase the opportunity for intermediate II to follow path b, leading to aldehyde and ultimately alcohol.

Experimental Section

Preparation of Amides.—All amides were prepared by bubbling ammonia, methylamine, or dimethylamine through the corresponding carboxylic acids at reflux temperature followed by vacuum distillation of the product.

Electrolytic Reduction of Amides to Alcohols.—Primary, secondary, and tertiary amides were reduced to alcohols in an undivided electrolytic cell[5] consisting of a three-neck flask fitted with a Dry Ice condenser and two platinum electrodes. The flask was charged with lithium chloride (34 g, 0.8 mol), anhydrous monomethylamine (350–700 cc) and the amide (0.008–0.05 mol). A current of 2 A was passed through the solution, after which solvent was allowed to evaporate through a condenser maintained at −5°. The resulting residue was hydrolyzed with water (30–200 cc) and the aqueous solution was extracted with ether. The latter was dried with $MgSO_4$. Table I summarizes the results.

Electrolytic Reduction of Amides to Aldehydes.—Primary, secondary, and tertiary aliphatic amides were reduced to aliphatic aldehydes as described above except that the flask was charged with lithium chloride (17 g, 0.4 mol), anhydrous monomethylamine (300–600 cc), absolute ethanol (5 g, 0.1 mol), and the amide (0.005–0.05 mol). A current of 2 A was passed through the solution for *ca.* 2 hr (*ca.* 14,400 C). At the end of this time, solvent was allowed to evaporate through a condenser which was maintained at −5°. The resulting residue was hydrolyzed with water (20–30 cc) and the aqueous solution was extracted with ether. After removal of ether at room temperature under reduced pressure, the residue was acidified with 10% HCl at 0° and extracted with ether. Drying of the ether layer and removal of solvent at room temperature yielded products which were identified by their 2,4-dinitrophenylhydrazones, glpc, and ir. Table I summarizes the results.

Electrolytic Reduction of the N-Methylimine of Hexanal.—The reduction was carried out in a three-neck flask fitted with a Dry Ice condenser and two platinum electrodes. A current of 0.6 A was passed through a solution of anhydrous monomethylamine containing lithium chloride (4 g, 0.1 mol) and the N-methylimine of hexanal (1.1 g, 0.01 mol) for a period of 2 hr. The usual work-up gave 0.8 g of residue following hydrolysis with water (10 cc). Analysis by glpc showed the residue to consist of starting imine (56%) and N-hexylmethylamine (44%). The yield of amine was 32%.

Registry No.—$CH_3(CH_2)_4CONH_2$, 628-02-4; $CH_3(CH_2)_6CONH_2$, 629-01-6; $CH_3(CH_2)_8CONH_2$, 2319-29-1; $CH_3(CH_2)_{12}CONH_2$, 638-58-4; $CH_3(CH_2)_{14}CONH_2$, 629-54-9; $CH_3(CH_2)_{16}CONH_2$, 124-26-5; $CH_3(CH_2)_4CONHCH_3$, 3418-05-1; $CH_3(CH_2)_8CONHCH_3$, 23220-25-9; $CH_3(CH_2)_8CON(CH_3)_2$, 14433-76-2; $CH_3(CH_2)_{14}CON(CH_3)_2$, 3886-91-7.

Acknowledgment.—This research was sponsored by the Air Force Office of Scientific Research, Office of Aerospace Research, U. S. Air Force, under AFOSR Grant 822-67.

(6) R. A. Benkeser and S. Mels, *J. Org. Chem.*, **34**, 3970 (1969).

Reactions of α-Dichloromethylene Ketones[1a]

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β-Chlorovinyl ketones are readily prepared and their high reactivity has led to their use as intermediates in the synthesis of a variety of aliphatic, aromatic, and heterocyclic compounds.[2] Techniques for the preparation of β-β-dichlorovinyl ketones are rather limited and studies of their reactions have been restricted to acyclic analogs.[2-4] We recently described a convenient route to β,β-dichlorovinyl ketones involving the reaction of enamines and carbon tetrachloride[5] which makes available a variety of acyclic and cyclic derivatives. With the ready accessibility of the

(1) (a) Abstracted from part of the thesis submitted by R. V. K. in partial fulfillment of the requirements for the Ph.D. degree, Purdue University, August 1966; (b) David Ross Research Fellow, Purdue University, 1964–1966.

(2) A. Pohland and W. Benson, *Chem. Rev.*, **66**, 161 (1966).

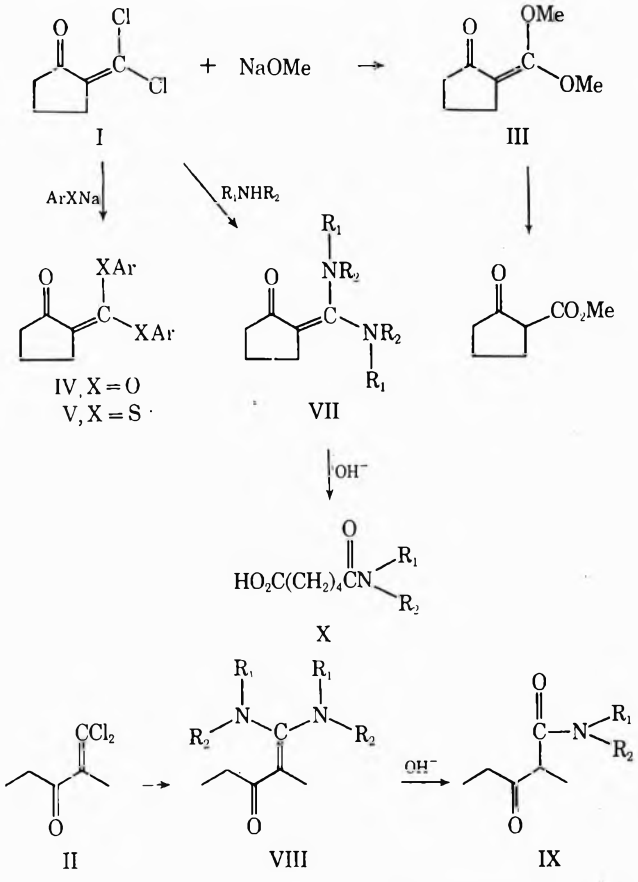
(3) S. Searles, R. A. Sanchez, R. L. Soulen, and D. G. Kundiger, *J. Org. Chem.*, **32**, 2655 (1967).

(4) R. L. Soulen, D. G. Kundiger, S. Searles, and R. A. Sanchez, *ibid.*, **32**, 2661 (1967).

(5) J. Wolinsky and D. Chan, *Chem. Commun.*, 567 (1966).

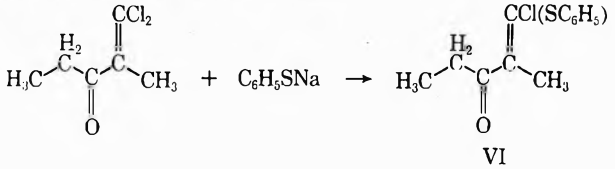
cyclic derivatives, it became of interest to examine their reactions, and, in particular, to compare their behavior with that of acyclic analogs. In this study we have focussed our attention on the reactions of nucleophiles with 2-dichloromethylenecyclopentanone (I) and 2-dichloromethylene-3-pentanone (II).

Reaction at the β-carbon atom with concomitant replacement of chlorine atoms occurs with alkoxides, thiolates, and primary and secondary amines. The addition of I to sodium methoxide in methanol gave a mixture of 2-dimethoxymethylenecyclopentanone (III) and 2-carbomethoxycyclopentanone. The dimethoxyvinyl ether III is easily hydrolyzed, even by atmospheric moisture, and was difficult to isolate in a high state of purity. On standing in contact with air it was converted into 2-carbomethoxycyclopentanone.



The reaction of I with sodium phenoxide and thiophenoxide gave IV and V in low yield. These aromatic derivatives were quite stable to atmospheric moisture.

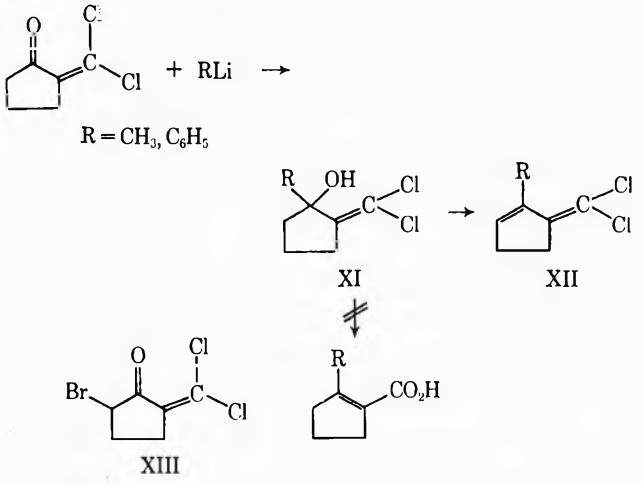
In contrast with the reactivity of I, the acyclic analog II gave an 83% yield of monosubstituted product VI when reacted with sodium thiophenoxides.



The reactions of I and II with amines were best conducted employing the amine as a solvent. Primary and secondary amines reacted smoothly to afford enamine derivatives VII and VIII in good yield. The enamines VII and VIII were quite stable and even after prolonged treatment with dilute acid were recovered unchanged. Dilute base, on the other hand, rapidly transformed enamines VIII into the corresponding amide IX. The hydrolysis of VII proved to be anamolous, since the cyclopentane ring was ruptured and afforded the monoamide derivative of adipic acid X.

Weaker bases such as phenylhydrazine, 2,4-dinitrophenylhydrazine, and hydroxylamine reacted exclusively with the carbonyl group of I and II to yield stable hydrazides and oximes. Various attempts to convert these derivatives into isooxazoles met with no success. For example, stirring the oxime of II with a slurry of sodium hydride and benzene gave a quantitative yield of a sodium salt. Attempts to cyclize the salt by heating in solvents such as acetonitrile, dimethylformamide, or dimethyl sulfoxide led to recovery of oxime or complete degradation of the starting material.

Organolithium reagents also reacted exclusively with the carbonyl group to give unsaturated tertiary alcohols XI. Dehydration of these alcohols gave only dienes XII and no unsaturated acid.[6]



The double bond in I proved to be inert to electrophillic reagents. Thus bromine or pyridinium hydrobromide perbromide transformed I into the rather unstable bromo derivative XIII.

Experimental Section[7]

2-Dichloromethylene-3-pentanone (II).—A stirred mixture of 100 ml of carbon tetrachloride, 20 g (0.13 mol) of 3-pentanone piperidine enamine, and 26.5 g (0.26 mol) of triethylamine was kept at 82° for 81 hr. Triethylamine hydrochloride, 19.77 g, was removed by filtration. The carbon tetrachloride was evaporated under diminished pressure and the residue was stirred at room temperature with water and then extracted with ether. The ether extracts were extracted with hydrochloric acid. The acid extracts were combined with the original aqueous phase and heated for 10–18 hr. The mixture was steam distilled and the distillate was saturated with salt and extracted with ether. The ether solution was dried and distilled to give 6.0 g (30%) of 2-dichloromethylene-3-pentanone (II), bp 40–44° (1.4 mm), n^{25}D 1.4720, which was contaminated by *ca.* 2% 2-chloromethylene-3-pentanone.

A pure sample of II was isolated by vpc: n^{25}D 1.4742; ir 5.90 and 6.20 μ; λ_{max}^{EtOH} 244 mμ (ϵ 3490); nmr (CCl_4) 1.08 (t, 3, CH_3-CH_2), 1.98 (s, 3, CH_3C=C), and 2.67 ppm (q, 2, CH_3CH_2).

Anal. Calcd for $C_6H_8Cl_2O$: C, 43.14; H, 4.83; Cl, 42.45. Found: C, 43.47; H, 5.09; Cl, 42.09.

(6) *Cf.* E. Jones and B. Weedon, *J. Chem. Soc.*, 937 (1946).

(7) All boiling and melting points are uncorrected. Nmr spectra were measured with a Varian Associates A-60 spectrometer. Microanalyses were performed by Dr. C. S. Yeh and associates.

The 2,4-dinitrophenylhydrazone derivative of II crystallized as glistening orange plates from dilute ethanol, mp 83–84.5°.

Anal. Calcd for $C_{12}H_{12}Cl_2N_4O_4$: C, 41.51; H, 3.49; N, 16.14; Cl, 20.43. Found: C, 41.17; H, 3.48; N, 15.84; Cl, 20.32.

The phenylhydrazone of 2-dichloromethylene-3-pentanone was crystallized from hexane: mp 64–65°; ir 2.90, 6.20, 6.62, and 6.70 μ; nmr 1.10 (t, 3), 2.08 (s, 3), 2.38 (q, 2), and 7.00 ppm (m, 6).

Anal. Calcd for $C_{12}H_{14}Cl_2N_2$: C, 56.03; H, 5.45. Found: C, 55.64; H, 5.30.

Heating the phenylhydrazone with pyrrolidine under mild conditions led to recovery of hydrazone, while more vigorous conditions (refluxing in benzene) gave a complex mixture from which a pure product could not be isolated.

The oxime of 2-dichloromethylene-3-pentanone was obtained as a colorless liquid: $n^{28}D$ 1.5034; ir 3.00, 3.29, 6.08, 6.15, and 11.0 μ; nmr 1.14 (t, 3), 2.01 (s, 3), 2.55 (q, 2), and 9.12 ppm (s, 1).

Anal. Calcd for $C_6H_9Cl_2NO$: C, 39.56; H, 4.94. Found: C, 40.42; H, 5.16.

2-Dichloromethylenecyclopentanone (I).—A stirred solution of 100 ml of carbon tetrachloride, 20 g of cyclopentanonone piperidine enamine, and 26.5 g of triethylamine was heated at 85° for 18 hr. The reaction mixture was worked up as described above to give 13.0 g of a colorless solid: mp 49–50° (from pentane); ir (CCl_4) 5.82, 6.37, and 11.20 μ; λ_{max}^{EtOH} 256 mμ (ε 13,820); nmr (CCl_4) multiplets at 2.00, 2.42, and 2.83 ppm.

Anal. Calcd for $C_6H_6OCl_2$: C, 43.67; H, 3.67; Cl, 42.97. Found: C, 43.71; H, 3.63; Cl, 43.26.

The 2,4-dinitrophenylhydrazone derivative of 2-dichloromethylenecyclopentanone was recrystallized from hot chloroform, mp 244–245°.

Anal. Calcd for $C_{12}H_{10}N_4O_4Cl_2$: C, 41.76; H, 2.92; N, 16.23; Cl, 20.54. Found: C, 41.61; H, 2.92; N, 16.17; Cl, 20.76.

The phenylhydrazone derivative of 2-dichloromethylenecyclopentanone was recrystallized from methanol: mp 111.5–113.5°; ir 2.95, 6.24, 6.45, 6.63, and 6.70 μ; nmr 1.80 (m, 2), 2.50 (m, 4), and 7.00 ppm (m, 6).

Anal. Calcd for $C_{12}H_{12}Cl_2N_2$: C, 56.47; H, 4.72. Found: C, 56.73; H, 4.81.

The oxime of 2-dichloromethylenecyclopentanone was purified by sublimation *in vacuo:* mp 147°; ir 2.85, 3.1, and 6.1 μ; nmr 1.8 (m, 2), 2.17 (m, 4), and 9.7 ppm (broad s, 1).

Anal. Calcd for $C_6H_7NOCl_2$: C, 40.01; H, 3.88; N, 7.88; Cl, 39.44. Found: C, 40.36; H, 4.14; N, 7.73; Cl, 39.58.

To a slurry of 450 mg (10 mmol) of sodium hydride in 20 ml of benzene was added a solution of 2-dichloromethylenecyclopentanone oxime in 4 ml of benzene and the resulting mixture was refluxed for 3 days. The sodium salt of the oxime was collected and dried: yield 2.0 g (100%); ir 3.4, 6.2, and 11.25 μ.

2-Dichloromethylenecyclohexanone.—A mixture of 1 l. of carbon tetrachloride, 200 g of cyclohexanone piperidine enamine, and 243 g of triethylamine was refluxed for 48 hr. The usual work-up and distillation of the organic phase gave 66 g of cyclohexanone and 14 g of a mixture of cyclohexanone and 2-chloromethylenecyclohexanone, bp 60–75° (1 mm).[5] The aqueous phase was distilled and the distillate was extracted with ether. The ether extract was distilled to give 25.5 g of 2-dichloromethylenecyclohexanone, bp 86–88° (2 mm), $n^{56}D$ 1.5252.

Anal. Calcd for $C_7H_8OCl_2$: C, 46.95; G, 5.50; Cl, 39.61. Found: C, 47.26; H, 4.72; Cl, 39.82.

The oxime of 2-dichloromethylenecyclohexanone was crystallized from hexane: mp 86–100°; ir 3.0, 6.20, and 11.21 μ; nmr 1.75 (m, 4), 2.68 (m, 4), and 9.75 (s, 1) ppm.

Anal. Calcd for $C_7H_9Cl_2NO$: C, 43.35; H, 4.64; Cl, 36.60. Found: C, 43.76; H, 5.11; Cl, 36.20.

A solution of 200 mg of the oxime was stirred in 20 ml of pyrollidine at ambient temperature for 4 hr. Evaporation of pyrollidine gave a quantitative recovery of oxime.

The phenylhydrazone derivative of 2-dichloromethylenecyclohexanone was purified by recrystallization from pentane: mp 72.5–73°; ir 2.95, 6.23, and 11.20 μ; nmr 1.65 (m, 4), 2.43 (m, 4), and 7.0 ppm (m, 6).

Anal. Calcd for $C_{13}H_{14}Cl_2N_2$: C, 57.99; H, 5.20; Cl, 26.38. Found: C, 57.32; H, 5.02; Cl, 26.50.

2-Dithiophenoxymethylenecyclopentanone (V).—To a slurry of sodium thiophenoxide, prepared from 450 mg of sodium hydride and 1.1 g of thiophenol, in ether was added 830 mg of 2-dichloromethylenecyclopentanone over a period of 1 hr. The resulting deep purple mixture was filtered and the ether was evaporated. The residue was taken up in 3% chloroform in hexane and a small amount of solid was removed. On cooling there was obtained 578 mg of yellow crystals: mp 94–95°; ir 5.95 μ; λ_{max}^{EtOH} 214 mμ (ε 19,500), 260 (7800), and 336 (14,000); nmr ($CDCl_3$) 2.0 (q, 2), 2.4 (t, 2), 2.8 (t, 2), and 7.1 ppm (s, 10).

Anal. Calcd for $C_{18}H_{16}OS_2$: C, 69.23; H, 5.12; S, 20.52. Found: C, 69.01; H, 5.32; S, 20.74.

2-Diphenoxymethylenecyclopentanone (IV).—2-Dichloromethylenecyclopentanone, 830 mg, was treated with 1.16 g of sodium phenoxide as described above to give 754 mg of crude product. Recrystallization from 2:1 hexane–chloroform, with Darco KB treatment, afforded 342 mg of solid: mp 95–95.5°; ir 5.85, 6.15, 6.35, and 6.8 μ; λ_{max}^{EtOH} 272 mμ (ε 17,800) and 310 (11,900); nmr ($CDCl_3$) 2.05 (m, 4), 2.68 (t, 2), and 7.02 ppm (d, 10).

Anal. Calcd for $C_{18}H_{16}O_3$: C, 77.14; H, 5.71. Found: C, 77.09; H, 5.56.

1-Chloro-2-methyl-1-thiophenoxy-1-penten-3-one (VI).—To a slurry of 1.32 g (10 mmol) of sodium thiophenolate in 20 ml of ether was slowly added 835 mg (5 mmol) of 2-dichloromethylene-3-pentanone. After stirring for 1 hr at room temperature the solids were removed by filtration. Distillation of the filtrate gave 1.3 g of a yellow oil. A sample was redistilled: bp 116–116.5° (1 mm); $n^{23}D$ 1.5800; ir 3.22, 5.90, 6.35, and 6.68 μ; λ_{max}^{EtOH} 211 mμ (ε 14,100) and 252 (6670); nmr (CCl_4) 1.10 (t, 3), 2.05 (s, 3) 2.65 (q, 2), and 7.35 ppm (s, 5).

Anal. Calcd for $C_{12}H_{13}ClOS$: C, 59.87; H, 5.40. Found: C, 60.35; H, 5.27.

2-Diisopropylaminomethylenecyclopentanone.—A solution of 1.0 g of 2-dichloromethylenecyclopentanone in 15 ml of isopropylamine was stirred at room temperature for 15 min. Ether was added and the solid was removed by filtration. The ether and excess amine were removed under diminished pressure and the residue was extracted with hot hexane. The hexane was evaporated, leaving 980 mg (76.6%) of an oil which solidified on standing. Recrystallization from pentane gave yellow crystals: mp 81.82°; ir 3.00, 3.35, 6.18, and 6.40 μ; nmr ($CDCl_3$) 1.20 (d, 12), 1.80 and 2.35 (m, 8), and 3.75 ppm (m, 2).

Anal. Calcd for $C_{12}H_{22}N_2O$: C, 68.57; H, 10.47; N, 13.32. Found: C, 68.38; H, 10.41; N, 13.24.

2-Di-*n*-butylaminomethylenecyclopentanone was obtained from the reaction of 2-dichloromethylenecyclopentanone and *n*-butylamine. A sample was purified by preparative thin layer chromatography: ir 3.05, 3.2, and 6.4 μ; λ_{max}^{EtOH} 219 mμ (ε 6060) and 309 (12,700); nmr ($CDCl_3$) 0.95 (m, 7), 1.50 (m, 11), 2.40 (m, 4), and 3.25 ppm (m, 4).

Anal. Calcd for $C_{14}H_{26}N_2O$: C, 70.59; H, 11.92; N, 12.84. Found: C, 70.71; H, 11.97; N, 12.50.

2-Dipyrrolidinomethylenecyclopentanone was isolated in 34% yield from the reaction of pyrrolidine and 2-dichloromethylenecyclopentanone carried out as described above. A pure sample of this amino ketone was obtained by sublimation *in vacuo:* mp 96–100°; ir 6.20 and 6.75 μ; λ_{max}^{EtOH} 255 mμ (ε 3240) and 330 (7140); nmr ($CDCl_3$) 1.9 (m, 12), 2.3 (t, 2), and 3.3 ppm (m, 12).

Anal. Calcd for $C_{14}H_{22}N_2O$: C, 71.76; H, 9.41; N, 11.98. Found: C, 71.80; H, 9.66; N, 11.76.

2-Dipyrrolidinomethyllenecyclopentanone was recovered after treatment with 20% sulfuric acid at 100° for 6 hr. Heating 500 mg of the amino ketone for 45 min at 100° with 5 ml of 10% sodium hydroxide gave a homogeneous solution. The solution was cooled and extracted with chloroform to give 80 mg of unaltered amino ketone. Acidification of the aqueous solution and extraction with chloroform gave 229 mg of an oil which slowly solidified. Recrystallization from ethyl acetate gave a pure sample of X: mp 84–85°; ir 3.35, 5.8, and 6.25 μ; nmr 1.8 (m, 8), 2.4 (m, 4), 3.5 (m, 4), and 11.50 ppm (s, 1).

Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.30; H, 8.54. Found: C, 60.72; H, 8.45.

2-Dipyrrolidinomethylene-3-pentanone (VIII) was obtained in 93% yield as a viscous, straw-yellow oil, $n^{25}D$ 1.554, from the reaction of excess pyrrolidine with 2-dichloromethylene-3-pentanone. The amino ketone was heated for 15 min at 100° with 10 ml of 10% sodium hydroxide. The mixture was worked up as described above to give 50% of an oil. A pure sample of keto amide IX was obtained by evaporative distillation: $n^{25}D$ 1.4796; ir 2.90, 3.32, 5.79, and 6.08 μ; nmr 1.15 (t, 3), 1.35 (d, 3), 1.95 (m, 4), 2.42 (q, 2), and 3.50 ppm (m, 5).

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.49; H, 9.29. Found: C, 65.57; H, 9.56.

5-Bromo-2-dichloromethylenecyclopentanone (XIII).—Pyridinium bromide perbromide, 1.9 g(5 mmol) was added to a solution of 830 mg (5 mmol) of 2-dichloromethylenecyclopentanone in 15 ml of carbon tetrachloride. The mixture was stirred at ambient temperature for 15 min and filtered. The filtrate was treated with anhydrous sodium carbonate. Evaporation of the solvent left 1.2 g of an oil which solidified on cooling. Recrystallization from pentane gave white crystals: mp 63–64°; ir 5.80 and 6.30 μ; nmr 2.32 (m, 2), 2.95 (m, 2), and 4.40 ppm (q, 1, CHBr).

Anal. Calcd for $C_6H_5BrCl_2O$: C, 29.50; H, 2.05. Found: C, 29.01; H, 2.13.

2-Dichloromethylene-1-hydroxy-1-methylcyclopentane.—A mixture of 830 mg (5 mmol) of 2-dichloromethylenecyclopentanone and 8 mmol of methyllithium in ether was prepared at −70° and then kept at ambient temperature for 10 hr. After the addition of 10 ml of 3.7% hydrochloric acid, the mixture was extracted with methylene chloride. The solution was dried and the solvents were removed, leaving an oil. The oil was triturated with four 10-ml portions of pentane. The pentane solution was treated with Darco KB and the volume was reduced to *ca.* 3 ml. On cooling to −70° unreacted 2-dichloromethylenecyclopentanone crystallized. The solid was removed and the remaining solvent was evaporated, leaving 390 mg (43%) of an oil which solidified on standing. Sublimation *in vacuo* gave a pure sample of the alcohol: mp 45.5–46°; ir 2.98, 6.15, and 6.31 μ; nmr 1.52 (s, 3, CH_3CO) ,1.87 (m, 4), and 2.50 ppm (m, 3).

Anal. Calcd for $C_7H_{10}Cl_2O$: C, 46.45; H, 5.50; Cl, 39.25. Found: C, 46.50; H, 5.58; Cl, 39.24.

3-Dichloromethylene-2-methylcyclopentene.—A mixture of 300 mg of 2-dichloromethylene-1-hydroxy-1-methylcyclopentane, 10 ml of 10% sulfuric acid, and 10 ml of methanol was stirred for 4 hr. The mixture was made basic with 10% sodium hydroxide solution and extracted with methylene chloride. After drying, the solvent was evaporated to leave 284 mg of an oil. Purification by vpc gave a colorless liquid: ir 5.80 (w), 6.17, 6.22, and 11.30 μ; λ_{max}^{EtOH} 230 mμ (ϵ 7280); nmr 2.08 (m, 3), 2.35 (m, 2), 2.70 (m, 2), and 5.98 ppm (br s, 1).

Anal. Calcd for $C_7H_8Cl_2$: C, 51.55; H, 4.90. Found: C, 51.50; H, 4.91.

3-Dichloromethylene-2-phenylcyclopentene.—A solution of phenylithium in ether, prepared from 1.18 g of bromobenzene and 105 mg of lithium, was added to a Dry Ice cooled solution of 2-dichloromethylenecyclopentanone in tetrahydrofuran. The reaction was worked up in the usual manner to give 1.08 g of an oil whose ir spectrum indicated the presence of a mixture of alcohol and starting ketone. A 243-mg portion of this oil was stirred for 2 hr at 25° with 0.5 ml of boron trifluoride etherate in 10 ml of ether. The ether solution was washed with sodium bicarbonate solution, dried, and evaporated to leave 201 mg of an oil. The oil was placed on a short alumina column and eluted with hexane to give 150 mg of diene. An analytical sample was prepared by evaporative distillation: ir 3.20, 6.24, 6.70, and 11.20 μ; nmr 2.60 (m, 2), 2.90 (m, 2), 6.15 (t, 1, HC=C), and 7.22 ppm (s, 5, ArH).

Anal. Calcd for $C_{12}H_{10}Cl_2$: C, 64.00; H, 4.44. Found: C, 64.20; H, 4.38.

Registry No.—I, 10412-35-8; II, 13017-26-0; 2,4-dinitrophenylhydrazone derivative of II, 23231-13-2; phenylhydrazone of 2-dichloromethylene-3-pentanone, 23231-14-3; oxime of 2-dichloromethylene-3-pentanone, 23231-15-4; 2,4-dinitrophenylhydrazone derivative of 2-dichloromethylenecyclopentanone, 23231-16-5; phenylhydrazone derivative of 2-dichloromethylenecyclopentanone, 23231-17-6; oxime of 2-dichloromethylenecyclopentanone, 23231-18-7; 2-dichloromethylenecyclohexanone, 10412-36-9; oxime of 2-dichloromethylenecyclohexanone, 23231-20-1; phenylhydrazone derivative of 2-dichloromethylenecyclohexanone, 23231-21-2; IV, 23231-22-3; V, 23231-23-4; VI, 23231-24-5; 2-diisopropylaminomethylenecyclopentanone, 23231-25-6; 2-di-*n*-butylaminomethylenecyclopentanone, 23231-26-7; 2-dipyrrolidinomethylenecyclopentanone, 23263-81-2; IX, 23231-27-8; X, 23231-28-9; XIII, 23240-69-9; 2-dichloromethylene-1-hydroxy-1-methylcyclopentane, 23240-70-2; 3-dichloromethylene-2-methylcyclopentene, 23240-71-3; 3-dichloromethylene-2-phenylcyclopentene, 23240-72-4.

Intermediates in Nucleophilic Aromatic Substitution. III.[1] Visible Absorption Spectra of the Acid and Basic Form of the 1,3,5-Trinitrobenzene–Piperidine Meisenheimer Complex in 10% Dioxane–90% Water

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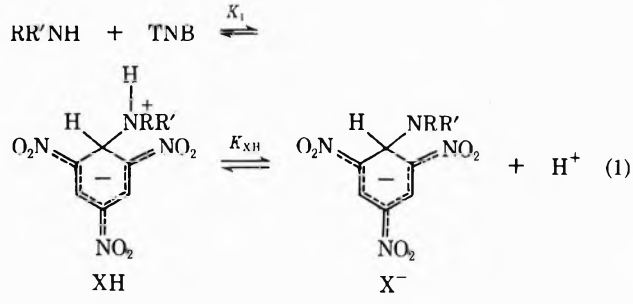
Received August 28, 1969

There exist a number of reports on the absorption spectra of the Meisenheimer complexes produced by the interaction of 1,3,5-trinitrobenzene (TNB) with aliphatic amines in a variety of solvents.[2–7] With primary and secondary amines, equilibrium 1 has



R′ = Alkyl or H

consistently been found to strongly favor X^- over XH, so that the spectra always referred to the basic form X^-. We wish now to report the spectrum of the zwitterionic form XH of the piperidine–TNB complex in 10% dioxane–90% water at 25°.

Figure 1 shows spectra of TNB in two different piperidine–piperidine hydrochloride buffer solutions, at different pH[8] but equal ionic strength. Knowledge of the equilibrium constants K_1 and K_{XH} and of the easily obtained spectrum of pure X^- would allow one to dissect the respective contributions of both species to the overall spectrum and thus to find the spectrum of pure XH by difference. The matter is, however, more complex for two reasons. (1) TNB and piperidine undergo another interaction to form the oxyhydroxylamine YH and its conjugate anion Y^-;[1] though YH and Y^- do not contribute to the visible spectrum, they appreciably reduce the equilibrium concentrations of XH and X^-. (2) There is also some concurrent for-

(1) Part II: C. F. Bernasconi, *J. Amer. Chem. Soc.*, **92**, 129 (1970).
(2) R. E. Miller and W. F. K. Wynne-Jones, *J. Chem. Soc.*, 2375 (1959).
(3) R. Foster, *ibid.*, 3508 (1959).
(4) G. Briegleb, W. Liptay, and M. Cantner, *Z. Phys. Chem.* (Frankfurt am Main), **26**, 55 (1960).
(5) (a) R. Foster and R. K. Mackie, *Tetrahedron*, **16**, 119 (1961); (b) R. Foster and R. K. Mackie, *ibid.*, **22**, 1831 (1966).
(6) J. Osugi and M. Sasaki, *Rev. Phys. Chem. Jap.*, **37**, 43 (1967).
(7) M. R. Crampton and V. Gold, *J. Chem. Soc., B*, 23 (1967).
(8) For our definition of pH in 10% dioxane–90% water, see ref 1.

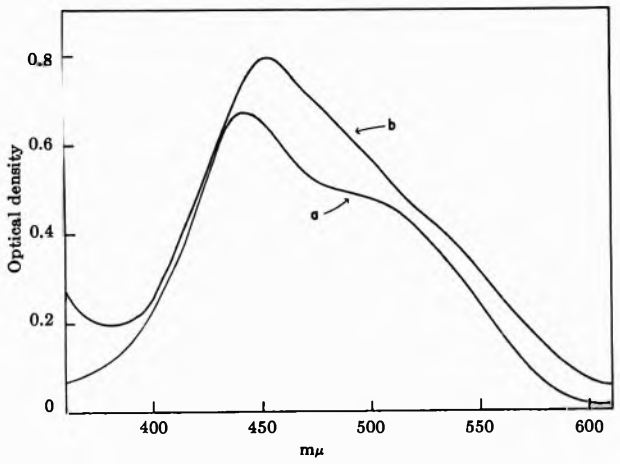
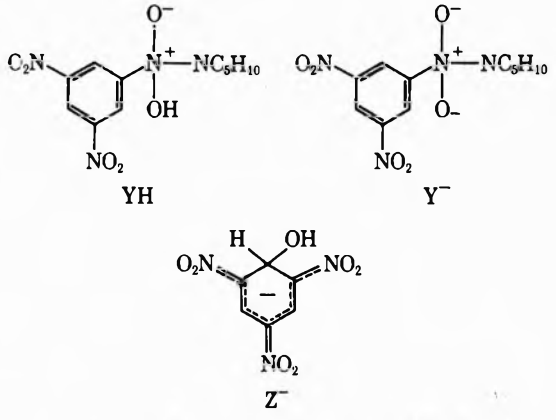


Figure 1.—Absorption spectra of TNB in the presence of a piperidine–piperidine hydrochloride buffer in 10% dioxane–90% water at 25°: a, [Pip] = 0.045 M, [Pip HCl] = 0.005 M, [NaCl] = 0.49 M, $[TNB]_0 = 1.60 \times 10^{-4}$ M, pH 12.02; b, [Pip] = 0.10 M, [Pip HCl] = 0.50 M, $[TNB]_0 = 1.20 \times 10^{-3}$ M; pH 10.65.

mation of a Meisenheimer complex (Z^-) between TNB and the hydroxide ion, which significantly contributes to the spectra in Figure 1.



A kinetic analysis of all relevant equilibria has been reported in the preceding paper[1] of this series. It yielded the following results: $K_1 = 0.20 \pm 0.04$ l. M^{-1}; $K_{XH} = 1.5 \pm 0.2 \times 10^{-11}$ M l.$^{-1}$; K_2 (formation of YH form piperidine and TNB) $= 4.3 \pm 1.3$ l. M^{-1}; K_{YH} (acid dissociation constant of HY to produce Y^-) $= 2.5 \pm 0.3 \times 10^{-12}$ M l.$^{-1}$; K_3 (formation of Z^- from OH^- and TNB) $= 5.0 \pm 0.2$ l. M^{-1}. These data allow the calculation of the concentrations of XH, X^-, and Z^- by use of eq 2–4; $[TNB]_0$ stands for the stoichiometric concentration of TNB.

$$[XH] = \frac{K_1[Pip][TNB]_0}{D} \quad (2)$$

$$[X^-] = \frac{K_1(K_{XH}/[H^+])[Pip][TNB]_0}{D} \quad (3)$$

$$[Z^-] = \frac{K_3[OH^-][TNB]_0}{D} \quad (4)$$

$$D = 1 + \left(K_1 + K_1\frac{K_{XH}}{[H^+]} + K_2 + K_2\frac{K_Y}{[H^+]}\right)[Pip] + K_3[OH^-]$$

For the solution giving rise to spectrum a in Figure 1 ([Pip] = 0.045 M, [Pip HCl] = 0.005 M, [NaCl] = 0.49 M, $[TNB]_0 = 1.60 \times 10^{-4}$ M, pH 12.02), the following complex concentrations were computed: [XH] = 8.22×10^{-7} M; $[X^-] = 1.28 \times 10^{-5}$ M; $[Z^-] = 4.75 \times 10^{-6}$ M. Spectrum a is made up by the combined contribution of XH, X^-, and Z^- in the proportion of their respective concentrations and extinction coefficients. In a first approximation, XH can be neglected owing to its low concentration. Hence, to find the spectrum of pure X^-, the contribution of Z^- has to be substracted from spectrum a in Figure 1. This has been done using a spectrum of pure Z^- (not shown); the result is spectrum a in Figure 2, with λ_{max} 445 mμ.

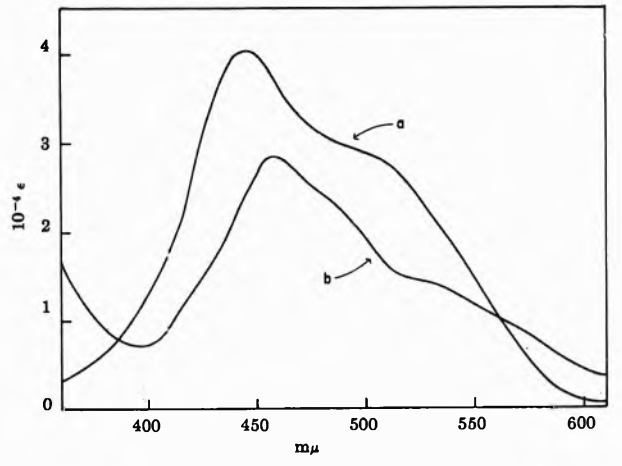


Figure 2.—Spectra of piperidine–TNB Meisenheimer complexes: a, X^-; b, XH.

The solution producing spectrum b in Figure 1 {[Pip] = 0.10 M, [Pip HCl] = 0.50 M, $(TNB)_0 = 1.20 \times 10^{-3}$ M, pH 10.65} contains the following complex concentrations: $[XH] = 1.38 \times 10^{-5}$ M; $[X^-] = 0.93 \times 10^{-5}$ M; $[Z^-] = 1.55 \times 10^{-6}$ M.[9] By subtracting from this spectrum the contributions of X^- and Z^- in the appropriate manner, one ends up with spectrum b in Figure 2, which is for pure XH and has λ_{max} 458 mμ.

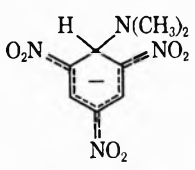
The equilibrium constants not being known with high enough accuracy, particularly at high piperidine hydrochloride concentration, the uncertainty in actual complex concentrations and thus in the quantitative aspect of the foregoing procedure is considerable and may be *ca.* ±25%. Furthermore, the spectra of piperidine–TNB solutions, changing rather rapidly with time owing to decomposition of TNB,[1] had to be extrapolated to zero time, which is an additional source of error.

Nevertheless the following statements can be made. (1) The shape of the absorption spectrum of X^- is probably precise within ±4% at all wavelengths; it may well be, however, that all extinction coefficients are too high by some constant factor. The basis of this supposition is that in acetonitrile, ε of the same complex at 444 mμ is 33,000,[4] whereas here it is 40,500. The possibility of a solvent effect on ε cannot be excluded, however; solvent-dependent extinction coefficients of other Meisenheimer complexes are well documented.[10] (2) Insofar as all extinction coefficients of X^- may be too high by *ca.* 20%, the extinction coefficients of XH in Figure 2 may have come out too

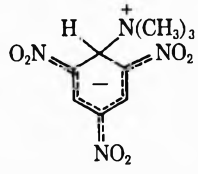
(9) These concentrations were calculated by using K_2 and K_{YH} values which are 50% higher than the ones listed above. This is a conservative estimate of the expected increase of those constants owing to the effect of the high piperidine hydrochloride concentration.[1]

(10) R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966).

low. The shape should not be affected drastically by this possible error, however. Thus there can be no doubt that the general character of the spectrum of XH is definitely different from that of X^-; for obvious reasons we do not attach importance to the lower extinction coefficient at the absorption maximum. (3) It is interesting that the effect of attaching a proton to the amine nitrogen on X^- brings about a bathochromic shift of *ca.* 13 mμ. An analogous creation of a positive charge through addition of a methyl or ethyl group either does not change the absorption maximum or shifts it slightly to *shorter* wavelengths, as seen by comparing I and II[5a] or the ethyl analog.[2] This may



I



II

be related to the capability of forming an intramolecular hydrogen bond to the *ortho* nitro group in the present case and the lack of this possibility when the nitrogen bears three alkyl groups. Other evidence for such intramolecular hydrogen bonding has been discussed.[1] (4) The fact that the calculation of spectra based on complex concentrations derived from kinetic equilibrium data gives satisfactory extinction coefficients shows convincingly that Y^- and YH do not significantly absorb in the visible, an observation which had been used as partial evidence in assigning the structure of YH and Y^-.[1] However, the experimental uncertainties in this system are too large to allow complete exclusion of the possibility of a fourth interaction of CT[11]-complex formation.[4] If a fourth complex were formed with a small equilibrium constant, an additional term would need to be added to D in eq 2-4; if it were small enough (*e.g.*, *ca.* 0.5 l. M^{-1} as in acetonitrile[4]) so as not to alter D significantly, it would escape unnoticed.

Registry No.—Piperidine–TNB complex (XH), 12402-43-6; piperidine–TNB complex (X^-), 12402-42-5; 1,3,5-trinitrobenzene, 99-35-4.

Acknowledgment.—Partial support of this research by PHS Research Grant GM 14647 from the National Instituted of General Medical Sciences is gratefully acknowledged.

(11) Charge transfer.

1,2 Cycloaddition of Singlet Oxygen to 9,9′-Bifluorenylidene

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Received August 12, 1969

Typically the reactions of singlet oxygen with olefins has been studied with olefins possessing allylic hydrogen atoms.[1] The resulting allylic hydroperoxides were suggested to arise by an "ene"-type mechanism.[2] In contrast, there are few reports of 1,2 cycloadditions of singlet oxygen to olefins. Cycloaddition of singlet oxygen to olefins is suggested when nitrogen is conjugated with the olefinic site. Thus, enamines[1a,3] and 10,10′-dimethyl-9,9′-biacridylidene[4] undergo cleavage of the double bond with singlet oxygen, a result expected from decomposition of the 1,2-dioxetane intermediate produced by cycloaddition. It can be noted that tetraaminoethylenes give analogous products, ureas, with ground-state triplet oxygen.[5] Recently, cycloaddition of singlet oxygen to indene and methylated indenes was demonstrated[6] even though allylic hydrogen atoms were present. This is to be contrasted with the lack of reaction of norbornene with singlet oxygen.[1e] The bridgehead location of the allylic hydrogens voids the "ene"-type reaction which would lead to a bridgehead double bond, but the possibility of 1,2 cycloaddition exists. We report here some of our results in the search for 1,2 cycloaddition of singlet oxygen to olefins.

Our interest in 1,2-dioxetane intermediates[7] led us to investigate the possible intervention of this intermediate in the reaction of singlet oxygen with an olefin devoid of allylic hydrogens and heteroatoms. For this purpose we chose to study the reaction of 9,9′-bifluorenylidene (I) with singlet oxygen, which is generated both chemically and photochemically. A 1,2-dioxetane intermediate, resulting from a cycloaddition reaction between I and singlet oxygen, will give fluorenone by analogy to the decomposition of other such intermediates.[7,8]

Singlet oxygen was generated chemically from hydrogen peroxide and sodium hypochlorite[9] as well as photochemically from oxygen with methylene blue sensitizer.[9b] Competitive oxidations with mixtures of I and 2-methyl-2-butene (II) were carried out. Chemical generation of singlet oxidation gave fluorenone in 44% yield from I and 41% reaction of II. Fluorenone was isolated and characterized from a reaction where II was excluded. Photosensitized oxidation of the olefin mixture gave fluorenone in 91% yield along with 66% reaction of II. To verify that fluorenone was generated from singlet oxygen, which in turn was produced from the sensitizer, a control reaction was crrried out under the conditions of the sensitized oxygenation, but without the sensitizer. The yield of fluorenone was reduced

(1) (a) C. S. Foote, *Accounts Chem. Res.*, **1**, 104 (1968); (b) K. Gollnick, *Advan. Photochem.*, **6**, 1 (1938); (c) K. Gollnick, "Oxidation of Organic Compounds," Vol. III, Advances in Chemistry Series, No. 77, American Chemical Society, Washington, D. C., 1968, p 78; (d) R. Higgins, C. S. Foote, and H. Cheng, ref 1e, p 102; (e) F. A. Litt and A. Nickon, ref 1c, p 118; (f) S. J. Arnold, M. Kubo, and E. A. Ogryzlo, ref 1c, p 133; (g) A. U. Khan and D. R. Kearns, ref 1c, p 143.

(2) (a) A. Nickon and J. F. Bagli, *J. Amer. Chem. Soc.*, **83**, 1498 (1961); (b) C. S. Foote, S. Wexler, and W. Ando, *Tetrahedron Lett.*, 4111 (1965).

(3) C. S. Foote and J. W.-P. Lin, *ibid.*, 3267 (1968).

(4) F. McCapra and R. A. Hann, *Chem. Commun.*, 442 (1969).

(5) (a) D. M. Lemal, "The Chemistry of the Amino Group," S. Patai, Ed., Interscience Publishers, New York, N. Y., 1968, p 729; (b) W. H. Urry and J. Sheeto, *Photochem. Photobiol.*, **4**, 1067 (1965); (c) H. E. Winberg, J. E. Carnahan, D. D. Coffman, and M. Brown, *J. Amer. Chem. Soc.*, **87**, 2055 (1965); (d) A. N. Fletcher and C. A. Heller, *J. Catal.*, **6**, 263 (1966); (e) A. N. Fletcher and C. A. Heller, *J. Phys. Chem.*, **71**, 1507 (1967).

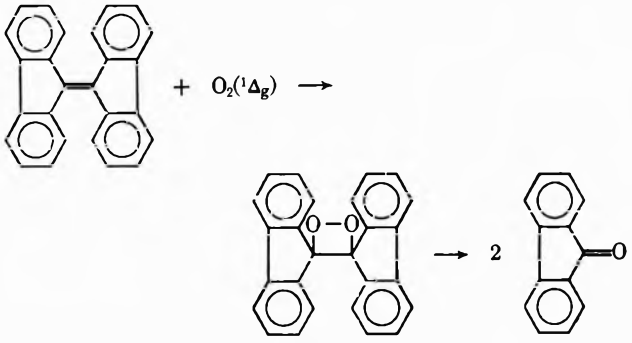
(6) W. Fenical, D. R. Kearns, and P. Radlick, *J. Amer. Chem. Soc.*, **91**, 3396 (1969).

(7) W. H. Richardson, J. W. Peters, and W. P. Konopka, *Tetrahedron Lett.*, 5531 (1966).

(8) (a) M. Schulz, A. Rieche, and K. Kirschke, *Ber.*, **100**, 370 (1967); (b) K. R. Kopecky and C. Mumford, *Can. J. Chem.*, **47**, 709 (1969).

(9) (a) C. S. Foote and S. Wexler, *J. Amer. Chem. Soc.*, **86**, 3879 (1964); (b) C. S. Foote, S. Wexler, W. Ando, and R. Higgins, *ibid.*, **90**, 975 (1968).

to 0.2%. The ratio of per cent reaction of I/II in the chemical and photochemical reaction is 1.1 and 1.4, respectively. The similarity of these two ratios suggest that singlet oxygen is the oxidant.[1a,d] Foote[1a] has presented relative reactivities for a series of olefins with singlet oxygen. With II as the common olefin in this series and the present data, I may be placed in the series. It is found that I is 0.034 times as reactive with singlet oxygen as tetramethylethylene, which is the most reactive monoolefin in the series. However, I is 720 times as reactive as *trans*-4-methyl-2-pentene, the least reactive olefin. The results indicate that allylic hydrogen atoms are not a prerequisite for facile reaction of singlet oxygen with an appropriately substituted olefin. The most reasonable mechanism for the reaction is *via* a 1,2-dioxetane intermediate as shown below.



The generation of the 1,2-dioxetane by methods previously employed by us[7] and the initial electronic state of fluorenone are currently under investigation.

Experimental Section[10]

Materials.—9,9′-Bifluorenylidene (I) (Matheson Coleman and Bell), mp 193–194° (lit.[11] mp 188–190°), was used as received. The nmr spectrum of three multiplets centered at 7.12, 7.50, and 8.20 with relative areas of 2:1:1 was consistent with that previously reported.[12] The ir spectrum was void of significant absorption in the carbonyl region. The following chemicals were obtained from Matheson Coleman and Bell and were used without further purification: 2-methyl-2-butene (II), 30% hydrogen hydroperoxide, methylene blue chloride, and biphenyl. A 5% sodium hypochlorite (Purex) solution was used. The reagent grade solvents, methanol, dioxane, and methylene chloride, were used as received. Reagent grade tetrahydrofuran was distilled from calcium hydride.

Photosensitized Oxygenations.—An immersion photochemical reactor similar to the design given by Gollnick and Schenck[13] was used with circulating ice-cooled water. Oxygen was passed in a slow stream through a glass frit in the bottom of the reactor. Irradiation was carried out with a Sylvania Type DWY-625W tungsten–iodine lamp operated at 60 V. In a typical reaction, the reactor was charged with 0.3304 g (1.00 mmol) of I, 70.2 mg (1.00 mmol) of II, 50 mg of methylene blue, and 133.5 g of methylene chloride. Photooxygenation was conducted for 2.33 hr. At this time an aliquot was removed and weighed. Biphenyl and tetrahydrofuran (THF) were weighed into the aliquot as standards for glpc analysis. The samples were kept cool and immediately subjected to glpc analysis. Analyses for II and the THF internal standard were carried out on a PAR-2, 5 ft × 1/8 in. column, operated at 103° (injector 220°, detector 250°) with a 29-ml/min flow of nitrogen. Retention times for a 1-μl injection were 10 and 19 min, respectively, for I and THF. Analyses for fluorenone and the biphenyl internal standard were performed on a 15% Apiezon L on Chromosorb G, 10 ft × 1/8 in. column, operated at 220° (injector 220°, detector 250°) with a 29-ml/min flow of nitrogen. Retention times for a 1-μl injection were 5.6 and 21 min, respectively, for biphenyl and fluorenone. Yields and per cent reaction, based on initial amounts of I and II, were calculated from the glpc data by comparison with standard mixtures of the solvent, II, fluorenone, and the internal standards. In one reaction with I, the methylene chloride solvent was removed on a rotary evaporator. The remaining mixture was triturated with ether and then filtered to remove methylene blue. The concentrated filtrate was subjected to column chromatography on Merck acid-washed alumina to give fluorenone, mp 82.5–83.5° (lit.[14] mp 83°). Nmr and ir spectra of the sample were identical with those given in the Sadler spectra.

Oxygenation with Sodium Hypochlorite–Hydrogen Peroxide.—In a typical reaction, 15 ml of 5% Purex (0.67 *M*, 10 mmol) was added with mechanical stirring to an ice-cold solution of 0.3304 g (1.00 mmol) I, 74.6 mg (1.07 mmol) II, 2.1 ml of 30% hydrogen peroxide (9.4 *M*, 20 mmol), 20 ml of methanol, and 80 ml of dioxane. After a 7-min addition period, followed by stirring for 1 hr, an aliquot was withdrawn and subjected to glpc analysis for II as described in the previous section. Glpc analysis for fluorenone was carried out as described above, but after work-up by extracting with ether, drying over magnesium sulfate, and concentrating on a rotary evaporator. Fluorenone was identified in these reactions by comparison of glpc retention times and by thin layer chromatography.

Registry No.—I, 746-47-4; II, 513-35-9.

Acknowledgments.—This investigation was supported by the Petroleum Research Fund, Administered by the American Chemical Society.

(14) M. Frankel and S. Patai, "Tables for Identification of Organic Compounds," The Chemical Rubber Co., Cleveland, Ohio, 1964.

Cyclization of Arylthiovinyl Sulfonic Esters to Benzo[*b*]thiophenes. An Unusual 1,2-Sulfur Shift

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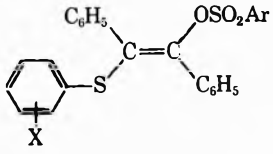
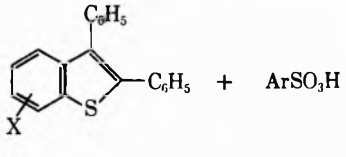
Received May 26, 1969

An unusual rearrangement was observed in the cyclization of some arylthiovinyl sulfonic esters **1** to benzo[*b*]thiophenes **2**[1] (eq 1).



(1)

1



2

(10) Gas–liquid partition chromatography (glpc) was performed on a Varian Aerograph Hy-F:III Series 1200 flame ionization instrument. Infrared spectra were measured in carbon tetrachloride with a Perkin-Elmer Model 621 spectrometer. Nmr spectra was determined in carbon tetrachloride solution with a Varian Model A-60 spectrometer. Chemical shifts are expressed in parts per million (ppm) relative to internal tetramethylsilane as 0 ppm (δ scale). All melting points are corrected and were determined with a Hoover–Thomas capillary melting point apparatus.

(11) R. C. Fuson and H. D. Porter, *J. Amer. Chem. Soc.*, **70**, 895 (1948).

(12) M. Rabinovitz, I. Agranat, and E. D. Bergmann, *Tetrahedron Lett.*, 1265 (1965).

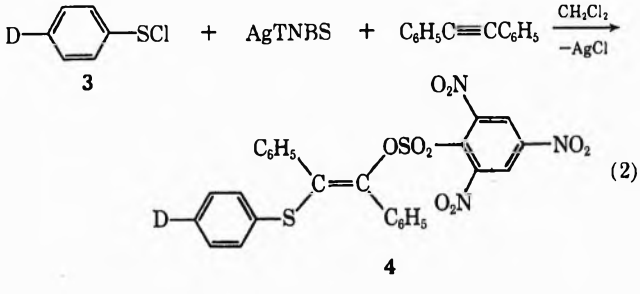
(13) K. Gollnick and G. O. Schenck, in "1,4-Cycloaddition Reactions," J. Hamer, Ed., Academic Press Inc., New York, N. Y., 1967, Chapter 10.

(1) (a) G. Capozzi, G. Melloni, G. Modena, and M. Piscitelli, *Tetrahedron Lett.*, 4039 (1968); (b) G. Capozzi, A. Di Bello, G. Melloni, and G. Modena, *Ric. Sci.*, **39**, 267 (1969).

When the substituent X (CH_3, CH_3O, Cl, Br) in **1** was *para* to the vinylthio group, the benzo[*b*]thiophene formed had the substituent in the 6 position, *i.e.*, *meta* to the sulfur, instead of the expected 5 position. No "formal migration" of the substituent was observed when X (CH_3O, Cl) in **1** was *meta* to the vinylthio group. In this case, the expected 4- and 6-substituted benzo[*b*]thiophenes were formed.

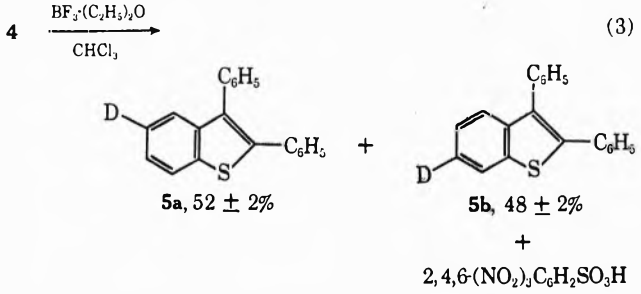
In order to obtain further information on the mechanism of the rearrangement and a better understanding of the effect of the substituents, the cyclization of a deuterium-labeled arylthiovinyl sulfonic ester was studied.

Reaction of *p*-deuteriophenylsulfenyl chloride (**3**) with silver 2,4,6-trinitrobenzenesulfonate (AgTNBS) and tolane in methylene chloride afforded 1,2-diphenyl-2-*p*-deuteriophenylthiovinyl 2,4,6-trinitrobenzenesulfonate (**4**), probably of *trans* configuration[1a] (eq 2).



(2)

Cyclization of **4** in the presence of BF_3 etherate afforded in good yield a mixture of deuterated 2,3-diphenylbenzo[*b*]thiophenes **5** (eq 3).

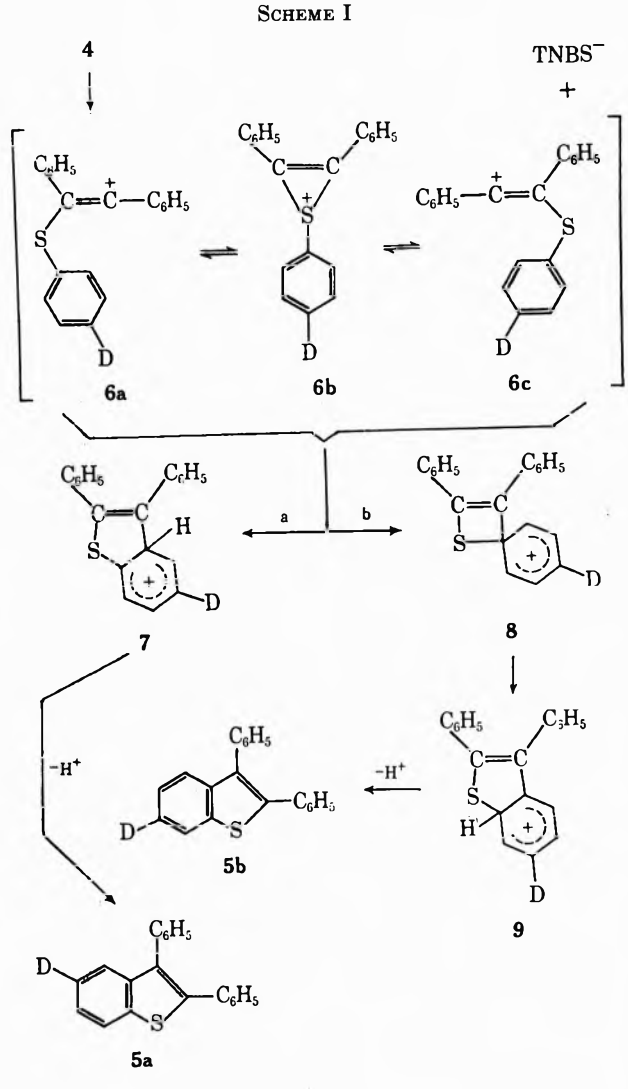


(3)

To determine the position of the deuterium atom in the benzo[*b*]thiophenes formed, authentic 5- and 6-deuterio-2,3-diphenylbenzo[*b*]thiophenes were prepared from the corresponding bromo derivatives. Infrared analysis[2] of mixtures of the two model compounds, based on the different aromatic substitution patterns in the 900–600-cm^{-1} region of their spectra, made it possible to ascertain that **5** was actually a mixture of 2,3-diphenyl-5-deuteriobenzo[*b*]thiophene (**5a**, 52 ± 2%) and 2,3-diphenyl-6-deuteriobenzo[*b*]thiophene (**5b**, 48 ± 2%).

Chemical and kinetic studies of the reactions of compounds **1** have suggested[1,3] that the rate-determining step of the reactions is the formation of a cationic species which can be formulated as **6a**, **6b**, or **6c**. The present results suggest that the cyclization may occur by two distinct pathways (a and b)[4] leading from **6** to benzo[*b*]thiophenes **5**, as illustrated in Scheme I.

SCHEME I



Path a is a Friedel–Crafts-like internal attack of the positive center at either *ortho* position adjacent to the sulfur of the phenylthio nucleus to give **7**, which then suffers loss of a proton. Path b implies attack of the positive center at the 1 position of the phenylthio nucleus[5] followed by a 1,2-sulfur shift and loss of a proton.

In our opinion, breaking of the S–phenyl bond before the formation of the new C–phenyl bond is unlikely and would have caused randomization of the label in all positions of the phenylthio nucleus or some loss in the deuterium content of the cyclization products, contrary to the experimental results.

The results indicate that paths a and b are almost equally probable in the unsubstituted derivative, and that even a small perturbing factor, like a substituent in the *meta* or *para* position with respect to sulfur, causes a distinct unbalance in the system, favoring either path a or b. This is consistent with the general scheme proposed for the reactions of compounds **1**, which considers the product-forming step as fast.

(2) An attempt to analyze mixture **5** by means of nmr techniques failed owing to the complexity of the multiplets corresponding to the aromatic protons.

(3) G. Modena and U. Tonellato, *Chem. Commun.*, 1676 (1968).

(4) In principle, one could also formulate a transition state common to both pathways in which the positive charge is distributed among the vinyl carbon, the sulfur, and the three apical carbons of the phenylthio nucleus in a kind of nonclassical ion. In any event, for the sake of simplicity, we will carry on the discussion on the basis of pathways a and b, which represent the limiting cases.

(5) This step, as well as the formation of **7** in path a, could also be formulated as a ring enlargement of the cyclic sulfonium cation **6b**.

Since the cationic intermediate is a highly reactive species, it is expected that it reacts by a transition state very "reactantlike," or in other terms that it is more sensitive to the charge distribution in the initial state than to the stability of the products.

As a matter of fact, if the course of the reaction is determined by the position of attack of the electrophilic center to the arylthio nucleus and independent of the energy and the fate of intermediates **7** and **8**, the results hitherto obtained may be rationalized on the basis of the directing effect of the substituents. Those so far studied are indeed of the *ortho,para*-directing type, and consequently when they are *para* they direct the attack at the 1 position (rearrangement), whereas when they are *meta* they direct the attack at the 2,6-positions (no rearrangement) of the phenylthio nucleus.

Experimental Section

Melting and boiling points are uncorrected. Infrared spectra were determined in carbon disulfide solution on a Perkin-Elmer Model 225 spectrophotometer.

p-Bromophenyl t-butyl sulfide was prepared in 61% yield by the method previously reported for the synthesis of phenyl *t*-butyl sulfide[5] as a colorless liquid, bp 153–155° (20 mm).

Anal. Calcd for $C_{10}H_{13}BrS$: C, 48.99; H, 5.34; Br, 32.59; S, 13.08. Found: C, 48.98; H, 5.24; Br, 32.22; S, 12.93.

p-Deuteriophenyl t-Butyl Sulfide.—*p*-(*t*-Butylthio)phenylmagnesium bromide from 9.5 g of *p*-bromophenyl *t*-butyl sulfide and 1.2 g of magnesium in 40 ml of anhydrous ether was hydrolyzed with a 15% solution of deuterium chloride in deuterium oxide. The ether solution was separated and dried (Na_2SO_4) and the solvent was removed. The liquid residue was distilled twice to give 4.6 g (71% yield) of *p*-deuteriophenyl *t*-butyl sulfide, bp 106–107° (20 mm) [lit.[6] bp 73° (5 mm) for phenyl *t*-butyl sulfide]; the corresponding sulfone was obtained, mp 99–100° (lit.[6] mp 98–99° for pheny *t*-butyl sulfone).

p-Deuteriophenylsulfenyl chloride (**3**) was prepared by chlorinolysis of *p*-deuteriophenyl *t*-butyl sulfide (4.6 g) by chlorine in carbon tetrachloride at −10°, following a modification of the procedure reported by Kharasch and Langford[7] for the synthesis of 2,4-dinitrophenylsulfenyl chloride, and purified by distillation. There were obtained 3.5 g (87% yield) of **3**, bp 90–92° (20 mm), identical with that of a sample of phenylsulfenyl chloride prepared by the same method.

1,2-Diphenyl-2-*p*-deuteriophenylthiovinyl 2,4,6-Trinitrobenzenesulfonate (**4**).—Tolane (1.78 g, 10 mmol) was dissolved in 60 ml of anhydrous methylene chloride, silver 2,4,6-trinitrobenzenesulfonate (acetonitrile complex,[8] 5.23 g, 10 mmol) was added, and the suspension was stirred for a few minutes. A solution of **3** (1.45 g, 10 mmol) in 15 ml of methylene chloride was added dropwise at 15° and the reaction mixture was stirred for 10 min. Filtration of the insoluble AgCl followed by addition of pentane to the clear solution resulted in the precipitation of **4** (2.8 g, 48% yield) as a yellow, crystalline solid, which was purified by crystallization from methylene chloride–pentane, mp 109–110° dec. A mixture melting point with 1,2-diphenyl-2-phenylthiovinyl 2,4,6-trinitrobenzenesulfonate (prepared by the same method)[1a] was 109–110° dec.

2,3-Diphenyl-5-bromobenzo[*b*]thiophene was prepared in 53% yield by cyclization of 2-phenyl-2-*p*-bromophenylthioacetophenone in polyphosphoric acid.[1a] Chromatography on silica gel (hexane) and recrystallization from ethanol gave white crystals, mp 175–176°.

Anal. Calcd for $C_{20}H_{13}BrS$: C, 65.75; H, 3.59; Br, 21.88; S, 8.78. Found: C, 66.04; H, 3.59; Br, 21.77; S, 8.77.

2,3-Diphenyl-5-deuteriobenzo[*b*]thiophene (**5a**).—The Grignard reagent prepared from 1.0 g of 2,3-diphenyl-5-bromobenzo[*b*]-thiophene and 0.15 g of magnesium in 100 ml of anhydrous ether was hydrolyzed with a 15% solution of deuterium chloride in deuterium oxide. The ether solution was separated, the solvent was removed, and the residue was chromatographed on silica gel. Elution with hexane gave 0.6 g (76% yield) of **5a**, which was recrystallized from ethanol, mp 113–114°.[9]

Mass spectrometric data indicated a deuterium content of 0.89 ± 0.02 atoms per molecule.

2,3-Diphenyl-6-bromobenzo[*b*]thiophene was prepared in 89% yield by cyclization of 1,2-diphenyl-2-*p*-bromophenylthiovinyl 2,4,6-trinitrobenzenesulfonate in the presence of gaseous BF_3.[1a] Recrystallization from ethanol gave white crystals, mp 169–171°.[1b]

Anal. Calcd for $C_{20}H_{13}BrS$: C, 65.75; H, 3.59; Br, 21.88; S, 8.78. Found: C, 66.25; H, 3.53; Br, 21.88; S, 8.72.

2,3-Diphenyl-6-deuteriobenzo[*b*]thiophene (**5b**) was prepared in 73% yield from 2,3-diphenyl-6-bromobenzo[*b*]thiophene by the same procedure reported for the preparation of **5a**, mp 113–114°.[9]

Mass spectrometric data indicated a deuterium content of 0.90 ± 0.02 atoms per molecule.

Treatment of 4 with BF_3 Etherate.—**4** (2.5 g, 4.3 mmol) was dissolved in 200 ml of anhydrous methylene chloride, 20 ml of boron trifluoride diethyletherate was added, and the reaction mixture was allowed to stand for 24 hr at room temperature. The 2,4,6-trinitrobenzenesulfonic acid formed was filtered, and the solution was washed with water and dried (Na_2SO_4). The solvent was evaporated and the residue was chromatographed on silica gel. Elution with hexane gave, after recrystallization from ethanol, 1.05 g (85% yield) of a mixture of deuterated 2,3-diphenylbenzo[*b*]thiophenes **5**, mp 113–114°.[9]

Mass spectrometric data indicated a total deuterium content of 0.90 ± 0.02 atoms per molecule.

The infrared analysis of the mixture was performed by means of calibration curves, based on a band at 821 cm^{-1} for **5a** and a band at 640 cm^{-1} for **5b**, obtained from mixtures of the two model compounds in various ratios.

Registry No.—**3**, 23042-80-0; **4**, 23042-81-1; 2,3-diphenyl-5-bromobenzo[*b*]thiophene, 23042-82-2.

Acknowledgments.—This work was supported by the Consiglio Nazionale delle Ricerche, Rome. We wish to thank Dr. Tito Salvatori, of the SNAM-ENI Laboratories, S. Donato Milanese, for the mass spectra.

(9) Identical with that of an authentic sample of 2,3-diphenylbenzo[*b*]-thiophene.[1]

(6) V. N. Ipatieff, H. Pines, and B. S. Friedman, *J. Amer. Chem. Soc.*, **60**, 2731 (1938).

(7) N. Kharasch and R. B. Langford, *J. Org. Chem.*, **28**, 1903 (1963).

(8) D. J. Pettitt and G. K. Helmkamp, *ibid.*, **29**, 2702 (1964).

The Photoreactions of 2,4-Dimethoxyacetanilide[1-3]

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Received June 23, 1969

Aryl esters and N-arylamides have been found to undergo photo Fries rearrangements.[4-6] Recently, we reported that, when 2,4-dimethoxyphenyl acetate (I) was irradiated, not only a normal photo-Fries rearrangement to the unoccupied *ortho* position took place but

(1) Supported by the Research Division, Brigham Young University, and the United Fund of Utah County.

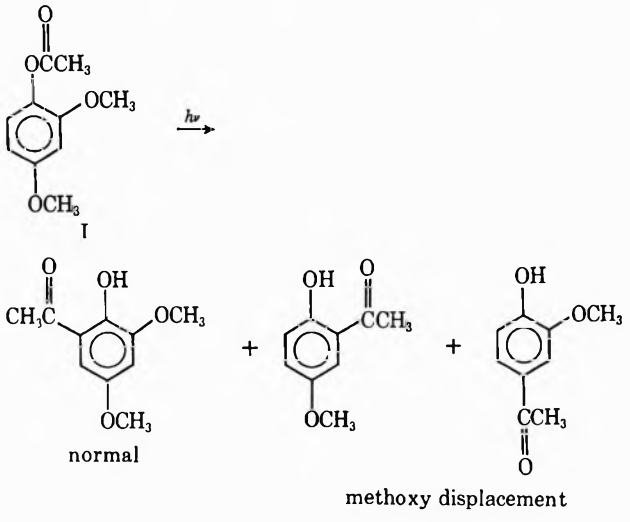
(2) Nuclear magnetic resonance spectra were obtained on a Varian A-60A spectrometer purchased under the National Science Foundation Grant GP-6837.

(3) Presented at the Pacific Northwest Regional Meeting, Salt Lake City, Utah, June 1969.

(4) (a) J. C. Anderson and C. B. Reese, *Proc. Chem. Soc.*, 217 (1960); (b) J. C. Anderson and C. B. Reese, *J. Chem. Soc.*, 1781, (1963).

(5) See D. Bellus and P. Hrdlovic, *Chem. Rev.*, **67**, 599 (1967), for a review of the photo-Fries and related reactions.

(6) (a) D. Elad, *Tetrahedron Lett.*, 873 (1963); (b) D. Elad, D. V. Rao, and V. I. Stenberg, *J. Org. Chem.*, **30**, 3252 (1965).



also a methoxy group could be displaced if it were in the *ortho* or *para* position. In addition, decarboxylation and cleavage products were obtained.[7]

In the present study, we have irradiated 2,4-dimethoxyacetanilide (II) to see if methoxy-displaced rearrangements would also take place in the N-arylamide system. We also wanted to see if a reaction similar to the decarboxylation of certain phenyl esters[7,8] could be observed in this system (that is the loss of CONH). This latter reaction was not observed even with 2,4,6-trimethylacetanilide where no photo-Fries rearrangement could take place.[9]

The products of the ultraviolet (uv) irradiation of II in benzene were found to be 2-amino-3,5-dimethoxyacetophenone (III, 63%) from the *ortho* photo-Fries reaction to the unoccupied position; 2-amino-5-methoxyacetophenone (IV, 5%) and 4-amino-3-methoxyacetophenone (V, 11%) from displaced *ortho*- and *para*-methoxy photo-Fries reactions; 2,4-dimethoxyaniline (8%) from the cleavage reaction; and five other products which could not be isolated in sufficient quantity to characterize.

The structures of the photo-Fries rearrangement products (III, IV, and V) were determined by their spectra. The nuclear magnetic resonance (nmr) spectra were quite definitive. Compounds IV and V each exhibited a peak attributable to NH_2 groups at δ 5.65 for IV and 4.3 for V. The difference in chemical shift for these two peaks is a result of hydrogen bonding in 2-aminoacetophenone-type compounds. This hydrogen bonding causes the NH_2 bond to shift from about δ 4.3 to 5.5–6.0.[10] The carbonyl bond in the infrared (ir) may also be shifted to lower wavenumbers by as much as 50 cm^{-1} owing to hydrogen bonding in the *ortho* position.[11] Such a shift was exhibited by the ir spectrum for compound IV (1640 cm^{-1}) in comparison with V (1660 cm^{-1}). Thus we feel confident that IV is 2-amino-5-methoxyacetophenone and V is 4-amino-3-methoxyacetophenone. The nmr and ir spectra of 2-amino-3,5-dimethoxyacetophenone (III), the major photo-Fries reaction product, also exhibit the typical 2-aminoacetophenone spectra (1640 cm^{-1} in the ir spectrum and a singlet at δ 6.1 in the nmr spectrum).

Shizuka and Tanaka have shown that the acetanilide photo-Fries reaction occurred from the lowest lying excited singlet state resulting in the fission of the C–N bond and the liberation of C_6H_5NH and $COCH_3$ radicals.[12] They also found that rearrangements to the 4 position did not take place when it was occupied by methyl or chloro groups; however, 4-iodo and 4-bromo groups were displaced by the migrating acyl group.[12c] They attributed the latter results to a predissociation of C–Br and C–I bonds caused by the irradiation.[12c] The fact that the chloro group was not displaced is somewhat surprising since Kobsa observed a displacement of the chloro group when he irradiated 4-*t*-butyl-2,6-dichlorophenyl acetate.[13]

The mechanism of the photo-Fries reaction of 2,4-dimethoxyacetanilide is probably the same as that reported by Shizuka and Tanaka.[12] However, we do not believe that the methoxy displacement reaction is taking place by way of a predissociation of the C–OCH_3 bond. If this were the case, we could have expected to find some 2-methoxyacetanilide as well as some 4-methoxyacetanilide in the reaction products. Neither of these compounds could be isolated in our reaction. We, therefore, propose a concerted type of mechanism for this reaction as we previously postulated.[7]

Experimental Section

Materials and Apparatus.—2,4-Dimethoxyaniline and 2,4,6-trimethylaniline were purchased from the Aldrich Chemical Co. Acetyl chloride, reagent grade benzene, and pyridine were purchased from J. T. Baker Co. An Aerograph 202-B temperature-programming vapor phase chromatograph was used to analyze and separate all photochemical products. All ir spectra were obtained on a Perkin-Elmer Model 700 spectrophotometer. The nmr spectra were taken on a Varian A-60A spectrometer.[2] A Hanovia 450-W, medium-pressure lamp was used.

Preparation of 2,4-Dimethoxyacetanilide (II).—An excess of acetyl chloride was slowly added to 20 g (0.13 mol) 2,4-dimethoxyaniline in 80 ml of cold pyridine. The resulting dark red solution was allowed to warm to room temperature and then added to 100 ml of ice water. The crude 2,4-dimethoxyacetanilide (II) was filtered (11.5 g, 47%). The product II was purified by recrystallization from water, mp 114–115°.[14]

Anal. Calcd for $C_{10}H_{13}O_3N$: C, 61.53; H, 6.71. Found: C, 61.51; H, 6.67.

Preparation of 2,4,6-Trimethylacetanilide.—This was prepared by the above procedure to obtain an 80% yield, mp 215–216°.

Anal. Calcd for $C_{11}H_{15}ON$: C, 74.54; H, 8.53. Found: C, 74.63; H, 8.75.

Irradiation of 2,4-Dimethoxyacetanilide (II).—The substrate (2 g) was dissolved in 200 ml of benzene and the solution was placed in the reactor. A quartz immersion well was fitted into the reactor. A small stream of pure nitrogen was sparged into the bottom of the reactor for 40 min before the reaction was started and then continued throughout the irradiation. The irradiation was carried out for 19 hr. Upon completion of the irradiation, the solvent was removed under vacuum (30–40 mm). The remaining almost-black oil was subjected to vpc analysis using a 20% SE-30 on Chromosorb W column and programming the temperature from 100 to 275°. Ten vpc peaks were observed. Some of these fractions were collected and analyzed.

Fractions 1–3 (4%) could not be isolated.

(7) J. S. Bradshaw, E. L. Loveridge, and L. White, *J. Org. Chem.*, **33**, 4127 (1968).

(8) See R. A. Finnegan and D. Knutson, *J. Amer. Chem. Soc.*, **89**, 1970 (1967), and other papers of that series.

(9) *ortho* and *para* displacements of alkyl groups in the photo-Fries reaction have never been observed; see ref 5.

(10) Similar shifts have been observed in the case of 4-aminoacetophenone (NH_2 peak at δ 4.43) and 2-aminoacetophenone (NH_2 peak at δ 6.12). See Sadtler Nuclear Magnetic Resonance Spectra No. 242 and No. 4987, published by Sadtler Research Laboratories Inc., Philadelphia, Pa.

(11) See K. Nakanishi "Infrared Absorption Spectroscopy," Holden-Day Inc., San Francisco, Calif., 1962, p 42.

(12) (a) H. Shizuka and I. Tanaka, *Bull. Chem. Soc. Jap.*, **41**, 2343 (1968); (b) H. Shizuka, *ibid.*, **42**, 52 (1969); (c) H. Shizuka, *ibid.*, **42**, 57 (1969).

(13) H. Kobsa, *J. Org. Chem.*, **27**, 2293 (1962).

(14) All melting points are uncorrected.

Fraction 4 (8%) exhibited ir and nmr spectra that were the same as those of 2,4-dimethoxyaniline.

Fraction 5, compound IV (5%), exhibited ir (KBr) 3450, 3340, and 1640 cm^{-1}; nmr (CCl_4) δ 2.45 (s, 3), 3.75 (s, 3), 5.7 (s, 2), and 6.8 (m, 3).

Fraction 6, compound V (11%), exhibited ir (KBr) 3460, 3360, and 1660 cm^{-1}; nmr (CCl_4) δ 2.40 (s, 3), 3.85 (s, 3), 4.30 (s, 2), 6.55 (m, 1), and 7.30 (m, 2).

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71. Found: C, 65.17; H, 6.79.

Fraction 7, compound III (63%), exhibited ir (KBr) 3460, 3340, 1640 cm^{-1}; nmr (CCl_4) δ 2.45 (s, 3), 3.70 (s, 3), 3.85 (s, 3), 6.10 (s, 2), and 6.50 (m, 2).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 61.53; H, 6.71. Found: C, 61.29; H, 6.59.

Fraction 8, compound II, exhibited ir and nmr spectra which were the same as those of the starting material.

Fractions 9 and 10 (9%) could not be isolated.

Irradiation of 2,4,6-Trimethylacetanilide.—The substrate (1 g) was dissolved in 240 ml of pure benzene and irradiated as described above. After the solvent was removed, only 2,4,6-trimethylaniline and starting anilide could be isolated from the reaction mixture. No material was observed in the vpc chromatogram with a retention time the same that of as 1,2,3,5-tetramethylbenzene.

Registry No.—II, 23042-75-3; III, 23042-76-4; IV, 23042-77-5; V, 22106-40-7; 2,4,6-triethylacetanilide, 5096-21-9.

A Photochemical Preparation of 4,11-Diphenylbisanthene

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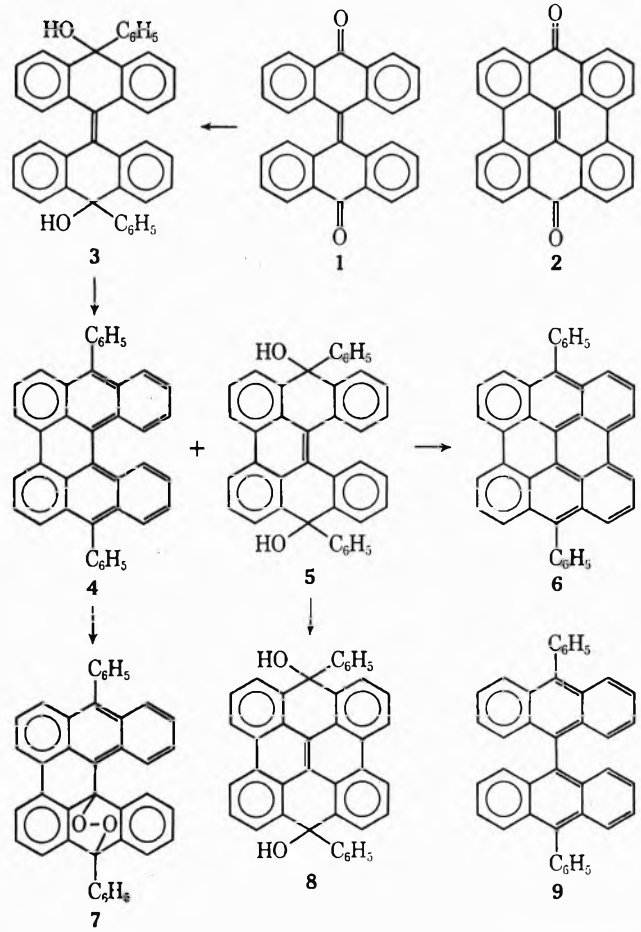
4,11-Diphenylbisanthene (**6**) is one of a few aromatic hydrocarbons from which fluorescence (Φ_F = 0.18, λ_{max} 720 mμ in benzene) of moderate intensity has been detected in the infrared region.[1] A three-step synthesis of **6** with an overall yield of 20% had been described earlier by the sequence bianthrone (**1**) → 4,11-bisanthenequinone (**2**) → 4,11-dihydroxy-4,11-diphenyldihydrobisanthene (**8**) → **6**.[2] A more convenient approach appeared to be the photocyclization of the diphenylbianthracenediol **3**, which can be prepared from bianthrone in good yield.[3]

Ultraviolet irradiation of benzene solutions of **3** [λ_{max} 327 mμ (log ϵ 4.08)] and iodine exposed to the atmosphere did indeed produce hydrocarbon **6** in moderate yield. The only two products isolated were the deep blue diphenylbisanthene and the highly blue-fluorescing photooxide **7**. The easily identifiable intense bands at 683 and 625 mμ for product **6** facilitated the following of the reaction spectrophotometrically. A maximum buildup of diphenylbisanthene was quickly attained, but on prolonged irradiation the product was slowly decomposed. The concurrent appearance of a broad band centered near 400 mμ and the decrease in intensity of the peaks at 683 and 625 mμ imply the formation of a photooxide, since the absorption at shorter wavelengths is in the same region as that of the photooxide of bisanthene.[4] The photooxide of **6** could not be isolated; instead, only resinous material was obtained, as had been observed previously.[2]

Thus, the limiting factor in maximizing the yield of **6** is the photoinstability of the hydrocarbon. While yields were greatest when the reaction was carried out open to the atmosphere, the photooxidation of the product was also occurring. When following the reaction of 5.9×10^{-5} *M* **3** and 5.9×10^{-5} *M* iodine in a 1-cc cell, a yield of **6** as high as 59% was detected. On a larger scale, however, diphenylbisanthene was isolated in 20% yield.

Contrary to the observation that the yield of triphenylene in the photoaryl coupling of *o*-terphenyl is dependent on the iodine concentrations,[5] varying the amounts of iodine in the reaction of **3** to **6** had little affect on the yield, as demonstrated by the yields of **6** (50, 59, and 49%) when the ratios of diol **3**/I_2 were 10, 1.0, and 0.5. Iodine is essential to the reaction, however, since without it, **6** was not formed as **3** was slowly consumed. Heating the product of the noncatalyzed reaction with hydriodic acid did not yield diphenylbisanthene. This result rules out dihydroxydiphenyldihydrobisanthene **8** as a product in the photochemical reaction in which iodine is not used.

Since the decomposition of **6** was much slower when irradiated under nitrogen, rather than when exposed to the air, solutions of **3** and iodine were irradiated in a nitrogen atmosphere. Under these conditions the yield of diphenylbisanthene was decreased to 5% and



(1) M. M. Rauhut, D. R. Maulding, W. Bergmark, B. G. Roberts, R. A. Clarke and R. Coleman, unpublished work.

(2) G. Sauvage, *Ann. Chim.*, **2**,844 (1947).

(3) A. Schonberg and A. Ismail, *J. Chem. Soc.*, 201 (1945).

(4) H. Kuroda, *J. Chem. Phys.*, **33**, 1586 (1960).

(5) T. Sato, Y. Goto and K. Hata, *Bull. Chem. Soc. Jap.*, **40**, 1994 (1967).

diphenyldibenzoperylene **4** [λ_{max} 582 mμ (log ε 4.45) and λ_{max} 542 mμ (log ε 4.24)] became the major product. When exposed to oxygen hydrocarbon **4** was rapidly converted into a light yellow solid, mp 302–304°, having absorption peaks at 427, 403, and 382 mμ. The compound appears to be a photooxide of **4**, although the only known photooxide has a thermal decomposition point of 180°.[2] Other evidence which supports the photooxide structure is the elemental analysis, the bands in in infrared at 10.16, 10.53 (shoulder), and 10.62 μ (compare cluster of four bands centered at 11.0 μ for 9,10-diphenylanthracene photooxide), and the mass spectrum, with *m/e* 536, 431, and 353. The fragment at 431 (536 − $C_6H_5CO^+$) also indicates that one oxygen appears to be bonded to a carbon bearing a phenyl group, such as in structure **7**. This structure is also compatible with the absorption at 427, 403, and 382 mμ. Finally, the extreme photosensitivity of diphenyldibenzoperylene has already been observed.[2]

The possibility of **4** being an intermediate in the formation of **6** was considered, even though the related photocyclization of 1,1′-binaphthyl to perylene has not been observed.[6] The dehydrogenation of **4** to **6** might be expected to be a more favorable reaction because of the fixed geometry of **4** and its greater ability to stabilize the transition state. It is clear, however, from the isolation of only photooxide **7** from **4**, that diol **5** and not hydrocarbon **4** is responsible for the formation of diphenylbisanthene.

To confirm its intermediacy in the cyclization of **3** to **6**, diol **5** was prepared from helianthrone according to the method outlined by Sauvage.[2] Irradiation of benzene solutions of **5** in the presence of iodine gave **6** in 79% yield; however, without iodine the highly colored diphenylbisanthene was not formed. Hydriodic acid reduction of the crude product of the noncatalyzed reaction did form **6** in a moderate yield, thereby indicating the formation of **8**.[7]

10-10′-Diphenyl-9,9′-bianthranyl (**9**) was not detected in the reaction, and the possibility that it or its photooxide was an intermediate or product was excluded by recovering **9** unchanged after exposure to the same reaction conditions necessary for the conversion of **3** into **6**. This observation is in agreement with the report that **9** is resistant to photooxide formation.[8]

The photochemical transformation of **3** to **6** may be considered similar to the stilbene–phenanthrene and bianthrone–bisanthenequinone photocyclizations,[9] and the existence of dihydrophenanthrene-type intermediates is probable. It appears that the quantum yield of the reaction diol **5** to **6** is considerably less than that for reaction **3** to **5**, since the time required for the attainment of the maximum absorbance of diphenylbisanthene at 683 and 625 mμ in the reaction **5** to **6** was the same as that in the conversion of **3** into **6**.

Experimental Section

Equipment and Materials.—A General Electric BH6 lamp and a Pyrex filter were used in all of the photochemical experiments. The procedures described for making 10,10′-diphenyl-[$\Delta^{9,9'(10H,10'H)}$-bianthracene]-10,10′-diol (**3**)[3] and 3,10-dihydroxy-3,10-diphenyl-3,10-dihydro-1,2,11,12-dibenzoperylene (**5**)[2] from bianthrone (Aldrich) and helianthrone[2] were used without modification.

4,11-Diphenylbisanthene (6) from Diol 3.—A solution of 216 mg of **3**, 12 mg of iodine, and 500 ml of benzene was irradiated for 4 hr while exposed to the atmosphere. The visible absorption spectrum of an aliquot indicated that the yield of product was 33%. The benzene was removed and the dark solid was treated with boiling xylene. The cooled solution was passed through a column containing Woelm neutral alumina and xylene. Evaporation of xylene gave 54 mg of deep blue solid. Recrystallization from xylene gave 41 mg (20%): mp 300° (lit.[2] mp 430°); mass spectrum *m/e* 502; visible absorption in benzene, λ_{max} 683 mμ (log ε 4.69) and 625 (4.43) [lit.[2] λ_{max} 690 mμ (log ε 5.01) and 630 (4.75)].

Although the extinction coefficients are lower than those reported,[2] additional recrystallization from xylene or chromotography experiments did not increase the log ε values. Moreover, fluorescence measurements indicated that no visible fluorescing materials were present.

Anal. Calcd for $C_{40}H_{20}$: C, 95.62; H, 4.38. Found: C, 95.28; H, 4.16.

The filtrate contained 8 mg (4%) of a light yellow solid: mp 302–304° (toluene); visible absorption in benzene, λ_{max} 427 mμ (log ε 4.26), 403 (4.24), and 382 (3.97); infrared (Nujol) 10.16, 10.53 (shoulder), and 10.62 μ (compare cluster of four bands centered at 11.0 μ for the photooxide of 9,10-diphenylanthracene); mass spectrum *m/e* 536, 431, and 353. Benzene solutions gave strong blue fluorescence.

Anal. Calcd for $C_{40}H_{24}O_2$: C, 89.55; H, 4.48. Found: C, 89.21; H, 4.52.

Benzene solutions of **3** were irradiated in a 1-cc cell and the maximum yield of **6** was estimated by recording the visible absorption with a Cary 15 spectrophotometer. The yields of diphenylbisanthene with varied concentrations of iodine are given in Table I.

TABLE I
YIELDS OF 6 FROM 3 WITH VARIED IODINE CONCENTRATIONS

Concn of **3**, 10^4 *M*	Concn of I_2, 10^5 *M*	Yield of **6**,[a] %
8.22	0	0
1.35	1.35	50[b]
0.59	5.90	59
0.75	15.0	49

[a] Yields were based on log ε 4.69 for peak at 683 mμ. [b] Replacement of the Pyrex filter with a 250–370-mμ Corning glass filter lowered the yield of **6** to 36%.

4,11-Diphenylbisanthene from Diol 5.—The maximum yields of **6**, based on its absorption at 683 and 625 mμ, were obtained after irradiating benzene solutions of **5** and iodine at various concentrations (see Table II).

TABLE II
YIELDS OF 6 FROM 5 WITH VARIED IODINE CONCENTRATIONS

Concn of **5**, 10^5 *M*	Concn of I_2, 10^5 *M*	Yield of **6**, %
8.15[a]	0	0
8.15[a]	1.53	44
8.15[a]	8.15	56
8.15[a]	16.30	58
7.14[b]	15.30	79

[a] Reaction solution was exposed to atmosphere. [b] Reaction was carried out in nitrogen atmosphere.

Irradiation of 5 without Iodine.—A solution of 45 mg of **5** in 200 ml of benzene was irradiated for 2 hr. Evaporation of solvent gave a light yellow solid. A benzene solution of the product had no absorption in the 600–750-mμ region. The solid was heated in 20 ml of glacial acetic acid and 1 ml of 48% hydriodic acid on a steam bath for 10 min. Dilution with water gave 31 mg of blue-black material. The yield of diphenylbisanthene as determined by the visible absorption of the crude product was 65%.

10,10′-Diphenyl-9,9′-bianthranyl (9).—A solution of 175 mg of **3** in 40 ml of glacial acetic acid and 2 ml of 48% hydriodic acid

(6) G. M. Badger and C. P. Whittle, *Aust. J. Chem.*, **16**, 440 (1963).

(7) Although experimental details were not given, Sauvage reported that diol **8** was formed when an ether solution of **5** was exposed to ultraviolet light. See G. Sauvage, *Compt. Rend.*, **225**, 247 (1947).

(8) C. Dufraisse and J. LeBras, *ibid.*, **216**, 60 (1943).

(9) F. R. Stermitz, in "Organic Photochemistry," Vol. I, O. Chapman, Ed., Marcel Dekker, Inc., New York, N. Y., 1967, p 247.

was heated on a steam bath for 15 min. Dilution with water gave a solid which was recrystallized from toluene. The yield of light yellow solid,[3] mp >300°, mass spectrum *m/e* 506, was 73 mg or 45%. Benzene solutions gave strong blue fluorescence. The absorption spectrum of **9** in benzene had peaks at 403 mμ (log ε 4.47), 380 (4.36), and 360 (4.06).

Anal. Calcd for $C_{40}H_{26}$: C, 94.87; H, 5.13. Found: C, 94.63; H, 4.95.

Irradiation of 10,10′-Diphenyl-9,9′-bianthranyl (9).—The absorption spectrum of a solution of 43 mg of **9** and 2 mg of iodine in 400 ml of benzene, which has been irradiated for 6 hr, showed that only 1% of **9** had been destroyed.

3,10-Diphenyl-1,2,11,12-dibenzoperylene (4) from Diol 3.—Nitrogen was bubbled into a solution of 324 mg of **3** and 168 mg of iodine in 600 ml of benzene for 20 min. The bubbling of nitrogen was continued while the solution was irradiated for 6 hr. The solvent was evaporated and the solid was stirred in 30 ml of ethanol. Filtration gave 196 mg of red-purple solid: mp 366–369° (lit.[2] mp 371°); visible absorption at 582 mμ (log ε 4.45) and 452 (4.24) [lit.[2] 580 mμ (log ε 4.99) and 548 (4.80)]. The absorption spectrum indicated that 5% diphenylbisanthene was aso present.

Anal. Calcd for $C_{40}H_{24}$: C, 95.23; H, 4.77. Found: C, 94.62; H, 4.31.

Photooxidation of 4.—A blue-green solution with bright blue fluorescence developed when a red-purple solution of 50 mg of **4** in 100 ml of benzene was irradiated for 30 min. Evaporation of the solvent gave 48 mg of a green solid, mp 295–299°. Recrystallization from toluene gave light yellow crystals: mp 302–304°; visible absorption in benzene at 427, 430, and 382 mμ (log ε 4.28, 4.26, and 4.00).

Registry No.—**6**, 23102-61-1; **9**, 23102-67-2.

Acknowledgments.—The author gratefully acknowledges the financial support of the work reported here by the Pyrotechnics Laboratory, Picatinny Arsenal, Dover, N. J., and the helpful suggestions contributed by Dr. W. A. Henderson.

Thermal Decomposition of Some *t*-Alkyl Peroxyoxalates

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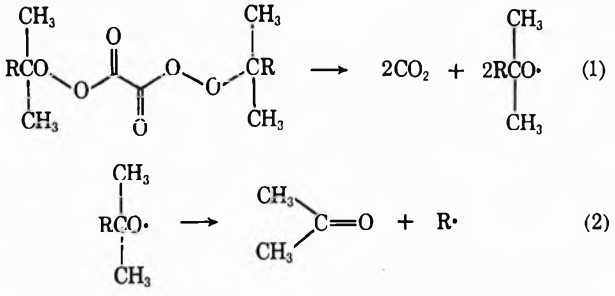
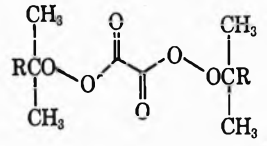
Received September 15, 1969

The thermal decomposition of di-*t*-butyl peroxyoxalate has previously been investigated by Bartlett,[1] Traylor,[2] and coworkers. It was shown that decomposition is quite facile at room temperature, and there is negligible cage recombination of the *t*-butoxy radicals formed.

A variety of *t*-alkoxy radicals is known to undergo β scission to afford a ketone and an alkyl radical.[3] The efficiency with which this fragmentation occurs is markedly dependent on both the structure of the *t*-alkoxy radical and on the solvent.

We sought *t*-alkyl peroxyoxalates as useful precursors for alkyl radicals at low temperatures in a process uncomplicated by cage reactions (eq 1, 2).[4] In this paper we wish to report the preparation of a series of *t*-alkyl peroxyoxalates I and the investigation of the rates and products of their thermal decomposition.





Ia, R = CH_3 c, R = $(CH_3)_2CH$
b, R = CH_3CH_2 d, R = $PhCH_2$

The peroxyoxalates were prepared by the method of Bartlett, *et al.*,[1] from the corresponding *t*-alkyl hydroperoxide and oxalyl chloride. *t*-Butyl peroxyoxalate is a white, crystalline solid which is stable at room temperature for short periods of time but explodes on pounding or scratching.[1] Compounds Ib[5] and Id were also obtained as white needles by crystallization from pentane at −30° or below. Compound Ic was an oil which we were unable to crystallize. All three of these compounds were unstable at room temperature. Compounds Ic and Id decomposed spontaneously with vigorous evolution of gas when allowed to warm to room temperature. All of these compounds were more stable in dilute pentane solutions and could be stored at −30° for days without appreciable decomposition.

The purities of the peroxyoxalates were determined by examination of their infrared spectra and by the yields of the carbon dioxide liberated in the thermal decomposition. Compounds Ia and Ib could also be analyzed by iodometric titration in acetic acid.[6] However, Ic and Id gave very low titres by this method owing to the rapid ionic decomposition in acetic acid solutions.

The rates of thermal decomposition of the four peroxyoxalates were measured in pentane solution at 25° by following the appearance of carbon dioxide. These results are shown in Table I. The reaction was first

TABLE I

RATES OF DECOMPOSITION OF *t*-ALKYL PEROXYOXALATES IN PENTANE AT 25°[a]

Compd	R	k, sec^{-1}	$t_{1/2}$, min
Ia	Methyl[b]	1.7×10^{-5}	700
Ib	Ethyl	2.6×10^{-5}	450
Ic	Isopropyl	6.0×10^{-5}	190
Id	Benzyl	6.7×10^{-5}	173

[a] Average of at least two determinations. [b] Literature[1] k = 7.9×10^{-6} sec^{-1} at 20° in benzene.

(1) P. Bartlett, E. Benzing, and R. Pincock, *J. Amer. Chem. Soc.*, **82**, 1762 (1960).

(2) (a) H. Kiefer and T. Traylor, *ibid.*, **89**, 6667 (1967); (b) R. Hiatt and T. G. Traylor, *ibid.*, **87**, 3766 (1965).

(3) (a) F. D. Greene, M. L. Savitz, F. D. Osterholz, H. H. Lau, W. N. Smith, and P. M. Zanet, *J. Org. Chem.*, **28**, 55 (1963); (b) C. Walling and A. Padwa, *J. Amer. Chem. Soc.*, **85**, 1593 (1963); (c) C. Walling and P. Wagner, *ibid.*, **85**, 2333 (1963); (d) J. Bacha and J. Kochi, *J. Org. Chem.*, **30**, 3272 (1965).

(4) A source of free alkyl radicals uncomplicated by cage reactions would be useful for measuring rates of bimolecular reactions of alkyl radicals in solution, *e.g.*, disproportionation–combination ratios which have been unambiguously measured heretofore only in the gas phase.

(5) C. Walling and J. A. McGuinness [*J. Amer. Chem. Soc.*, **91**, 2053 (1969)] have also recently prepared Ib.

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

order in peroxyoxalate over at least one half-life. There was a slight increase in rate in the order R = CH_3 < CH_3CH_2 < $(CH_3)_2CH$ < $PhCH_2$.[7]

The presence of excess galvinoxyl had no effect on the rate of decomposition of Ic, although galvinoxyl was consumed throughout the reaction. Galvinoxyl is an efficient scavenger for both alkoxy and alkyl radicals.[8] The insensitivity of the rate of thermolysis in the presence of galvinoxyl showed that induced decomposition of the peroxyoxalate was unimportant under these conditions.[8] The products of the thermal decomposition of the peroxyoxalates were studied in three different solvents (Table II). Pentane represented a nonpolar solvent in which heterolytic processes would be minimized, whereas acetic acid and acetonitrile were chosen because β scission of *t*-alkoxy radicals is facile in these solvents.[3c,d]

Table II

Thermal Decomposition of Peroxyoxalates[a]

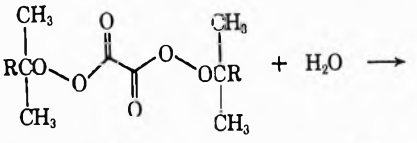
Compd	Solvent	Temp, °C	Reaction[b] time, hr	Products: CO_2, mmol	RH, mmol	R(−H), mmol	R–R, mmol	$(CH_3)_2CO$, mmol	$RC(CH_3)_2OH$, mmol	R–OH, mmol
Ia	Pentane	25	48	0.44	Trace[c]			Trace[c]	0.47[d]	None
Ib	Pentane	25	24	0.45	0.03	Trace[c]	Trace[c]	0.04	0.43	None
Ic	Pentane	25	18	0.45	0.10	0.075	0.07	0.35	0.12	Trace[c]
Ic	Pentane[e]	25	18	0.47	None	~0.01	None			
Id	Pentane	25	18	0.47	None		0.07	0.25	0.20	0.07[f]
Ia	CH_3CN	40	6	0.46	0.20		None	0.24	0.25[g]	None
Ib	CH_3CN	40	1	0.46	0.04	Trace[c]	Trace[c]	0.19	0.20	0.15
Ic	CH_3CN	25	1	0.48	Trace[c]	Trace[c]	None	0.25	0.21	0.25
Id	CH_3CN	25	1	0.47	None		Trace[c]	0.23	0.26	0.20[g]
Ia	HOAc	40	6	0.48	0.33		None	0.40	0.08	None
Ib	HOAc	40	1	0.45	Trace[c]	Trace[c]	None	0.24	0.21	0.21
Ic	HOAc	25	1	0.45	Trace[c]	Trace[c]	None	0.22	0.23	0.19[h]

[a] 0.25 mmol of peroxyoxalate in 5 cc of solvent (0.05 *M*). [b] Indicates the time the reaction mixture was left in the bath for complete reaction. Unrelated to rate studies. [c] Less than 0.01 mmol. [d] Trace of $(CH_3)_3COOC(CH_3)_3$ found, no $(CH_3)_3COCH_3$ detected. At 45°, Traylor, *et al.*,[2] found 4% di-*t*-butyl peroxide. [e] 0.5 mmol of galvinoxyl added. [f] 0.07 mmol of PhCHO found. [g] 0.03 mmol of PhCHO found. [h] ~0.01 mmol of $(CH_3)_2CHOAc$ also found.

Good yields of the expected products of homolytic decomposition were obtained in pentane solutions from all of these peroxyoxalates with the exception of Id (see Table II). The β scission of the *t*-alkoxy radicals into alkyl radicals and acetone was the major reaction only with Ic. It gave substantial amounts of products derived from the isopropyl radical (propane, propylene, 2,3-dimethylbutane).[9] In the presence of excess galvinoxyl, no propane or 2,3-dimethylbutane was formed from Ic. Only a small amount of propylene was detected. These results show that 96% of the isopropyl products was generated *via* free isopropyl radicals. The small amount of propylene formed in the presence of galvinoxyl may have arisen *via* a molecular rearrangement or *via* disproportionation of an isopropyl and a 2,3-dimethyl-2-butoxy radical. The latter is less likely than the former, since no 2,3-dimethyl-2-butyl isopropyl ether was found.[10]

In addition to bibenzyl, the decomposition of Id in pentane afforded benzyl alcohol and benzaldehyde. The formation of these products indicated that the homolytic decomposition of Id was complicated by a competing heterolytic decomposition (*vide infra*). A small amount of induced decomposition *via* the hydroxybenzyl radical (formed by hydrogen transfer from benzyl alcohol) could account for the benzaldehyde.

t-Butyl peroxyoxalate also gave products expected from the radical intermediates in both acetonitrile and acetic acid. Thus the marked increase in the yields of methane and acetone paralleled the importance of β scission of the *t*-butoxy radicals in these solvents (compared with pentane). However, Ib, Ic, and Id produced carbon dioxide, acetone, and the two alcohols, ROH and $RC(CH_3)_2OH$, in these solvents, according to the stoichiometry given by eq 3. A molecule of



$$ROH + (CH_3)_2CO + 2CO_2 + RC(CH_3)_2OH \quad (3)$$

water is needed to balance the reaction as written. The solvent contained enough water (*ca.* 0.1%) to react with all the peroxyoxalate.[11] We interpret the decomposition of Ib, Ic, and Id in acetonitrile and acetic acid as occurring *via* a Criegee rearrangement.[12] Such a process is represented *schematically* by eq 4–6. Alkyl peroxyoxalate ion is known to lose carbon dioxide spon-

(7) These rate differences are too small to warrant further studies of temperature dependence. Steric and electronic effects or the multibond fragmentation of these peroxyoxalates are, no doubt, minor. (b) *Cf.* R. Hiatt and W. M. J. Strachan, *J. Org. Chem.*, **28**, 1893 (1963).

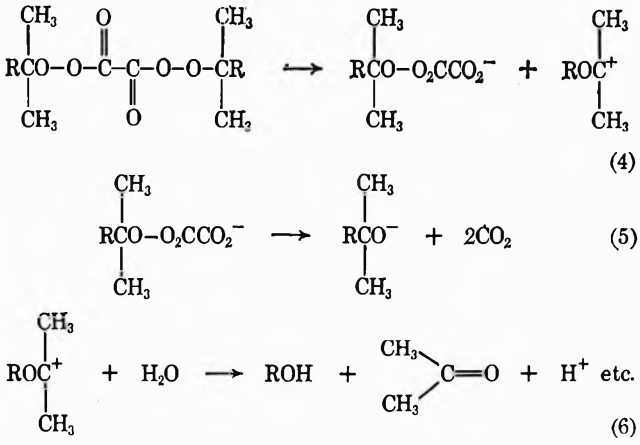
(8) P. D. Bartlett and T. Funahashi, *J. Amer. Chem. Soc.*, **84**, 2596 (1962).

(9) The ratio of the rates of disproportionation and combination of isopropyl radicals is 1.1 (*cf.* Table II). This ratio compares favorably with values obtained in the gas phase [Trotman-Dickenson, *Progr. React. Kinet.*, **1**, 107 (1961)] and in solution from diacyl peroxides (R. A. Sheldon, unpublished results).

(10) It has been shown that the cage reaction of isopropyl and 2,3-dimethyl-2-butoxy radicals gives this ether by combination as well as propylene from disproportionation: R. A. Sheldon, unpublished observation.

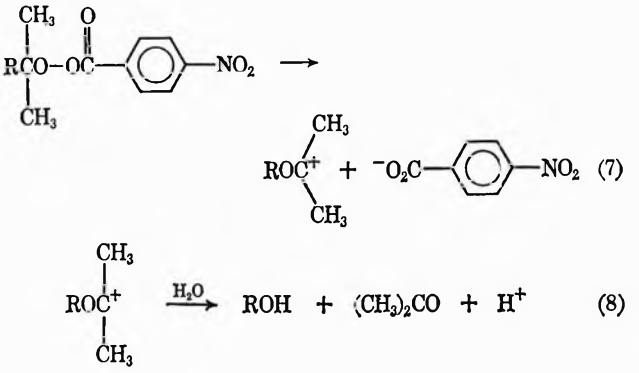
(11) The amount of water in these systems was not determined directly. It is possible that other protic sources would effect similar transformations.

(12) (a) R. Criegee, *Justus Liebigs Ann. Chem.*, **560**, 127 (1948); (b) Y. K. Syrkin and I. I. Moiseev, *Russ. Chem. Rev.*, 193 (1960).



taneously.[1] The rate of decomposition of Ic and Id in acetic acid and acetonitrile was very fast. Although accurate measurements were not made, these peroxyoxalates had half-lives of *ca.* 5 min in acetonitrile at 25°.

Hedaya and Winstein[13] showed that the rate of heterolytic decomposition (*via* a Criegee rearrangement) of a series of alkyl *p*-nitroperbenzoates in methanol increased in the order (R) Me < Et < $PhCH_2$ < *i*-Pr. The products were the alcohol (ROH), acetone, and *p*-nitrobenzoic acid. The results were interpreted according to eq 7–8.



The ease of the Criegee rearrangement is also influenced by the anion. When the anion is a good leaving group, the Criegee rearrangement is facile. Thus *t*-butyl pertosylate[14] and *t*-butyl N-succinimidepercarboxylate[15] decompose heterolytically even in nonpolar solvents at room temperature. We also expect the alkyl peroxyoxalate anion to be a good leaving group.

In conclusion, we find that *t*-alkyl peroxyoxalates are of limited utility as low-temperature precursors for alkyl radicals. In polar solvents they undergo facile heterolysis, whereas in hydrocarbon solvents many *t*-alkoxy radicals produced in the homolysis do not undergo β scission efficiently at low temperatures.

Isopropyl radicals, however, could be generated in good yields in pentane solutions. We feel that analogous alkyl peroxyoxalates should be useful for the production of a variety of secondary and tertiary alkyl radicals in nonpolar solvents.

(13) E. Hedaya and S. Winstein, *J. Amer. Chem. Soc.*, **89**, 1661 (1967).
(14) P. Bartlett and T. Traylor, *ibid.*, **83**, 856 (1961).
(15) (a) E. Hedaya, R. L. Hinman, L. Kibler, and S. Theodoropulos, *ibid.*, **86**, 2727 (1964); (b) T. Koenig and W. Brewer, *ibid.*, **86**, 2729 (1964).

Experimental Section

t-Butyl hydroperoxide (Lucidol Corp., 90%) was vacuum distilled and was 99% pure by iodometric titration. *t*-Amyl hydroperoxide was prepared from *t*-amyl alcohol and hydrogen peroxide by the Milas[16] procedure. 2,3-Dimethyl-2-butanol was prepared from isopropylmagnesium bromide and acetone, bp 115–116° (lit.[17] bp 117–122°). 2,3-Dimethyl-2-butyl hydroperoxide was prepared by the method of Criegee,[18] bp 37° (3 mm). α,α-Dimethylphenethyl hydroperoxide was prepared from α,α-dimethylphenethyl alcohol (Givaudan Co.) and hydrogen peroxide, mp 45–46° (lit.[19] mp 38–41°). Galvinoxyl was generously donated by Dr. Galvin Coppinger. Di-*t*-butylperoxy oxalate was prepared from oxalyl chloride and *t*-butyl hydroperoxide by the Bartlett procedure,[1] mp 49–51° dec (heating rate 2°/min, lit.[1] mp 50.5–51.5°). Iodometric titration in acetic acid required 1.85 equiv of sodium thiosulphate per 1 mol of peroxalate (lit.[1] 1.89 equiv).

The three peroxyoxalates Ib, Ic, and Id were similarly prepared in virtually quantitative yields (based on the carbon dioxide evolved from an aliquot of the reaction solution in pentane) from the corresponding hydroperoxide and oxalyl chloride. Compounds Ib and Id could be crystallized as white needles from pentane at −30°, but Ic was an oil which could not be crystallized. On warming to room temperature, Ib melted; it decomposed in a short time if kept at room temperature. Compounds Ic and Id, on warming to room temperature, spontaneously decomposed with vigorous evolution of gas. The compounds were more stable in dilute solution and were usually stored as 0.05 *M* solutions in pentane at −30°. Infrared spectra (in pentane) of all four peroxyoxalates showed no absorption owing to a hydroxyl group and showed a doublet in the carbonyl region (1820 and 1780 cm^{-1}) characteristic of peroxyoxalates. Iodometric titration of Ib in acetic acid required 1.83 equiv of sodium thiosulphate per 1 mol of peroxyoxalate. Compounds Ic and Id gave low and inconsistent titres under these conditions.

For the reactions in acetic acid and acetonitrile, aliquots of the 0.05 *M* solution of the peroxyoxalates in pentane were evaporated *in vacuo* while being cooled in a Dry Ice–acetone bath and then dissolved in the corresponding amount of acetic acid or acetonitrile. For the reactions of Ib, Ic, and Id in these solvents the solutions were not degassed with helium because of the rapidity of the decomposition under these conditions.

Kinetic runs were carried out using 3-ml aliquots of a 0.05 *M* solution of the peroxyoxalate in glass tubes capped with a gas-tight rubber serum cap. The solutions were degassed quickly with a stream of helium while cooled in ice. The log [$CO_{2\infty}$ − CO_2^t] value was plotted against time. Linearity was obtained in all cases over at least one half-life.

Gas chromatographic analyses of gaseous products were performed on instruments equipped with thermal conductivity detectors. Other analyses were performed on instruments with hydrogen flame ionization detectors: Varian Areograph Model 1200 and Areograph HiFy Model 600. The following are the conditions used in determining yields of products (product, marker, column, temperature): carbon dioxide, ethylene or methane, 2-ft Porapak Q, room temperature; methane, ethylene, 2-ft Porapak Q, room temperature; ethylene, methane, 2-ft Porapak Q, room temperature; ethane, methane or ethane, 2-ft Porapak Q, room temperature; propane, isobutane, 15-ft 30% Dowtherm on firebrick, room temperature; propylene, isobutane, 5-ft 30% Dowtherm on firebrick, room temperature; *n*-butane, isobutane, 15-ft 30% Dowtherm on firebrick, room temperature; 2,3-dimethylbutane, *n*-hexane, 15-ft SF-96 on firebrick, 90°; acetone, 2-propanol or *t*-butyl alcohol, 9-ft FFAP, 90°; *t*-butyl alcohol, 2-propanol, 9-ft FFAP, 90°; 2-propanol, *t*-butyl alcohol, 9-ft FFAP, 90°; *t*-amyl alcohol, 2-propanol, 9-ft FFAP, 90°; 2,3-dimethyl-2-butanol, *t*-amyl alcohol, 9-ft FFAP, 90°; ethanol, 2-propanol, 9-ft FFAP, 90°; di-*t*-butyl peroxide, 2-propanol, 9-ft FFAP, 90°; *t*-butyl methyl ether, 9-ft FFAP, 90°; benzyl alcohol, *n*-heptanol, 6-ft 15% Carbowax 20M on acid-washed Chromosorb P, 140°; benzaldehyde, *n*-heptanol, 6-ft 15% Carbowax 20M on acid-washed Chromosorb P, 140°; α,α-dimethylphenethyl alcohol, *n*-heptanol, 6-ft 15% Carbowax

(16) N. Milas and D. Surgenor, *ibid.*, **68**, 205 (1946).
(17) M. Delacre *Chem. Zentr.*, **77**, 1234 (1906).
(18) R. Criegee and H. Dietrich, *Justus Liebigs Ann. Chem.*, 135 (1948).
(19) J. K. Kochi and F. F. Rust, *J. Amer. Chem. Soc.*, **83**, 2007 (1961); **86**, 5264 (1964).

20M on acid-washed Chromosorb P; toluene, 9-ft FFAP, 90°; dibenzyl, diphenyl, 4-ft XF 1150, 130°.

Registry No.—Ia, 1876-22-8; Ib, 23042-72-0; Ic, 23042-73-1; Id, 23042-74-2.

Acknowledgment.—We wish to thank the Air Force Office of Scientific Research and the National Science Foundation for their generous financial support.

α Alkylation of Alkyl Alkanesulfonates

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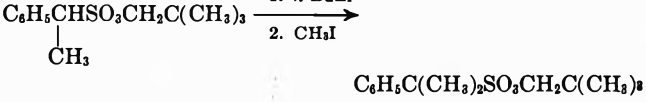
Received August 20, 1969

Recently, the facile α metalation (by *n*-butyllithium) and subsequent alkylation of alkyl α-toluenesulfonates were described.[1] Almost simultaneously, the α metalation and subsequent reactions of various sultones were reported.[2] The present work concerns the successful extension of our method of metalation and alkylation to simple alkyl alkanesulfonates.

The metalation of the starting sulfonates shown in Table I proceeds quantitatively and apparently instantaneously at Dry Ice bath temperatures. The time required for subsequent alkylation is a function of the alkylating agent. Contrary to what may have been implied earlier,[1] *n*-butyllithium is a superior metalating agent over potassium hydride, which requires a much longer time for metalation and a more complicated work-up procedure.

Using the method described herein, all of the α hydrogens of an alkyl alkanesulfonate can be replaced by alkyl groups. Thus a useful route to esters of tertiary sulfonic acids is at hand.[3] For example, a derivative (1) of α-cumenesulfonic acid is easily prepared by alkylation, while the acid itself has probably not been prepared.[4]



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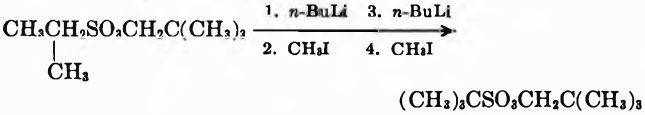
Also, as shown in the preparation of neopentyl 2-methyl-2-propanesulfonate (**9b**), the metalation and alkylation can be repeated without isolation of the first-formed product (**9a**).



9b

From the examples given in Table I, it is evident that, regardless of the alcohol portion of the ester, at Dry Ice bath temperatures metalation α to the sulfonyl group is preferred over other possible reactions, *i.e.*, elimination or displacement. As reported by Durst,[2] however, if the solution of the metalated species is allowed to warm, to *ca.* −30°, rapid exothermic decomposition takes place. The decomposition products are unknown, but with α-lithio methyl methanesulfonate an intractable, syrupy oil that shows strong sulfonyl bands in the ir spectrum separates from the reaction mixture. Therefore, alkylations with 1-bromopropane, and presumably with others of the less reactive alkylating agents, cannot be speeded by simply allowing the reaction mixture to warm, but, rather, the time for alkylation must be greatly extended while the reaction mixture is kept well cooled.

Experimental Section[5]

Materials.—*n*-Butyllithium in hexane was purchased from the Foote Mineral Co. or from Alfa Inorganics, Inc. Tetrahydrofuran (Baker Analyzed Reagent) was used directly from freshly opened bottles, or after storage over Linde Molecular Sieves. The alkyl halides (Columbia), sulfonyl chlorides (Eastman), and neopentyl alcohol (Aldrich) were used as obtained. All reactions described herein were carried out in thoroughly dried equipment under a nitrogen atmosphere. Starting sulfonates, prepared as described below, were distilled shortly before use.

General Method for the Preparation of Starting Alkyl Alkanesulfonates.—To a benzene solution of 1.0 equiv of the alcohol and 1.03 equiv of triethylamine cooled in an ice bath, a benzene solution of 1.0 equiv of the sulfonyl chloride was added dropwise. After the addition was complete, triethylammonium chloride was filtered and washed with benzene. The combined filtrate and washings were extracted once with 10% HCl and thrice with distilled water, dried (Na_2SO_4), and evaporated *in vacuo*, yielding the crude ester. Vacuum distillation yielded the pure product.

Neopentyl methanesulfonate was prepared in 78.4% yield on a 0.50-mol scale according to the general procedure: bp 93.5–94.5° (9 mm); ir (neat) 2980 (CH) and 1360 and 1180 cm^{-1} (SO_3); nmr δ 0.98 [s, 9, $(CH_3)_3$], 2.98 (s, 3, CH_3), and 3.82 (s, 2, CH_2). The analytical sample was prepared by vpc.

Anal. Calcd for $C_6H_{14}O_3S$: C, 43.35; H, 8.49; S, 19.29. Found: C, 43.53; H, 8.58; S, 19.01.

Neopentyl ethanesulfonate was prepared in 90.0% yield on a 0.23-mol scale according to the general procedure: bp 58–60° (0.15 mm); ir (neat) 2970 (CH) and 1355 and 1175 cm^{-1} (SO_3); nmr δ 0.98 [s, 9, $(CH_3)_3$], 1.37 (t, 3, J = 8 Hz, CH_3), 3.12 (q, 2, J = 8 Hz, CH_2S), and 3.82 (s, 2, OCH_2), The analytical sample was prepared by vpc.

Anal. Calcd for $C_7H_{16}O_3S$: C, 46.69; H, 8.95; S, 17.79. Found: C, 46.57; H, 9.12; S, 17.61.

Methyl methanesulfonate was prepared in 60% yield on a 1.0-mol scale: bp 71–73° (5.0 mm) [lit.[6] bp 100.5–101.5° (25 mm)]; ir (neat) 1360 and 1185 cm^{-1} (SO_3); nmr δ 3.00 (s, 3, CH_3S) and 3.88 (s, 3, OCH_3).

Ethyl methanesulfonate was prepared in 65% yield on a 0.10-mol scale: by 78–79° (7.5 mm) [lit.[7] bp 85–86° (10 mm)]; ir (neat) 1350 and 1180 cm^{-1} (SO_3); nmr δ 1.39 (t, 3, J = 7 Hz, CH_2CH_3), 2.99 (s, 3, CH_3S), and 4.27 (q, 2, J = 7 Hz, OCH_2CH_3).

2-Propyl methanesulfonate was prepared in 68% yield on a 0.50-mol scale: bp 39–41° (0.15 mm) [lit.[8] bp 86–88° (12 mm)];

(1) W. E. Truce and D. J. Vrencur, *Can. J. Chem.*, **47**, 860 (1969).

(2) T. Durst and J. du Manoir, *ibid.*, **47**, 1230 (1969).

(3) The only other route to esters of this type is the reaction of a tertiary sulfonic acid with a diazo alkane, a method limited chiefly by the availability of the sulfonic acid: F. Asinger, B. Fell, and A. Commichau, *Chem. Ber.*, **98**, 2154 (1965); R. B. Scott, Jr., and W. S. Heller, *J Org. Chem.*, **31**, 1999 (1966).

(4) The preparation of α-cumenesulfonic acid has been claimed *via* treatment of cumene with the pyridine–sulfur trioxide complex. The product was characterized only by a nitrogen analysis of its S-benzylthiouronium derivative. See Y. S. Shabarov, R. Y. Levina, and V. K. Potapov, *Zh. Obshch. Khim.*, **32**, 3184 (1962); *J. Gen. Chem. USSR*, **32**, 3129 (1962).

(5) Melting and boiling points are uncorrected. Infrared spectra were recorded on an Infracord spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates A-60A spectrometer in deuteriochloroform with tetramethylsilane as internal standard. Microanalyses were performed by Dr. C. S. Yeh and staff.

(6) W. E. Bissinger, F. E. Kung, and C. W. Hamilton, *J. Amer. Chem. Soc.*, **70**, 3940 (1948).

(7) H. Billeter, *Chem. Ber.*, **38**, 2018 (1905).

(8) J. H. Markgraf, B. A. Hess, Jr., C. W. Nichols, and R. W. King, *J. Org. Chem.*, **29**, 1499 (1964).

TABLE I

$$R_1R_2CHSO_3R_4 \xrightarrow[R_3X]{n\text{-BuLi}} R_1R_2R_3CSO_3R_4 + LiX$$

Compd	R_1	R_2	R_3X	R_4	Yield, %	Bp, °C (mm)
1	C_6H_5	CH_3	CH_3I	$CH_2C(CH_3)_3$	89.8	107–109.5 (0.30)
2	H	H	CH_3I	$CH_2C(CH_3)_3$	87.9	58–60 (0.15)
3	H	H	CH_3I	CH_2CH_3	83.4	79.5–81 (8)
4	H	H	CH_3I	CH_3	89.0	73.5–74.5 (5)
5	H	H	CH_3I	$CH(CH_3)_2$	85.8	44–46 (0.15)
6	CH_3	H	CH_3I	$CH(CH_3)_2$	83.0	39–41 (0.25)
7	CH_3	CH_3	CH_3I	$CH(CH_3)_2$	84.5	35.5–36 (0.35)
8	H	H	$CH_3CH_2CH_2Br$	$CH_2C(CH_3)_3$	70.2	112–115 (5)
9a	CH_3	H	CH_3I	$CH_2C(CH_3)_3$	[a]	
9b	CH_3	CH_3	CH_3I	$CH_2C(CH_3)_3$	77.5	46–49 (0.20)

[a] Intermediate product not isolated.

ir (neat) 1350 and 1185 cm^{-1} (SO_3); nmr δ 1.40 [d, 6, J = 7 Hz, $CH(CH_3)_2$], 2.98 (s, 3, CH_3S), and 4.90 [septet, 1, J = 7 Hz, $CH(CH_3)_2$].

Neopentyl 1-phenylethanesulfonate was prepared as described in ref 2 by the methylation of neopentyl α-toluenesulfonate in a procedure identical with that described below, bp 110–113° (0.25 mm).

General Procedure for the α Alkylation of Alkyl Alkanesulfonates.—The starting sulfonate was dissolved in tetrahydrofuran (*ca.* 10 ml per 1 g of sulfonate), and the solution was cooled in a Dry Ice–isopropyl alcohol bath. *n*-Butyllithium in hexane solution was then added from a syringe (1.1 equiv of *n*-butyllithium were used for all but the methyl ester, with which 1.0 equiv was used). After *ca.* 15 min, the alkylating agent was added dropwise and stirring was continued at Dry Ice bath temperatures for 1–2 hr with methyl iodide and for 12 hr with *n*-propyl bromide as alkylating agent. The reaction was then quenched with water, the resulting suspension was extracted with chloroform, and the chloroform extracts were combined, dried, and evaporated *in vacuo*, yielding the crude product. Careful vacuum distillation yielded the pure product.

Neopentyl α-cumenesulfonate (1) was prepared in 89.8% yield on a 0.0175-mol scale from neopentyl 1-phenylethanesulfonate and methyl iodide: bp 107–109.5° (0.30 mm); ir (neat) 3000 (CH) and 1350 and 1190 cm^{-1} (SO_3); nmr δ 0.82 [s, 9, $(CH_3)_3$], 1.92 [s, 6, $C_6H_5C(CH_3)_2$], 3.50 (s, 2, OCH_2), and 7.2–7.8 (m, 5, C_6H_5).

Anal. Calcd for $C_{14}H_{22}O_3S$: C, 62.19; H, 8.20; S, 11.86. Found: C, 62.42; H, 8.33; S, 11.58.

Neopentyl ethanesulfonate (2) was prepared in 87.9% yield on a 0.010-mol scale from neopentyl methanesulfonate and methyl iodide. The product was identical in all respects with that prepared from neopentyl alcohol and ethanesulfonyl chloride as described above.

Ethyl ethanesulfonate (3) was prepared in 83.4% yield on a 0.010-mol scale from ethyl methanesulfonate and methyl iodide: bp 79.5–81° (8 mm) [lit.[8] bp 101.5–102.5° (18 mm)]; ir (neat) 1350 and 1170 cm^{-1} (SO_3); nmr δ 1.4 (t, 6, J = 7 Hz, CH_3CH_2S and CCH_2CH_3), 3.14 (q, 2, CH_3CH_2S), and 4.30 (q, 2, OCH_2CH_3).

Methyl ethanesulfonate (4) was prepared in 89.0% yield on a 0.064-mol scale from methyl methanesulfonate and methyl iodide: bp 73.5–74.5° (5 mm) [lit.[9] bp 70–72° (7 mm)]; ir (neat) 1350 and 1174 cm^{-1} (SO_3); nmr δ 1.38 (t, 3, J = 7 Hz, CH_3CH_2), 3.16 (q, 2, J = 7 Hz, CH_2), and 3.88 (s, 3, OCH_3).

2-Propyl ethanesulfonate (5) was prepared in 85.8% yield on a 0.10-mol scale from 2-propyl methanesulfonate and methyl iodide: bp 44–46° (0.15 mm) [lit.[9] bp 71–73° (5 mm)]; ir (neat) 1350 and 1174 cm^{-1} (SO_3); nmr δ 1.36 (t, 3, J = 7 Hz, CH_3CH_2), 1.38 [d, 6, J = 6.5 Hz, $CH(CH_3)_2$], 3.08 (q, 2, J = 7 Hz, CH_3CH_2), and 4.90 [septet, 1, J = 6.5 Hz, $CH(CH_3)_2$].

2-Propyl 2-propanesulfonate (6) was prepared in 83.0% yield on a 0.0723-mol scale from 2-propyl ethanesulfonate and methyl iodide: bp 39–41° (0.25 mm); ir (neat) 1350 and 1175 cm^{-1} (SO_3); nmr δ 1.42 (d, 6, J = 6 Hz, four methyl groups of the two isopropyl groups), 3.25 (septet, 1, J = 6 Hz, HCS), and 4.92 (septet, 1, J = 6 Hz, OCH). The analytical sample was prepared by vpc.

Anal. Calcd for $C_6H_{14}O_3S$: C, 43.35; H, 8.49; S, 19.29. Found: C, 43.12; H, 8.55; S, 19.00.

2-Propyl 2-methyl-2-propanesulfonate (7) was prepared in a 84.5% yield on a 0.050-mol scale from 2-propyl 2-propanesulfonate and methyl iodide: bp 35.5–36° (0.35 mm); ir (neat) 1315 and 1145 cm^{-1} (SO_3); nmr δ 1.39 [s, 9, $(CH_3)_3$], 1.37 [d, 6, J = 6 Hz, $(CH_3)_2CH$], and 4.91 [septet, 1, J = 6 Hz, $CH(CH_3)_2$]. The analytical sample was prepared by vpc.

Anal. Calcd for $C_7H_{16}O_3S$: C, 46.64; H, 8.95; S, 17.78. Found: C, 46.76; H, 9.11; S, 17.50.

Neopentyl 1-butanesulfonate (8) was prepared in 70.2% yield on a 0.060-mol scale from neopentyl methanesulfonate and 1-bromopropane: bp 112–115° (5 mm); ir (neat) 3000 (CH) and 1360 and 1175 cm^{-1} (SO_3); nmr δ 0.98 [s, 9, $(CH_3)_3$], 0.90–2.0 (m, 7, $CH_3CH_2CH_2$), 3.12 (t, 2, CH_2S), and 3.85 (s, 2, OCH_2). The analytical sample was prepared by vpc.

Anal. Calcd for $C_9H_{20}O_3S$: C, 51.89; H, 9.68; S, 15.39. Found: C, 51.74; H, 9.84; S, 15.39.

Neopentyl 2-methyl-2-propanesulfonate (9b).—Neopentyl ethanesulfonate (3.60 g, 0.020 mol) was dissolved in 40 ml of THF and the solution was cooled in a Dry Ice–isopropyl alcohol bath. *n*-Butyllithium (0.020 mol) was added, and, after 10 min of stirring, methyl iodide (2.84 g, 0.020 mol) was added. After 25 min of additional stirring, the process was repeated; *i.e.*, *n*-butyllithium (0.022 mol) was added, and 10 min later an additional 0.022 mol of methyl iodide was added followed by 25 min of stirring. The reaction mixture was then worked up in the usual manner, yielding 3.22 g (77.5%) of the title compound that partially solidified after distillation: bp 46–49° (0.20 mm); ir (neat) 3000 (CH) and 1335 and 1150 cm^{-1} (SO_3); nmr δ 0.93 [s, 9, $OCH_2C(CH_3)_3$], 1.42 [s, 9, $(CH_3)_3CS$], and 3.83 (s, 2, OCH_2). The analytical sample was prepared by vpc.

Anal. Calcd for $C_9H_{20}O_3S$: C, 51.89; H, 9.68; S, 15.39. Found: C, 52.15; H, 9.81; S, 15.19.

Registry No.—**1**, 23230-57-1; **2**, 23230-58-2; **3**, 23230-59-3; **4**, 23214-45-1; **5**, 23214-46-2; **6**, 23263-79-8; **7**, 23214-47-3; **8**, 23214-48-4; **9b**, 23214-49-5; neopentyl methanesulfonate, 16427-42-2; methyl methanesulfonate, 66-27-3; ethyl methanesulfonate, 62-50-0; 2-propyl methanesulfonate, 926-06-7; neopentyl 1-phenylethanesulfonate, 22457-17-6.

Acknowledgment.—The authors are grateful to the Public Health Service for financial support of this work under Research Grant CA-04536-11 from the National Cancer Institute.

(9) S. Yoshikawa, O. K. Kim, and T. Hori, *Bull. Chem. Soc. Jap.*, **39**, 1937 (1966).

The Photolysis of Benzo[3.4]cyclobuta[1,2-*b*]quinoxaline[1,2]

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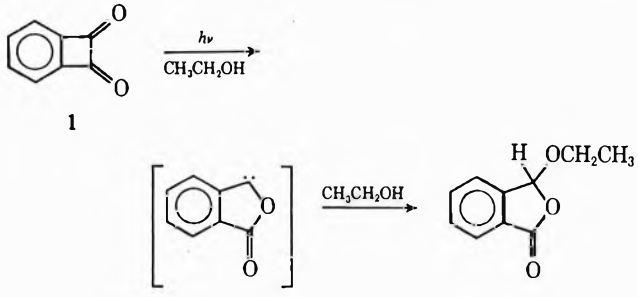
Received August 11, 1969

Benzocyclobutadienoquinone (**1**) has been shown to undergo a photochemical transformation which produces a species whose reactivity is characteristic of an intermediate containing a divalent carbon.[4] The reaction sequence shown in Scheme I has been offered as an explanation for the reaction of **1** with ethanol.

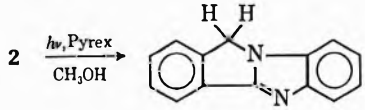
SCHEME I

PHOTOCHEMICAL REACTION OF BENZOCYCLOBUTADIENOQUINONE (1) WITH ETHANOL



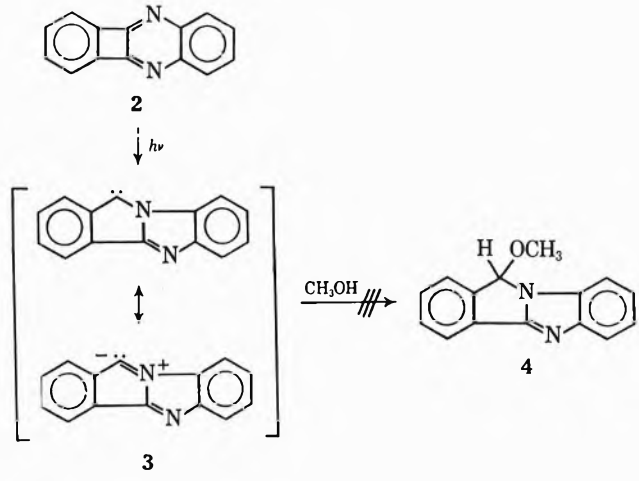
Our interest in the photochemistry of unsaturated nitrogen-containing systems[5] combined with this unusual photochemical transformation of benzocyclobutadienoquinone (**1**) prompted us to investigate the photochemistry of benzo[3.4]cyclobuta[1,2-*b*]quinoxaline, a nitrogen-containing analog of **1**. The particular reason for interest in compound **2** was the possibility that it might react in a manner similar to that suggested for **1** (Scheme II) and, if such reaction were to occur, the reactive intermediate **3** might have significant contribution from its zwitterionic resonance form. Significant participation by this resonance contributor would result in an intermediate which would possess a divalent center bearing considerable negative charge. In an effort to study the reactivity of **3**, benzo[3.4]cyclobuta[1,2-*b*]quinoxaline (**2**) was synthesized and irradiated.

Pyrex-filtered irradiation of a methanol solution of **2** under nitrogen produced, upon solvent removal, a yellow solid. Chromatography of this solid on silicic acid gave as the only product 11H-isoindolo[2,1-*a*]-benzimidazole (**5**, 80% yield); none of the initially



SCHEME II

POTENTIAL (BUT NOT OBSERVED) REACTION PATHWAY FOR 2

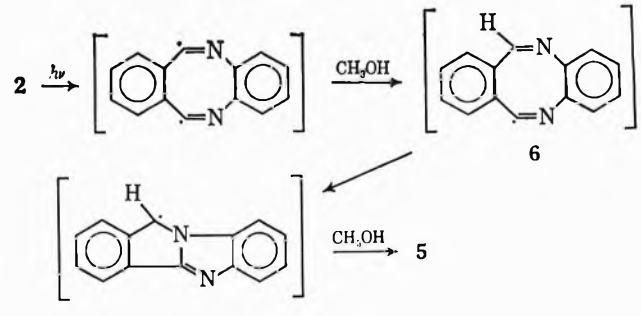


expected photoproduct **4** was detected. The fact that **5** undergoes photochemical decomposition suggests that the conversion of **2** into **5** may be essentially quantitative.

A possible mechanism for the photochemical formation of 11H-isoindolo[2,1-*a*]benzimidazole (**5**) is shown in Scheme III. The reason for the apparent failure of **2** to form a divalent intermediate is not known; however, the bridging of the ends of the nitrogen-containing diene system with a benzene ring may have restricted the movement of the atoms and altered the electronic nature of the molecule sufficiently to favor the observed reaction.[6]

SCHEME III

PROPOSED MECHANISM FOR FORMATION OF 5



Experimental Section[8]

Pyrex-Filtered Irradiation of Benzo[3.4]cyclobuta[1,2-*b*]quinoxaline.—Benzo[3.4]cyclobuta[1,2-*b*]quinoxaline (**2**, 204 mg) was irradiated for 6 hr at 15° with constant stirring using a 450-W Hanovia high-pressure quartz mercury-vapor lamp which had been lowered into a water-cooled quartz immersion well. Prepurified nitrogen was passed through the solution for 1 hr

(1) Part VI in a series entitled "The Photochemistry of Unsaturated Nitrogen Containing Compounds." Part V: R. W. Binkley, *Tetrahedron Lett.*, 1893 (1969).

(2) The title compound was synthesized according to the procedure of M. P. Cava, D. R. Napier, and R. J. Pohl, *J. Amer. Chem. Soc.*, **85**, 2076 (1963).

(3) Taken in part from the M.S. thesis of J. I. S.

(4) (a) R. F. C. Brown and R. K. Solly, *Tetrahedron Lett.*, 169 (1966); (b) H. A. Staab and J. Ipaktschi, *ibid.*, 583 (1966); (c) H. A. Staab and J. Ipaktschi, *Chem. Ber.*, **101**, 1457 (1968).

(5) R. W. Binkley, *J. Org. Chem.*, **33**, 2311 (1968).

(6) (a) A slight variation of the proposed mechanism would involve a reversal of the last two steps shown in Scheme III; that is, the second hydrogen abstraction would occur before the cyclization to give the benzimidazole structure. There is reason to believe[7] that, if **6** did abstract an hydrogen atom from the solvent, cyclization to 11H-isoindolo[2,1-*a*]benzimidazole (**5**) would quickly occur. (b) It is interesting to note that this reaction also takes place when run in *t*-butyl alcohol, a much less effective hydrogen-donating solvent than methanol. In *t*-butyl alcohol, however, the yield of **5** decreases to 49%.

(7) K. Hofmann, "Imidazole and Its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1953, part I, pp 267–270.

(8) The nmr spectra were taken on a Varian T-60 nmr spectrometer.

prior to irradiation and a slow stream of nitrogen was continued during photolysis. A Pyrex filter was placed between the light source and the reaction mixture.

After 6 hr, the solvent was removed by distillation *in vacuo* below 30°, producing a distillate which was transparent in the uv and leaving a yellow solid. The residual solid was chromatographed on an 85 × 2.5 cm silicic acid column slurry packed in 1:3 ether–hexane; 60-ml fractions were collected. The column was eluted as follows: 0.5 l. of 1:3 ether–hexane; 0.5 l. of 1:1 ether–hexane; 0.5 l. of 3:1 ether–hexane; and 0.5 l. of ether. Fractions 15–19 gave 175 mg of a pale yellow solid, mp 203–209°, recrystallized from ethanol–water to yield 164 mg of white crystals: mp 214–215° (the uv spectrum and the melting point of the photoproduct were identical with the reported spectrum[9] and melting point[10] for 11H-isoindolo[2,1-*a*]benzimidazole); nmr (CCl_4) τ 5.08 (s, 2) and 1.80–2.95 (m, 8). The identity of the photoproduct as 11H-isoindolo[2,1-*a*]benzimidazole (**5**) was confirmed by ir and mixture melting point comparison with an authentic sample[10] of **5**.

Test of the Stability of Benzo[3.4]cyclobuta[1,2-*b*]quinoxaline under Reaction and Isolation Conditions.—A control run in which 42 mg (0.21 mmol) of benzo[3.4]cyclobuta[1,2-*b*]quinoxaline (**2**) was subjected to the reaction and isolation conditions described in the previous experiment, except that no light was used, resulted in a quantitative recovery of starting material.

Pyrex-Filtered Irradiation of 11H-Isoindolo[2,1-*a*]benzimidazole (5) in Methanol.—11H-Isoindole[2,1-*a*]benzimidazole (**5**, 45 mg, 0.22 mmol) was irradiated in exactly the same manner as the irradiation of benzo[3.4]cyclobuta[1,2-*b*]quinoxaline (**2**). The isolation procedure was also the same. Fractions 14 and 15 from the chromatography column gave 30 mg of 11H-isoindolo[2,1-*a*]benzimidazole (**5**), mp 212–215°. No other compounds could be isolated. A stability test of **5** under reaction and isolation conditions but without the addition of light, similar to that described above for benzo[3.4]cyclobuta[1,2-*b*]quinoxaline (**2**), resulted in a quantitative recovery of **5**.

Registry No.—2, 259-57-4; 5, 248-72-6.

(9) D. Amos and R. G. Gillis, *Aust. J. Chem.*, **17**, 1440 (1964).
(10) J. Thiele and K. G. Falk, *Justus Liebigs Ann. Chem.*, **347**, 114 (1906).

Deoxygenation of Benzoyl Cyanide[1]

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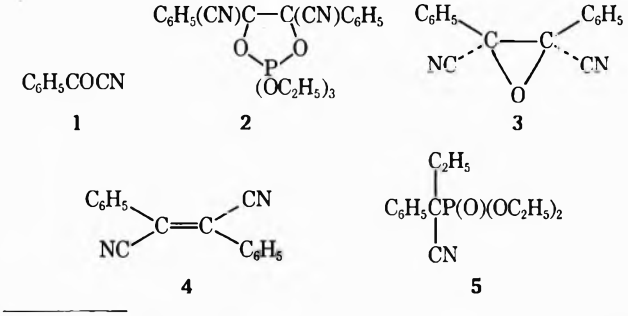
Received August 6, 1969

In refluxing benzene, triethyl phosphite and benzoyl cyanide (**1**) react over a period of 72 hr to form *cis*-α,β-dicyanostilbene oxide (**3**),[2,3] *trans*-α,β-dicyanostilbene (**4**),[2,3] and diethyl α-cyano-α-phenylpropylphosphonate



1 2 3 4 5

(1) Financial support was received from NASA Grant No. NGR 14-012-004.

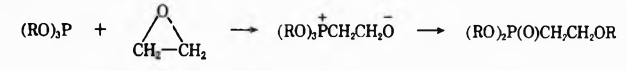
(2) J. H. Boyer and R. Selvarajan, Abstracts of 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, p S 111.

(3) C. J. Timmons and S. C. Wallwork [*Chem. Ind.* (London), 62 (1955)] conclusively established the configuration of *trans*-α,β-dicyanostilbene **4**, mp 161°, by X-ray analysis. M. V. Sargent and C. J. Timmons [*J. Chem. Soc.*, 2222 (1964)] established the configuration of *cis*-α,β-dicyanostilbene, mp 134°. Formation of **4**, in turn, provides a tentative *cis*-configurational assignment to **3**, since an inverted olefin is reported to predominate when an epoxide is deoxygenated by a tertiary phosphine [G. Wittig and W. Haag, *Chem. Ber.*, **88**, 1654 (1955); C. B. Scott, *J. Org. Chem.*, **22**, 1118 (1957); M. J. Boskin and D. B. Denney, *Chem. Ind.* (London), 330 (1959)].

(4) T. Mukaiyaka, I. Kuwajima, and K. Ohno, [*Bull. Chem. Soc. Jap.*, **38**, 1954 (1965)] incorrectly reversed the configurational assignments for **3** and **4**.

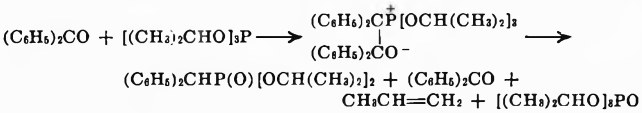
(5) P. C. Petrellis and G. W. Griffin [*Chem. Commun.*, 1099 (1968)] also observed the pyrolysis at 140° of **2** into **3**.[4]

(6) J. I. G. Cadogan [*Quart. Rev.*, **16**, 208 (1962)] discusses, p 216, a related reaction of epoxides with trialkyl phosphites which contain one or more secondary or tertiary alkyl groups. Phosphonates, rather than olefins and phosphates, are formed. An alkyl group migrates from oxygen to oxygen.

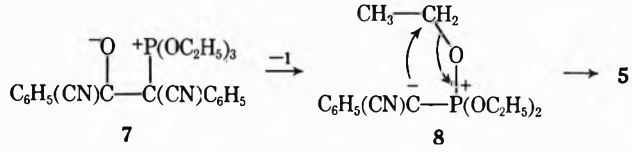


(7) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press Inc., New York, N. Y., 1965, pp 135–140.

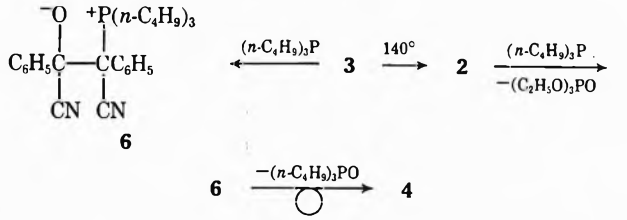
(8) A. C. Poshkus and J. E. Herweh [*J. Org. Chem.*, **29**, 2567 (1964)] reported phosphonate formation by a related 1,3 migration of hydrogen in a reaction between benzophenone and triisopropyl phosphite.



$$(RO)_3P \xrightarrow{R'X} (RO)_3\overset{+}{P}R'\ \overset{-}{X} \longrightarrow (RO)_2P(O)R' + RX$$



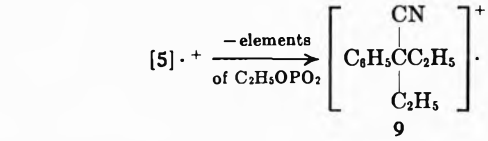
group from oxygen to carbon accounts for the formation of **5**.[6] The rearrangement is reminiscent of the Arbuzov reaction in which a monoalkylphosphonic ester is formed upon heating a mixture of an alkyl halide and a trialkyl phosphite with an unstable phosphonium salt presumably as an intermediate.[7,8]



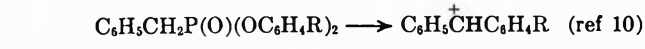
A comparable zwitterion intermediate **7** is now assigned to the transformation of both **2** and **3** into **4** when each is treated with triethyl phosphite. By an alternative dissociation of **7**, benzoyl cyanide **1** and the phosphonium ylide **8** are available. The latter is isomeric with **5** and, although unprecedented, its proposed rearrangement by 1,3 migration of an ethyl

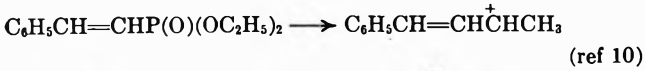
The ir spectrum of the phosphonate **5** shows strong $P^{+}-O^{-}$ and C≡N absorptions at 1255 and 2240 cm^{-1}, respectively. The nmr spectrum shows one quintet centered at δ 2.35, a second at 3.74, and a third at 4.20. Each quintet integrates for two protons. The two downfield absorptions are assigned to methylene groups attached to oxygen in agreement with reported nmr nonequivalence between methoxy[9a] and ethoxy[9b] groups attached to phosphorus. The upfield absorption at δ 2.35 is assigned to the protons of the methylene unit flanked by two carbon atoms. All six methylene protons exhibit long-range coupling with ^{31}P. By integration nine protons in methyl groups and five aromatic protons are observed.

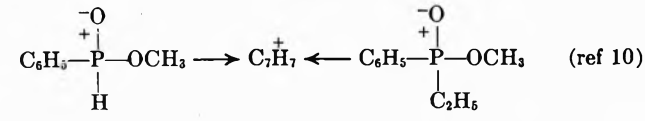
A mass spectrometric analysis of the phosphonate **5** reveals a molecular ion (also the base peak) at *m/e* 281. An electron impact induced rearrangement accounts for the peak at *m/e* 173 assigned to the fragment molecular cation for phenyldiethylacetonitrile **9**. A similar electron impact induced 1,3 migration from oxygen to carbon has been reported for several other phosphonates.[10]



9







Experimental Section

A mixture of benzoyl cyanide (2.62 g, 20 mmol) and excess triethyl phosphite (13.2 g, 80 mmol) in anhydrous benzene (50 ml) was refluxed under nitrogen for 72 hr. From the reaction mixture the solvent was removed under vacuum; the residual liquid was distilled under vacuum giving a mixture of triethyl phosphite and triethyl phosphate, 9.6 g, bp 65–70° (1.25 mm). The pot residue was chromatographed over a column of silica (12 in. × 1 in.). The elutions with a 4:1 hexane–benzene mixture afforded colorless crystals of *cis*-α,β-dicyanostilbene oxide: 0.64 g, 26%; mp 166–166.5°; ir ($CHCl_3$) 2240 (w, CN), 1590 (w, aromatic), and 790 and 870 cm^{-1} (epoxide ring); λ_{max} (methanol) 222 mμ (ϵ 269.2) 278 (588.8) and 324 (933.3); nmr (CCl_4) multiplet centered at δ 7.58 (phenyl).

The elutions with hexane–benzene (3:1) gave colorless crystals of *trans*-α,β-dicyanostilbene: 0.53 g, 23%; mp 161.5–162° (benzene–hexane); ir ($CHCl_3$) 2230 (s, CN) and 1600 cm^{-1} (m, aromatic); λ_{max} ($CHCl_3$) 280 mμ (ϵ 3467) and 324 (15,490); nmr (CCl_4) multiplet centered at δ 7.65 (phenyl).

The elutions with benzene–ether (3:1) gave α-cyano-α-phenyl propyl phosphonate (1.0 g, 17.8%), a colorless viscous liquid which was further purified by distillation under vacuum (short path): bp 148–148.5° (0.75 mm); $n^{27.5}D$ 1.4955; ir (film) 2240 (m, CN), 1590 (w, aromatic), and 1255 cm^{-1} (vs, P=O); λ_{max} ($CHCl_3$) 312 mμ (ϵ 169.8); nmr (CCl_4) δ 0.92 (t, 3 H, CCH_3), 1.02 (t, 3 H, CCH_3), 1.40 (t, 3 H, CCH_3), 2.35 (quintet, 2 H, $PCCH_2CH_3$), 3.74 (quintet, 2 H, $POCH_2CH_3$), 4.20 (quintet, 2 H, $POCH_2CH_3$), and a multiplet centered at 7.50 (5 H, phenyl); mass spectrum *m/e* 281 (M^+) base peak, 266 $(M - CH_3)^+$, 253 $(M - C_2H_4)^+$, 238 $(M - CH_3 - C_2H_4)^+$, 255 $(M - 2C_2H_4)^+$, 210 $(M - CH_3 - 2C_2H_4)^+$, 197 $(M - 3C_2H_4)$, 173 $[C_6H_5(CN)C(C_2H_5)_2]^+$, 158 $[C_6H_5(CN)C(C_2H_5)CH_2]^+$, 145 $[C_6H_5HC(CN)C_2H_5]^+$, 144 $[C_6H_5C(CN)C_2H_5]^+$, 130 $[C_6H_5(CN)CHCH_2]^+$, 129 $[C_6H_5(CN)C{=}CH_2]$, 117 $(C_6H_5CH_2CN)^+$, 116 $(C_6H_5CHCN)^+$, 102 $(C_6H_5C{\equiv}CH)^+$, 91 $(C_7H_7)^+$, and 51 $(NCC{\equiv}CH)^+$.

Anal. Calcd for $C_{14}H_{20}NO_3P$: C, 59.78; H, 7.11; N, 4.98; P, 11.03. Found: C, 60.03; H, 7.14; N, 4.71; P, 10.69.

Registry No.—**1**, 613-90-1; **3**, 23214-43-9; **4**, 2450-55-7; **5**, 23230-35-5.

(9) (a) F. Ramirez, A. V. Patwardhan, N. B. Desai, and S. R. Heller, *J. Amer. Chem. Soc.*, **87**, 549 (1965); (b) T. H. Siddall, III, and C. A. Prohaska, *ibid.*, **84**, 3467 (1962).

(10) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, Inc., San Francisco, Calif., 1967, p 649.

Lead(IV) Diacetate Difluoride. I. Reaction with Ketone Arylhydrazones[1]

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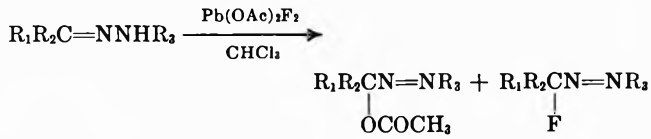
Received July 25, 1969

Recently, we reported the isolation of lead(IV) diacetate difluoride from the reaction of lead tetraacetate with liquid hydrogen fluoride in chloroform solution.[2] As part of a general study of the chemistry of this compound and because of a specific interest in its potential as a fluorinating agent, we have examined its action on a series of ketone arylhydrazones. It has been found that the reaction of lead(IV) diacetate difluoride with this class of compounds affords mixtures of azo acetates[3] and azo fluorides.[4] The former substances are well known and have been prepared by treatment of ketohydrazones[3] and ketazines[5] with lead tetraacetate; the azo fluorides, as far as we are aware, have not been prepared previously.



The yields and properties of five azo fluorides and their accompanying azo acetates are summarized in Table I. Although the yields of the azo fluorides are smaller than those of the companion azo acetates, the mild conditions and ease of carrying out the reaction make this fluorination useful. Generally, the reaction was conducted under reflux in chloroform; at lower temperatures the yields of the azo fluorides were unchanged, but those of the azo acetates were substantially decreased in some cases. Resolution of the mixtures of azo compounds was trouble free and was readily effected either by column chromatography or by fractional distillation.

As shown in Table II, and in accordance with expectations, the ultraviolet spectra of the azo fluorides are

(1) This research has been supported by National Science Foundation Grant GP-8672.

(2) J. Bornstein and L. Skarlos, *J. Amer. Chem. Soc.*, **90**, 5044 (1968).

(3) D. C. Iffland, L. Salisbury, and W. R. Schafer, *ibid.*, **83**, 749 (1961).

(4) For convenience and consistency, the term "azo fluoride" has been adopted for the general structure shown. See ref 3, footnote 3. The systematic fluoroarylazo alkane name is used throughout the text and Experimental Section.

(5) B. T. Gillis and M. P. La Montagne, *J. Org. Chem.*, **32**, 3318 (1967); **33**, 1294 (1968).

TABLE I

AZO FLUORIDES AND AZO ACETATES, $R_1R_2C(R)N{=}NR_3$

Compd[a]	R	R_1	R_2	R_3	Yield, %	Mp or bp, °C (mm)	Calcd, % C	H	F	N	Found, % C	H	F	N
1	F	CH_3	CH_3	$2,4\text{-}(NO_2)_2C_6H_3$	16	51–52	42.19	3.52	7.42	21.88	41.99	3.56	7.22	21.70
1a	OAc	CH_3	CH_3	$2,4\text{-}(NO_2)_2C_6H_3$	53	87–88[b]								
2	F	CH_3	CH_3	C_6H_5	10[c]	56 (1.50)	65.06	6.63	11.44	16.87	65.05	6.79	11.21	17.04
2a	OAc	CH_3	CH_3	C_6H_5	4[c]	95 (1.50)[b]								
3	F	CH_3	C_2H_5	C_6H_5	17[d,e]	65 (1.25)	66.67	7.22	10.55	15.56	66.49	7.05	10.33	15.73
3a	OAc	CH_3	C_2H_5	C_6H_5	42[e]	102 (1.25)[b]								
4	F	$(CH_2)_5$		$2,4\text{-}(NO_2)_2C_6H_3$	16	79–80	48.64	4.39	6.42	18.92	48.86	4.52	6.20	18.94
4a	OAc	$(CH_2)_5$		$2,4\text{-}(NO_2)_2C_6H_3$	52	111–112[f]								
5	F	C_6H_5	C_6H_5	$p\text{-}NO_2C_6H_4$	5	123–123.5	68.08	4.18	5.67	12.54	68.20	4.23	5.43	12.46
5a	OAc	C_6H_5	C_6H_5	$p\text{-}NO_2C_6H_4$	39	134–134.5	67.20	4.53		11.20	67.11	4.53		11.24

[a] All compounds are from reactions carried out under reflux in chloroform unless otherwise noted. Column chromatography, as described in the Experimental Section, was used to isolate all products except those for which a boiling point is recorded; these were isolated by distillation. [b] Reference 3. [c] $n^{31}D$ 1.5055. [d] $n^{28}D$ 1.5060. [e] From reaction carried out at 0°. [f] Reference 3 gives a melting point of 102–103°.

TABLE II

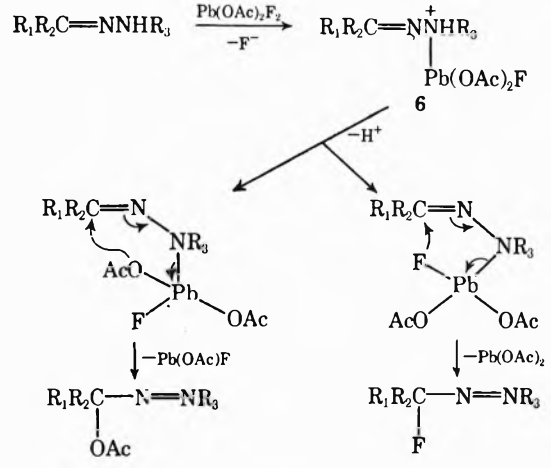
SPECTROPHOTOMETRIC PROPERTIES OF AZO FLUORIDES AND COMPANION AZO ACETATES

Compd	Uv, nm (log ε)[a]	Nmr, δ[b]
1	220 (5.14)	8.58 (m, 2, ArH), 7.44 (d, 1, J = 9 Hz, ArH), 1.58 [d, 6, J = 19 Hz, $C(CH_3)_2$]
	268 (5.13)	
1a	222 (5.15)	
	270 (5.16)	
2	269 (3.87)	7.53 (m, 5, ArH), 1.48 [d, 6, J = 19 Hz, $C(CH_3)_2$]
2a	267 (3.86)	
3	269 (4.13)	7.53 (m, 5, ArH), 1.88 (m, 2, CH_2-CH_3), 1.45 [d, 3, J = 19 Hz, $C(F)CH_3$], 0.95 (t, 3, J = 7.5 Hz, CH_3CH_2)
3a	268 (4.13)	
4	222 (5.15)	8.53 (m, 2, ArH), 7.45 (d, 1, J =
	270 (5.17)	9 Hz, ArH), 1.82 [m, 10, $(CH_2)_5$]
4a	221 (5.14)	
	272 (5.19)	
5	282 (4.15)	7.81 (m, ArH) (in $CDCl_3$)
5a	283 (4.16)	7.90 (m, 14, ArH), 2.38 (s, 3, CH_3) (in $CDCl_3$)

[a] λ_{max} determined in 95% ethanol with a Beckman Model DU spectrometer. [b] Spectra obtained at 60 Mcps with a Varian Associates Model HA-60 spectrometer in CCl_4 with tetramethylsilane as internal standard, except where noted: s, singlet; d, doublet; t, triplet; m, multiplet.

practically identical with those of the corresponding azo acetates. The nmr spectra of the azo fluorides are fully consistent with the proposed structures, for which additional evidence was obtained by synthesis. Thus stirring of a suspension of 2-acetoxy-2-(2,4-dinitrophenylazo)propane (**1a**) with liquid hydrogen fluoride[6] at −78° for 2–5 min afforded 2-fluoro-2-(2,4-dinitrophenylazo)propane (**1**) in 60% yield. In similar fashion, azo acetate **4a** was converted into 1-fluoro-1-(2,4-dinitrophenylazo)cyclohexane (**4**) in 66% yield. Presumably, this method can be extended to the preparation of other azo fluorides.

There is evidence, albeit of limited scope, to suggest that the reaction of lead(IV) diacetate difluoride with ketone arylhydrazones proceeds by an ionic mechanism. Thus the yields of azo compounds produced on treatment of acetone 2,4-dinitrophenylhydrazone with lead(IV) diacetate difluoride are essentially unchanged when the reaction is run in the presence of oxygen or nitrobenzene. On the basis of this observation and the mechanism proposed recently by Harrison, Norman, and Gladstone[7] to explain the oxidation of ketone arylhydrazones by lead tetraacetate, we wish to suggest that both the fluorination and acetoxylation occur *via* a pathway involving the common intermediate **6**. In this connection it should be noted that chelation[2] of the acetoxy groups to the lead atom in lead(IV) diacetate difluoride probably makes them less susceptible to displacement by the NH nitrogen of the hydrazone than the fluorine atoms.



Experimental Section[8]

The ketone arylhydrazones used in this study were prepared by standard procedures.[9] Chloroform, freshly purified by washing with concentrated sulfuric acid according to the method of Vogel,[10] was used as reaction medium.

The following typical examples illustrate the general procedures used to prepare the azo compounds.

Reaction of Lead(IV) Diacetate Difluoride with Acetone 2,4-Dinitrophenylhydrazone. A. 2-Fluoro-2-(2,4-dinitrophenylazo)propane (1).—This reaction was carried out in an atmosphere of dry nitrogen. To a stirred, refluxing slurry of 7.96 g (0.022 mol) of lead(IV) diacetate difluoride[2] in 50 ml of chloroform was added

(6) For a related reaction see J. Bornstein, M. R. Borden, F. Nunes, and H. I. Tarlin, *J. Amer. Chem. Soc.*, **85**, 1609 (1963).

(7) M. J. Harrison, R. O. C. Norman, and W. A. F. Gladstone, *J. Chem. Soc.*, 735 (1967).

(8) Melting points are corrected and boiling points are uncorrected. Infrared spectra were recorded on a Beckman Model IR-10 spectrometer. Calcium chloride was used as drying agent. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(9) E. H. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds," Order I, John Wiley & Sons, Inc., New York, N. Y., 1941, pp 354–397.

(10) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, John Wiley & Sons, Inc., New York, N. Y., 1966, p 176.

over a period of 5 min a solution of 5.22 g (0.022 mol) of acetone 2,4-dinitrophenylhydrazone in 60 ml of chloroform. The resulting orange mixture was stirred and heated under reflux for an additional 30 min prior to being cooled and poured into water. The suspension was filtered by suction and the chloroform solution was separated from the filtrate. The aqueous phase was extracted with a 100-ml portion of chloroform and the combined chloroform extracts were washed once with 5% sodium bicarbonate and then twice with water. The dried extract was concentrated under reduced pressure to yield an orange oil which was chromatographed on a column (25 × 2.5 cm diameter) of silica gel. Elution with 4:1 hexane–benzene gave an orange solid which, on recrystallization from methanol, afforded 0.88 g (16%) of azo fluoride **1**, having the properties recorded in Tables I and II.

B. 2-Acetoxy-2-(2,4-dinitrophenylazo)propane (1a).—Continued elution with pure benzene of the column from which azo fluoride **1** was obtained, as described above, gave a yellow solid which, on recrystallization from methanol, afforded 3.48 g (53%) of azo acetate **1a**, displaying strong peaks in the ir (CCl_4) at 1745, 1600, 1365, 1345, 1245, 1190, and 1155 cm^{-1}. Additional data are given in Tables I and II. A mixture melting point determination and ir spectral comparison showed **1a** to be identical with an authentic specimen.[3]

Reaction of Lead(IV) Diacetate Difluoride with 2-Butanone Phenylhydrazone. Formation of 2-Fluoro-2-phenylazobutane (3) and 2-Acetoxy-2-phenylazobutane (3a).—In a 300-ml, heavy-walled polyethylene jar sealed with a cap holding a drying tube filled with calcium chloride, a stainless steel dial thermometer, and an addition tube of polyethylene connected to a dropping funnel were placed 26.04 g (0.072 mol) of lead(IV) diacetate difluoride and 50 ml of chloroform. After the magnetically stirred suspension had been cooled to 0° in an ice bath, a solution of 11.60 g (0.072 mol) of 2-butanone phenylhydrazone in 15 ml of chloroform was added over a period of 30 min in order to maintain the temperature as close as possible to 0°. The mixture was stirred in the ice bath for an additional 30 min and the resulting amber suspension was then poured into water. The white solid was removed by suction filtration and the chloroform layer was separated from the filtrate. The aqueous layer was extracted with a 100-ml portion of chloroform and the combined chloroform extracts were washed once with 5% sodium bicarbonate and then twice with water. The dried extract was concentrated under reduced pressure to give a red oil which, on distillation under reduced pressure through a semimicro column, gave two main fractions.

Fraction 1, a yellow oil, was identified as azo fluoride **3**, yield 2.23 g (17%), bp 65–66° (1.25 mm). Some additional properties are indicated in Tables I and II.

Fraction 2, an orange oil, was identified as azo acetate **3a**, yield 6.70 g (42%), bp 102–103° (1.25 mm), $n^{28}D$ 1.5142 (lit.[3] $n^{25}D$ 1.5141). Its ir spectrum (neat) was indistinguishable from that of an authentic sample.[3]

Reaction of 2-Acetoxy-2-(2,4-dinitrophenylazo)propane (1a) with Hydrogen Fluoride. Formation of 2-Fluoro-2-(2,4-dinitrophenylazo)propane (1).—To 0.50 g (1.69 mmol) of azo acetate **1a** in a polyethylene test tube cooled in a Dry Ice–acetone bath was added 1.0 ml of liquid hydrogen fluoride. The brown suspension was stirred with a nickel spatula for 2 min and then a large excess of potassium fluoride was added. The reaction vessel was removed from the cooling bath and after standing at room temperature for 15 min the mixture was eluted with ether. The ether extract was washed once with 5% sodium bicarbonate and then twice with water. Evaporation at reduced pressure of the dried ether solution gave an orange oil which was chromatographed on a column (20 × 1.2 cm diameter) of silica gel with 6:1 benzene–hexane as eluent. An orange solid was thus obtained which was recrystallized from methanol to give 0.26 g (60%) of azo fluoride **1**, mp 51–52°. Compound **1** was shown by mixture melting point determination and ir spectral comparison to be identical with an authentic sample prepared above by reaction of lead(IV) diacetate difluoride with acetone 2,4-dinitrophenylhydrazone.

1-Fluoro-1-(2,4-dinitrophenylazo)cyclohexane (4).—Treatment of 0.50 g (1.49 mmol) of 1-acetoxy-1-(2,4-dinitrophenylazo)cyclohexane (**4a**) with liquid hydrogen fluoride for 5 min by the procedure used above to convert azo acetate **1a** into azo fluoride **1** afforded an orange solid which was recrystallized from methanol, yield 0.29 g (66%), mp 79–80°. It was identical in all respects with a sample of **4** prepared by fluorination of cyclohexanone 2,4-dinitrophenylhydrazone with lead(IV) diacetate difluoride (Table I).

Registry No.—Lead(IV) diacetate difluoride, 20706-24-5; **1**, 23386-00-7; **1a**, 23386-01-8; **2**, 23386-02-9; **2a**, 23386-03-0; **3**, 23383-04-1; **3a**, 23386-05-2; **4**, 23386-06-3; **4a**, 23386-07-4; **5**, 23386-08-5; **5a**, 14803-32-8.

Selective Electrochemical Reduction of Polyfunctional Molecules

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It has been recognized for a number of years that controlled-potential electrolysis, employing as it does constant electrode potential in order to discriminate between two or more electrode processes,[1] provides a considerably more selective method of effecting electrochemical reaction than does the method of constant-current electrolysis used in the older literature.[2] Controlled-potential electrolysis is in fact now widely used both in coulometric analysis of mixtures of reducible species[3] and in preparative-scale electrochemical synthesis. In most cases the latter application involves preparation of an electrolysis product in sufficient quantities for characterization by the usual chemical and spectroscopic methods, in order to test or confirm an electrode mechanism proposed, *e.g.*, from voltammetric data.[4] Despite the common use of controlled-potential electrolysis for the latter purpose, there are surprisingly few reports of its use for the specific purpose of carrying out oxidations or reductions not possible by the usual chemical means. This is unfortunate, for even a cursory examination of the organic polarographic literature[5] will reveal the possibility of many selective electrochemical reductions which would be either impossible or very difficult using the conventional reducing agents of organic chemistry. The principal criterion for the successful application of the electrochemical method is simply that, when a molecule contains two or more reducible functions, the electrode process of interest must be easier than any others by at least 0.2 V; if so, electrolysis at a potential corresponding to the first process will permit clean conversion into the product of this reduction process and no other.[6] The first instance (and still one of the best examples) where this principle was taken advantage of for explicitly synthetic purposes was reported by Lingane, Swain, and Fields.[7]

(1) J. J. Lingane, "Electroanalytical Chemistry," 2nd ed, Interscience Publishers, Inc., New York, N. Y., 1958.

(2) S. Swann, Jr., in "Technique of Organic Chemistry," Vol. 2, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1956, p 385.

(3) G. W. C. Milner and G. Phillips, "Coulometry in Analytical Chemistry," Pergamon Press, London, 1967.

(4) L. Meites, "Polarographic Techniques," 2nd ed, Interscience Publishers, Inc., New York, N. Y., 1965, Chapter 10.

(5) (a) D. J. Pietrzyk, *Anal. Chem.*, **40**, 194R (1968); **38**, 278R (1966). (b) P. Zuman, "Organic Polarographic Analysis," Pergamon Press, London, 1964.

(6) L. Meites in "Technique of Organic Chemistry," 3rd ed, Vol. 1, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., p 3281 ff.

(7) J. J. Lingane, C. G. Swain, and M. Fields, *J. Amer. Chem. Soc.*, **65**, 1348 (1943).

TABLE I[a]

HALF-WAVE POTENTIALS FOR REPRESENTATIVE ORGANIC COMPOUNDS[b]

Compd	$-E_{1/2}$, V
RC≡CR, $R_2C{=}CR_2$, RCN, RCO_2R, RCl (R = alkyl)	>2.6[c]
Acetone	2.46
Acetophenone	2.42
Bromobenzene	2.32
Ethyl bromide	2.27
Benzonitrile	2.26
Ethyl benzoate	2.14
Benzyl chloride	1.94
Ethyl iodide	1.67
Iodobenzene	1.62
Benzyl bromide	~1.3

[a] M. V. Stackelberg and W. Stracke, *Z. Elektrochim.*, **53**, 118 (1959). [b] Half-wave potentials are reported relative to the saturated calomel electrode; the solvent was 75% dioxane containing tetraethylammonium bromide as supporting electrolyte. [c] Material not reduced before the solvent decomposition potential (−2.6 V) is reached.

the potential at which a given solvent–electrolyte system is itself reduced places a natural limit upon the range of reductions which may be effected in that solvent. Unconjugated olefins, acetylenes, alkyl chlorides nitriles, and esters, for example, are not normally electrochemically reducible in most solvents, and ketones are only difficultly reducible. On the other hand, alkyl *and aryl* bromine and iodine are all easily reduced electrochemically under conditions where the preceding groups are stable against reduction. This order of ease of reduction, which differs in a number of respects from that observed with typical organic reducing agents such as complex metal hydrides, dissolving metals, catalytic hydrogenation, etc.,[8] may be put to good synthetic advantage. We have utilized the order of ease of reductions implied by Table I to effect in high yield a number of selective reductions, any one of which would have been difficult or impossible by other methods (Table II). No attempt was made to compile an exhaustive list of selective reductions, since, while many other interesting conversions are clearly implied in the data of Table I, further applications would be straightforward.

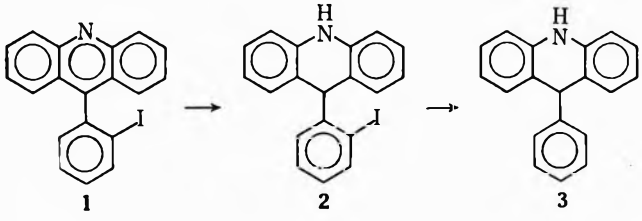
TABLE II

SELECTIVE ELECTROCHEMICAL REDUCTIONS[a]

Starting material[b]	Product	Yield, %[c]
p-Bromo-2-chloroethylbenzene	2-Chloroethylbenzene	99
m-Bromoacetophenone	Acetophenone	94
p-Bromoiodobenzene	Bromobenzene	98 (94)[d]
p-Bromo-γ-chlorobutyrophenone	γ-Chlorobutyrophenone	96

[a] Electrochemical reductions were carried out at 25° in dimethylformamide containing 0.1 *M* tetraethylammonium bromide. [b] Starting materials were purified by preparative vpc before use. [c] Yields were determined by direct gas chromatographic analysis of electrolysis mixtures. [d] Yield in parentheses is that for a preparative-scale electrolysis.

It was desired to convert 9-(*o*-iodophenyl)acridine (**1**) into the corresponding acridane **2**, but every chemical reducing agent tried effected simultaneous hydrogenolysis of the iodine atom to afford not **2**, but **3**.

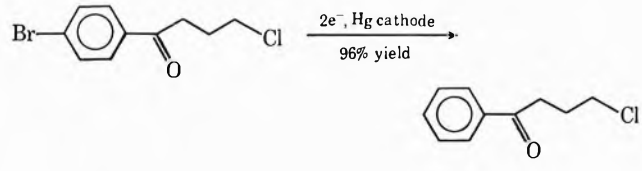


1 **2** **3**

Acridine **1** has, however, two polarographic waves in alkaline ethanol; the first, at −1.32 V *vs.* sce, corresponds to the desired reduction to **2**, and the second, at −1.62 V, corresponds to conversion into **3**. The two electrode processes are resolved sufficiently (0.3 V) to permit application of the electrochemical method. Electrolysis at −1.37 V readily afforded **2** in 90% (isolated) yield, and, furthermore, reduction of **2** at −1.70 V afforded **3** in 95% yield. Acridine **1** could thus be converted into either **2** or **3** by appropriate choice of cathode potential.

Polarographic half-wave potential data are available for thousands of compounds, primarily from the analytical literature.[5] An abbreviated list, adequate for suggesting many useful synthetic applications of controlled-potential electrolysis, is given in Table I. Compounds are listed in increasing ease of reducibility as one proceeds down the table. It should be pointed out that

The selective reduction of *p*-bromo-γ-chlorobutyrophenone, containing three potentially reducible functions, is a particularly striking demonstration of the utility of the electrochemical method.[9]



It should be noted that the electrochemical reduction of alkyl halides does *not* suffer, as has been suggested,[10] from the disadvantage that there are involved strongly basic conditions which preclude the use of base-sensitive reactants or products. Carbanions are indeed generated during the electrolysis of alkyl halides, but they are rapidly deactivated *via* Hoffmann dealkylation of the tetraalkylammonium salts used as supporting electrolyte; consequently, a much less basic tertiary amine is generated. In this connection, it is interesting to

(8) (a) R. L. Augustine, "Reduction," M. Dekker, Inc., New York, N. Y., 1968; (b) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965.

(9) Although bromobenzene and acetophenone differ in reduction potential by less than the above stated requisite of 0.2 V, a smaller difference can be tolerated when the first reduction is irreversible, as it is for alkyl halides.

(10) G. L. Grady and H. Kuivila, *J. Org. Chem.*, **34**, 2014 (1969).

note that *p*-bromoacetophenone is converted into acetophenone in only 13% yield using tri-*n*-butyltin hydride,[10] while *m*-bromoacetophenone is converted into acetophenone in 94% yield electrochemically, without appreciable base-catalyzed aldolization. The electrochemical method is, however, more difficult to scale up for large-scale preparations. For the occasional highly base-sensitive system, one may, furthermore, take advantage of the pH independence of the electrochemical reduction of alkyl halides[11] by purposely adding an acid (phenol or even mineral acid[12]) to the mixture to protonate the carbanion as formed.

Experimental Section

Apparatus and Chemicals.—Dimethylformamide was refluxed over calcium hydride [70° (0.1 mm)] for 1 hr, followed by distillation *in vacuo* through a 10 × 300 mm glass helix packed column. Tetraethylammonium bromide was recrystallized from an ethanol ether mixture and dried *in vacuo*. Controlled-potential electrolyses were carried out with the aid of a potentiostat based upon a Kepco KS-120-2.5 programmable power supply.[13]

Electrolyses.—A modified polarographic H cell was used for small-scale electrolyses; the dme was replaced by a mercury pool, for which electrical contact was maintained *via* a platinum contact piercing the cell wall. A mechanical stirrer and Cd(Hg)–$CdCl_2$ reference[14] (isolated by a methyl cellulose plug[15]) were positioned close to the mercury surface. One side of the cell contained the catholyte [5 ml of a solution of the organic substrate (10^{-2} *M*) and Et_4NBr (10^{-1} *M*) in DMF, and the other side of the cell contained a silver anode in a solution of 10^{-1} *M* Et_4NBr in DMF. A methyl cellulose plug[15] separated the two sides of the cell. Electrochemical reductions were carried out upon samples freshly purified by preparative glpc. After electrolysis, the contents of the cell were analyzed directly by vpc (Varian Aerograph Model 1740). Preparative electrolysis of *p*-iodobromobenzene was carried out in 90% ethanol containing 0.1 *M* tetraethylammonium bromide in a large crystallizing dish containing a platinum anode, mercury pool cathode, Cd(Hg)–$CdCl_2$ reference electrode, and mechanical stirrer. Hydrazine hydrate was added as the anodic depolarizer; its oxidation to nitrogen at the anode also generates protons to prevent the solution from becoming basic. From 28.3 g (0.1 mol) of *p*-iodobromobenzene was isolated, after dilution with water, extraction with pentane, and distillation of the solvent, 14.7 g (94%) of bromobenzene, homogeneous by vpc.

***p*-Bromo-2-chloroethylbenzene.**—*p*-Bromo-2-phenylethanol[16] was prepared through lithium aluminum hydride reduction of *p*-bromophenylacetic acid. A solution of 20.0 g each of the alcohol and thionyl chloride was refluxed overnight. Thionyl chloride was then removed with warming at the rotary evaporator. Distillation afforded *p*-bromo-2-chloroethylbenzene: yield 15 g (65%); bp 70° (0.15 mm); nmr (CCl_4) τ 2.73 and 3.07 (AB pattern, J = 8.5 Hz, area 4), 6.50 (t, J = 6.5 Hz, area 2), and 7.07 (t, J = 6.5 Hz, area 2).

Anal. Calcd for C_8H_8ClBr: C, 43.88; H, 3.62. Found: C, 43.61; H, 3.51.

Registry No.—*p*-Bromo-2-chloroethylbenzene, 23386-17-6.

Acknowledgment.—Financial support was provided by the National Science Foundation and the Petroleum Research Fund of the American Chemical Society.

(11) See footnote *a*, Table I.
(12) A. J. Fry and R. H. Moore, *J. Org. Chem.*, **33**, 1283 (1968).
(13) P. Birman, "Power Supply Handbook," Kepco Inc., Flushing, N. Y., 1965, p 129.
(14) L. W. Marple, *Anal. Chem.*, **39**, 844 (1967). This electrode is *ca.* −0.9 V relative to sce.
(15) G. Dryhurst and P. J. Elving, *ibid.*, **39**, 607 (1967).
(16) D. Sontag, *Ann. Chim.* (Paris), **1** (11), 359 (1934).

Base-Catalyzed Reactions of α-Cyano-β-furylacrylic Esters

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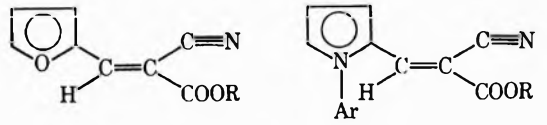
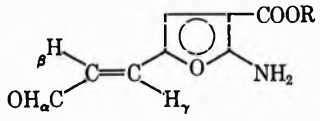
Received September 4, 1969

The ring-opening reactions of the furan derivatives with ammonia and amines have been extensively investigated by a number of authors.[2] Leditschke[3] reported that the reaction of α-cyano-β-furylacrylic esters (**1**) with primary arylamines afforded α-cyano-1-aryl-2-pyrroleacrylic esters (**2**). However, we have found that **1**, when treated with morpholine instead of the primary arylamines, gives rise to an unexpected colored product. We have shown this product to have the structure γ-(4-alkoxycarbonyl-5-aminofuryl)-acrolein (**3**).



1 **2**



3a, R = C_2H_5
b, R = $PhCH_2$

The product **3a** obtained from ethyl α-cyano-β-furylacrylate (**1**, R = C_2H_5) and morpholine, was recrystallized from chloroform as yellowish green needles, mp 174–175°, having a molecular ion peak at *m/e* 209, and a molecular formula of $C_{10}H_{11}NO_4$. When treated with 2,4-dinitrophenylhydrazine and semicarbazide, **3a** gave the corresponding hydrazone **4** and semicarbazone **5**, respectively, and when treated with fuchsin reagents, showed a positive test for aldehyde. All attempts to acetylate **3a** were unsuccessful, and catalytic hydrogenation led to a colorless polymer.

The ir spectrum of **3a** ($CHCl_3$) revealed the disappearance of the cyano group. The NH_2 and ester C=O stretching frequencies appeared at 3508 and 3382 and at 1672 cm^{-1}, respectively, comparable with those of ethyl 5,7-dimethyl-2-amino-3-benzofuroate (3480 and 3346, and 1679 cm^{-1}).[4] The aldehydic CH stretching bands are clearly observed at 2818 and 2730 cm^{-1}.

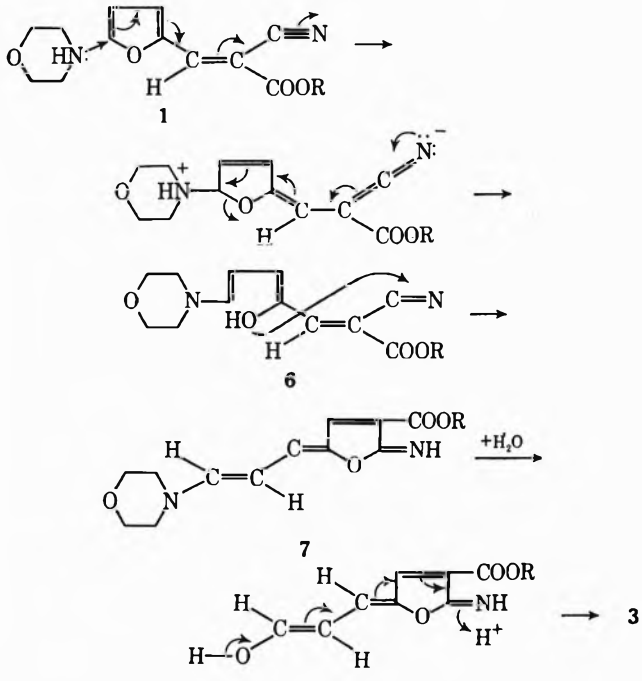
The nmr spectrum (deuterated DMSO) showed that morpholine used in the reaction is not entering into the reaction product. The presence of the CH=CHCHO system is supported by the fact that the two olefinic protons and aldehydic proton constitute the three spin AMX pattern. A rather large coupling constant between the two olefinic protons suggests the *trans* configuration about the C=C bond. The mass spec-

(1) Chemical Laboratory, Department of Education, University of Utsunomiya, Japan.
(2) P. Bosshard and C. H. Eugster, *Advan. Heterocycl. Chem.*, **7**, 378 (1966).
(3) H. Leditschke, *Chem. Ber.*, **85**, 483 (1952).
(4) J. Derkosch and I. Specht, *Monatsh. Chem.*, **92**, 542 (1961).

trum showed a fragment ion peak at m/e 163, which is considered to be generated by loss of C_2H_5OH from the parent ion peak by McLafferty rearrangement.[5]

A plausible reaction mechanism is postulated in Scheme I. It seems reasonable to assume that initially the base may attack the 5-position of the furan ring in **3**. Cyclization of the intermediate **6** may occur between the OH and CN groups to give the intermediate **7**, which then yields, when treated with water, the product **3**. When the primary arylamines are used as a base in the reaction, the resulting intermediate **8** similar to **6** would cyclize between the OH and NH groups to give the product **2**.

SCHEME I



Experimental Section

Nmr spectra were obtained on a JNM-C-60 high-resolution nmr spectrometer at a temperature of 19–20°. Tetramethylsilane (δ, 0) was used as an internal reference standard. Ir spectra were determined in the chloroform solution using a Perkin-Elmer 521 spectrophotometer. Mass spectra were measured with JMS-01S instrument operating at 75 eV.

Reaction of Ethyl α-Cyano-β-furylacrylate(1a) with Morpholine.—A mixture of 10 g (0.052 mol) of the ester and 40 ml of morpholine was stirred at room temperature for 30 min. The reaction was exothermic, and the solution immediately turned orange, then reddish brown, and finally dark red. After being allowed to stand overnight, the viscous solution was poured into 1.0 l. of water under vigorous stirring. The resulting solid matrial was recrystallized from chloroform to give 5.9 g (54% yield) of **3a** as yellowish green needles: mp 174–175°; uv max ($CHCl_3$) 284 mμ (ϵ 5200), 374 (34,000); (99.5% EtOH) 228 (10,100), 284 (7200), 387 (36,500); ir ($CHCl_3$) 3508, 3382 (NH_2), 2818, 2730 (aldehyde CH), 1685 (aldehyde C=O), 1672 (ester C=O), 1636 (C=C), 1612, 1378, 1312, and 985 cm^{-1} (furan ring); nmr (d_6-DMSO) δ 1.27, 4.23 ($COOCH_2CH_3$), 6.06 (quartet, H_β, $J_{\beta\gamma}$ = 15.0 Hz, $J_{\alpha\beta}$ = 7.8 Hz, $J_{\alpha\gamma}$ = *ca.* 0), 7.30 (d, H_γ, $J_{\beta\gamma}$ = 15.0 Hz), 9.78 (d, H_α, $J_{\alpha\beta}$, = 7.8 Hz), 7.14 (s, furan ring H), 7.82 (broad, NH_2).

Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.42; H, 5.26; N, 6.70. Found: C, 57.49; H, 5.17; N, 6.77.

The 2,4-dinitrophenylhydrazone (**4**) occurred as dark brown needles (from pyridine–methanol), mp over 250°.

Anal. Calcd for $C_{16}H_{15}N_5O_7$: N, 17.99. Found: N, 18.05.

The semicarbazone 5 occurred as yellow needles (from methanol), mp 203–204°.

Anal. Calcd for $C_{11}H_{14}N_4O_4$: N, 21.05. Found: N, 20.98.

Reaction of Benzyl α-Cyano-β-furylacrylate (1b) with Morpholine.—The reaction procedure was the same as described above. Recrystallizations of solid **3b** from chloroform and from glyme–ethanol gave brown needles: mp 188–189°; uv max ($CHCl_3$) 287 mμ (ϵ 5,100), 375 (30,600); (99.5% v/v EtOH) 227 (9400), 285 (7000), 385 (33,200); ir ($CHCl_3$) 3495, 3380 (NH_2), 2800, 2720 (aldehyde CH), 1685 (aldehyde C=O), 1672 (ester C=O), 1630 (C=C), 1613, 1382, 1303 cm^{-1} (furan ring); nmr (d_6-DMSO) δ 5.23 (s, $COOCH_2Ph$), 6.04 (quartet, H_β, $J_{\beta\gamma}$ = 15.0 Hz, $J_{\alpha\beta}$ = 7.8 Hz), 7.20 (s, furan ring H), 7.30 (d, H_γ, $J_{\beta\gamma}$ = 15.0), 7.99 (broad, NH_2), 9.45 (d, H_α, $J_{\alpha\beta}$ = 7.8); mass spectrum (75 eV) m/e 271 (molecular ion peak).

Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.82; H, 4.74; N, 5.04.

Registry No.—**3a**, 23386-18-7; **3b**, 23386-19-8; **4**, 23386-20-1; **5**, 23386-21-2.

(5) G. Spiteller, *Monatsh. Chem.*, **92**, 1142 (1961).

Chromous Sulfate Reduction of 2-Methyl-3-hexyne-2,5-diol

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The reduction of nonterminal acetylenes by chromous sulfate[2] has been reported[3] to lead stereoselectively to *trans* olefins in high yields. Sterically hindered alkylacetylenes are found to react slowly or to be inert to chromous sulfate. Conversely, the presence of hydroxyl or carboxyl substituents near the acetylenic bond enhances reduction.

We have found that the reduction of 2-methyl-3-hexyne-2,5-diol with aqueous chromous sulfate, while proceeding readily at room temperature, does not produce the expected *trans*-2-methyl-3-hexene-2,5-diol. Rather the reaction leads to three isomeric reduction products (Scheme I) in which the hydroxyl group rather than the triple bond is reduced. The overall yield of products is 70%, the balance being recovered starting material.

The hydrogenolysis of a hydroxyl group under such mild conditions is unusual and seems to have been previously observed only in reductions with lithium aluminum hydride.[4,5]

The reduction products (**1**, **2**, and **3**) were isolated in pure form by preparative gas chromatography (glpc) (see Experimental Section).

(1) To whom all correspondence should be directed: Chemistry Department, Stanford University, Stanford, California 94305.

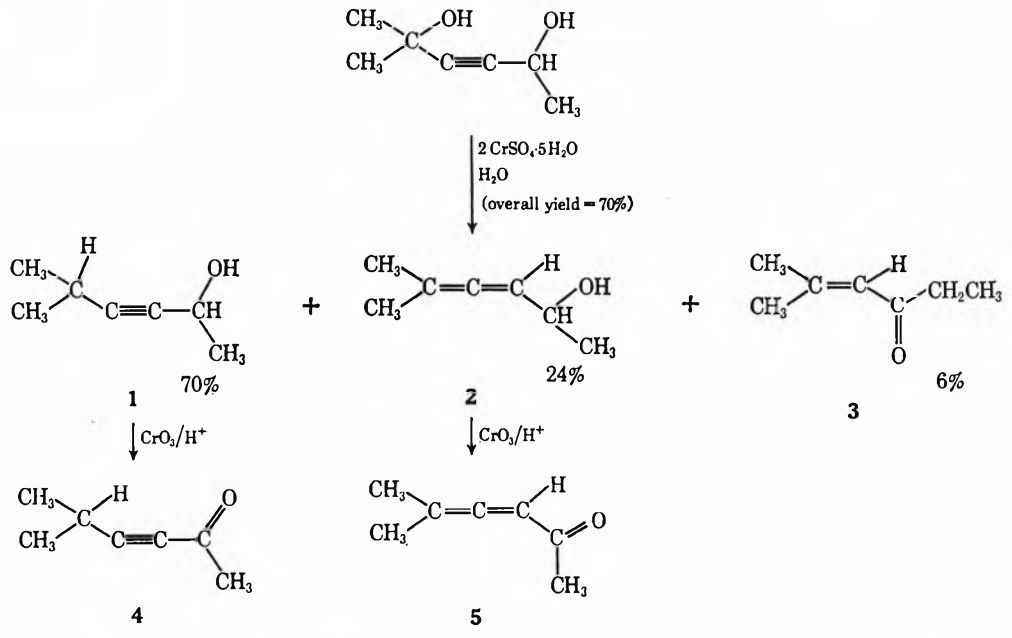
(2) For a review of the reactions of Cr(II), see J. R. Hanson and E. Premuzic, *Angew. Chem.*, **80**, 271(1968); *Angew. Chem., Int. Ed. Engl.*, **7**, 247 (1968).

(3) C. E. Castro and R. D. Stephens, *J. Amer. Chem. Soc.*, **86**, 4358-(1964).

(4) W. Oroshnik, A. D. Mebane, and G. Karmas, *ibid.*, **75**, 1050 (1953).

(5) J. Meinwald and L. Hendry, *Tetrahedron Lett.*, 1657 (1969).

SCHEME I



The previously known 5-methyl-3-hexyn-2-ol (**1**)[6] was identified by inspection of its ir and nmr spectra. The structural assignment was confirmed by Jones oxidation[7] of the alcohol to the corresponding ketone **4**,[6] identified as the 2,4-dinitrophenylhydrazone whose physical properties agreed with those reported.[6]

2-Methyl-2,3-hexadien-5-ol (**2**) was characterized by its ir[8] and nmr spectra, and elemental analysis. The structural assignment was more firmly established by oxidation[7] of the alcohol to the corresponding ketone **5** whose ir and nmr spectra were as expected for an allenic ketone (see Experimental Section).

2-Methyl-2-hexen-4-one (**3**) was identified by comparison of its ir and nmr spectra with those of authentic material (Aldrich Chemical Co.); the two sets of spectra were superimposable.

Experimental Section

Nmr spectra were recorded on a Varian A-60A instrument; samples were 50 vol. % solutions in chloroform-*d* with internal TMS as a reference. Infrared spectra were recorded on a Perkin-Elmer Model 237B instrument. Elemental analyses were performed by Mr. N. H. Tashinian at the University of California, Berkeley, Calif. Product separation was effected on a Varian-aerograph model A-90-P3 gas chromatograph with a 5 ft × $^3/_8$ in. aluminum column (packed with 60–80 mesh Chromosorb G coated with 6% Carbowax 20M) using a helium flow rate of 40 ml/min and a temperature of 128°.

2-Methyl-3-hexyne-2,5-diol was prepared as previously described[9] in 60% yield: bp 120–123° (10 mm); n^{22}D 1.4669 [lit.[9] bp 89–90° (3 mm), n^{20}D 1.4651]; nmr ($CDCl_3$) δ 1.44 (d, 3, J = 6.5 Hz, CH_3), 1.51 [s, 6, $(CH_3)_2C$], and 4.56 ppm (q, 1, J = 6.5 Hz, $CH(OH)CH_3$).

Oxidation of a small amount of the diol with activated magnesium dioxide by the method of Attenburrow[10] yielded 52% 2-methyl-2-hydroxy-3-hexyn-5-one: bp 76–79° (0.7 mm); n^{25}D 1.4593 [lit.[11] bp 60° (0.8 mm), n^{20}D 1.4619]: nmr (CCl_4) δ 1.56 [s, 6, $(CH_3)_2CH(OH)$] and 2.32 ppm (s, 3, $COCH_3$).

Cr(II) Reduction of 2-Methyl-3-hexyne-2,5-diol.—To 9.8 g (0.077 mol) of 2-methyl-3-hexyne-2,5-diol in 25 ml of nitrogen-purged (1 hr) water was added 37 g (0.16 mol) chromous sulfate pentahydrate [prepared (and handled) in a nitrogen atmosphere, in 47% yield, according to the method of Lux and Illman[12]] in 375 ml of nitrogen-purged (1 hr) water. The mixture was stirred to obtain a homogeneous solution and was then allowed to stand at room temperature in a glass-stoppered flask for 22 days. [Glpc analysis (FFAP at 230°) of aliquots of the reaction mixture showed that most of the conversion of starting material to products occurs within 48 hr.] The mixture was then extracted six times with 100-ml portions of ether, saturated with ammonium sulfate, and extracted twice more with 100-ml portions of ether. The combined extracts were dried ($MgSO_4$); the solvent was removed using a rotary evaporator. There was obtained 8.5 g of a colorless liquid, from which three compounds (70% of the mixture) in the ratio of 70:24:6 were isolated by preparative glpc as previously described (the remaining 30% of the mixture was largely starting material according to its glpc retention time). Each compound separated was rechromatographed (one or two times) to obtain the pure product and to demonstrate that isomerization did not occur during chromatography. Product 1 (5-methyl-3-hexyn-2-ol): nmr ($CDCl_3$) δ 1.15 (d, 6, J = 6.5 Hz, CH_3), 1.40 (d, 3, J = 6.5 Hz CH_3), 2.56 [m, 1, J = 6.5 and 1.5 Hz, $CH(CH_3)_2$], 4.51 [m, 1, J = 6.5 and 1.5 Hz, $CH(OH)CH_3$], and 3.4 ppm (s, 1, position concentration dependent, OH).

Oxidation of 1.—To 350 mg (3.12 mmol) of 5-methyl-3-hexyn-2-ol in 1 ml of acetone (redistilled over potassium permanganate) was added 0.8 ml of standard Jones reagent[7] (solution of 26.7 g of chromium trioxide in 23 ml of concentrated sulfuric acid diluted with water to a volume of 100 ml) at 0° over 1 hr. The resulting mixture was extracted four times with 50-ml portions of ether; combined extracts were washed once with water and dried overnight ($MgSO_4$). Solvent removal yielded 200 mg (58%) 5-methyl-3-hexyn-2-one (**4**): nmr ($CDCl_3$) δ 1.22 [d, 6, J = 6.5 Hz, $CH(CH_3)_2$], 2.29 (s, 3, CH_3), and 2.74 ppm [m, 1, J = 6.5 Hz, $(CH_3)_2CH$]; 2,4-dinitrophenylhydrazone,[13] mp 110–111° (recrystallized from 95% ethanol) (lit.[6] 110–110.5°). Product **2** (2-methyl-2,3-hexadien-5-ol): nmr ($CDCl_3$) δ 1.25 [d, 3, J = 6.0 Hz, $CH(OH)CH_3$], 1.70 [d, 6, J = 3.0 Hz, $=C(CH_3)_2$],

(6) L. I. Smith and R. E. Kelly, *J. Amer. Chem. Soc.*, **74**, 3305 (1952).

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

(8) For the characteristic ir absorptions of 2-methyl-2,3-hexadien-5-ol (**2**), see M. Bertrand and R. Maurin, *C.R. Acad. Sci., Paris*, **260**, 6122 (1965).

(9) M. F. Shostakovskii, V. M. Vlasov, and A. A. Vasil' eva, *Izv. Akad. Nauk, SSSR, Ser. Khim.*, 696 (1964); Engl. transl., *Bull. Acad. Sci. USSR*, 644 (1964).

(10) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(11) B. P. Gusev and V. F Kucherov, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 1318 (1964).

(12) H. Lux and G. Illman, *Chem. Ber.* **91**, 2148 (1958).

(13) For the general method of derivative formation, see R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, John Wiley & Sons, Inc., New York, N. Y., 1956, p 219.

3.0 (s, 1, concentration dependent position, OH), 4.27 [m, 1, J = 6.0 and 6.0 Hz, $CH(OH)CH_3$], and 5.11 ppm (m, 1, J = 3.0 and 6.0 Hz, =CH); ir (CCl_4)[8] 3613 (OH), 3352 (OH), and 1969 cm^{-1} (C=C=C).

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 75.30; H, 11.02.

Oxidation of 2.—Oxidation of 198 mg (1.77 mmol) of **2** by the method described above yielded 80 mg (41%) of 2-methyl-2,3-hexadien-5-one (**5**): nmr ($CDCl_3$) δ 1.84 [d, 6, J = 3.0 Hz, $(CH_3)_2C=$], 2.18 (s, 3, $COCH_3$), and 5.60 ppm (m, 1, J = 3.0 Hz, $=CHCOCH_3$); ir ($CDCl_3$) 1957 (C=C=C) and 1676 cm^{-1} (=C—C=O). Product **3** (2-methyl-2-hexen-4-one): nmr ($CDCl_3$) 1.06 (t, 3, J = 7.0 Hz, CH_2CH_3), 1.88 (d, 3, J = 1.0 Hz, CH_3), 2.14 (d, 3, J = 1.0 Hz, CH_3), and 2.42 (q, 2, J = 7.0 Hz, CH_2CH_3), and 6.08 ppm (q, 1, J = 1.0 Hz, =CHCO). The ir spectrum was identical with that of a commercial sample.

Registry No.—Chromous sulfate pentahydrate, 13825-86-0; 2-methyl-3-hexyne-2,5-diol, 5111-43-3; **1**, 23293-50-7; **2**, 2425-47-0; **3**, 13905-10-7.

A New Route to the 2-Oxabicyclo[3.2.0]hept-6-ene Ring System

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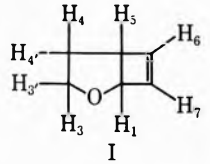
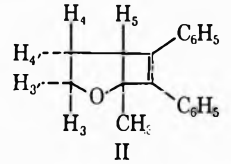
The valence-bond isomerizations of various substituted 1,3-heptadienes to the corresponding bicyclo[3.2.0]hept-6-enes is a well-documented reaction.[1,2] Paquette and coworkers[3] extended this reaction to compounds containing heteroatoms when they photolyzed 2,3-dihydrooxepin and recovered the valence isomer 2-oxabicyclo[3.2.0]hept-6-ene (I). Paquette utilized the parent compound and deuterated analogs to unravel a number of the many coupling constants present in the nmr spectra of the molecule, to which unusual interest had been attached. However, because of the long-range couplings present in the cyclobutene ring, the hydrogen-labeled H_5 was reported merely as a complex multiplet.

In order to elucidate the coupling constants of H_5 with H_4 and $H_{4'}$ and at the same time attempt to extend to the bicyclo[3.2.0]hept-6-ene system the reaction reported earlier, whereby an acetylene was photocycloadded to a cyclic vinyl ether,[4] a solution of diphenylacetylene in 2-methyl-4,5-dihydrofuran was photolyzed at 2537 Å. At the end of 24 hr, only one product and no diphenylacetylene could be detected by glpc. The product isolated by column chromatography was identified as 1-methyl-6,7-diphenyl-2-oxabicyclo[3.2.0]hept-6-ene (II) based on spectral evidence presented in the Experimental Section.



I



II

Because of the substitution pattern on II, all the cyclobutene couplings with H_5 are eliminated, and H_5 can couple its spin only with H_4 and $H_{1'}$. The nmr spectra for II was correspondingly simplified and showed H_5 to be a pair of doublets with J = 3.5 and 4.0 Hz. This would imply that the dihedral angles between the planes containing the hydrogen H_4 and H_5 and $H_{4'}$ and H_5 are nearly equal and not 90°.[5] In the 2-oxabicyclo[4.2.0]oct-7-ene system III the coupling constant for H_6–H_5 was found to be 0 Hz; this was attributed to a 90° dihedral angle between H_6–C_6 and H_5–C_5.

Sensitization and quenching experiments were performed in order to gain information regarding the reactive excited species involved in the reaction between 2-methyl-4,5-dihydrofuran and diphenylacetylene. It was found that pyrene [E_T = 48.7 kcal/mol[6]] inhibited the reaction between diphenylacetylene (E_T = 51 kcal/mol)[7] and 2-methyl-4,5-dihydrofuran. Equimolar concentration of diphenylacetylene and quencher were used. Since their molar extinction coefficients are about equal at the excitation wavelength (log ϵ 4.1 at 2437 Å), the quenching effect was due to triplet energy transfer rather than absorption of the exciting light by pyrene. However, the use of triphenylene (E_T = 66.6 kcal/mol)[6] as a sensitizer for the reaction run on a degassed sample in a Pyrex vessel at 3500 Å proved successful. The unsensitized reaction does not occur upon photolysis at this wavelength. Therefore, we conclude that the reaction proceeds through the first excited triplet state of diphenylacetylene.[8]

Finally, we would like to point out that this is only the second reported example of cyclobutene formation from the photocycloaddition of an acetylene to an olefin which is not part of an α,β-unsaturated carbonyl system, and the first example of this type of photocycloaddition in the bicyclo[3.2.0]hept-6-ene system.

Experimental Section

Melting points are uncorrected. Photolyses were conducted in a Rayonet photochemical reactor at 2537 or 3500 Å as indicated. The infrared spectra were obtained on a Perkin-Elmer Model 621 spectrophotometer. High resolution mass spectra were obtained on a CEC-21-110 instrument. Glpc were performed on a Varian Aerograph Model 1200 HYFI. Nmr spectra were taken on a Varian DP-60-IL instrument.

Reaction of Diphenylacetylene with 2-Methyl-4,5-dihydrofuran.—In a quartz vessel, a solution of diphenylacetylene (4 g, 0.022 mol) in 2-methyl-3,4-dihydrofuran (25 g, 0.3 mol) was irradiated at 2537 Å in a Rayonet photochemical reactor for 48 hr. After removal of the unreacted dihydrofuran under reduced pressure, the remaining liquid was subjected to column chromatography on alumina (80–200 mesh). Elution with petroleum ether (bp 30–60°) gave 1-methyl-6,7-diphenyl-2-oxabicyclo[3.2.0]hep-6-ene: 4.8 g, 82%; mp 52–54; parent peak 260.1487 ($C_{19}H_{18}O$); ir (thin film) 3035 (aromatic CH), 2920 (aliphatic CH), 1600, 1500 (aromatic C=C), 1090 (COC), and 745, 690 cm^{-1} (monosubstituted phenyl); nmr (C_6D_6) δ^{TMS} 7.5–7 (10 H, multiplet, aromatic CH), 3.9 (2 H, multiplet H_2, H_3), 3.15 (1 H, 2 doublets J = 3.5, 4.0 Hz), 1.6 (3 H, singlet, CH_3), 1.45 (2 H multiplet, H_4 and $H_{4'}$).

Registry No.—II, 23385-99-1; diphenylacetylene, 501-65-5; 2-methyl-4,5-dihydrofuran, 1487-15-6.

(1) O. L. Chapman, D. J. Pasto, G. W. Borden, and A. A. Griswold, *J. Amer. Chem. Soc.*, **84**, 1220 (1962).

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20,23-Dihydroxyspirostans[1]

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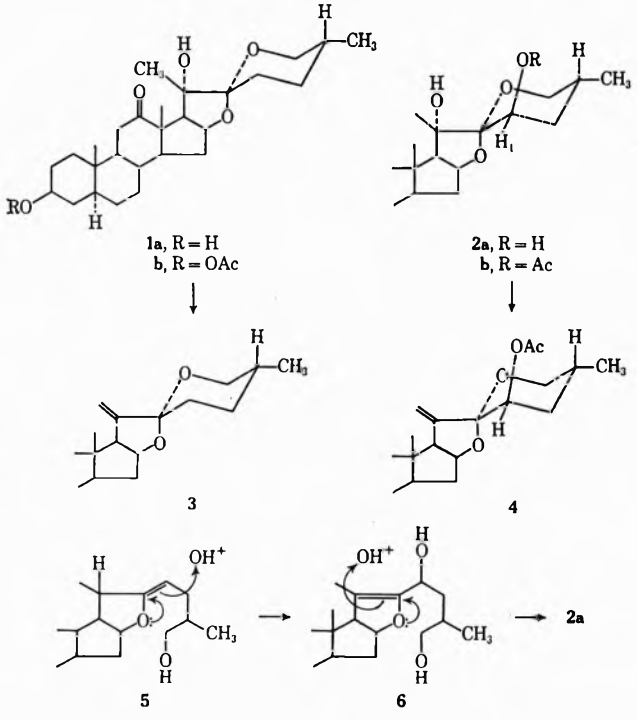
Received April 22, 1969

Chromic acid oxidation of 20-cyclopseudotigogenin[2] and pseudohecogenin[3,4] yields 20-hydroxyspirostans. This product is also produced by treatment of pseudosapogenins with peracids.[4,5]

During the preparation of 20-dehydrohecogenin acetate (**3**), we examined the oxidation of pseudohecogenin with *m*-chloroperbenzoic acid. Since the peracid product is difficult to purify as the diol **1a** and exhibits wide melting ranges,[4,6] the oxidation mixture was acetylated



and the C_3 acetate was removed by crystallization. Thin layer chromatographic analysis of the mother liquor then revealed the presence of a more polar material, **2b**. Careful chromatography on silica gel yielded **2b**, mp 288–289°, $[\alpha]D$ −21°, with an empirical composition in agreement with a hecogenin acetate derivative containing additional hydroxyl and acetoxyl substituents. This finding was substantiated by the ir hydroxyl band at 3510 cm^{-1} and the nmr signals for the acetate methyls at τ 7.92 and 8.02. The tertiary character of the hydroxyl group was indicated by its inability to be acetylated in pyridine with acetic anhydride, and its location at C_{20} was inferred by the appearance of the C_{21}-methyl signal in the nmr as a singlet at τ 8.67.

The polar material **2b** dehydrates to afford a 20-dehydrohecogenin acetate derivative **4** under conditions identical with those employed for the dehydration of **1b**.[2] The dehydrated material **4** retains the extra acetoxyl substituent.

The formation of an acetate and the appearance of a proton signal (H_1) at τ 5.23 in **2b** as a symmetrical triplet (J = 2.2 Hz) confirms the introduction of a secondary acetoxyl group into 20-hydroxyhecogenin acetate. The coupling constant is characteristic of diequatorial or equatorial–axial coupling, whereas diaxial coupling is 6–10 Hz.[7] The configuration of H_1 is therefore equatorial, to be consistent with the magnitude of the observed coupling of 2.2 Hz.

Based on the hydrogen-bonding interaction of the C_{20} hydroxyl with the C_{22} oxygen of sapogenins, Wall and Walens[5] have assigned C_{20} and C_{22} stereochemistry. Examination of the hydroxyl bands of **1b** and **2b** in carbon disulfide solutions showed intramolecular hydrogen bonding at 3510 cm^{-1}, indicating the *cis* C_{20}-hydroxyl and C_{22}-oxygen relationship. Support for the C_{22} (*R*) configuration is the observed negative rotation of **2b**, which is in accord with values previously found.[8] Thus the combined chemical and spectroscopic data are compatible with structure **2b**.

The reaction of 20-hydroxyhecogenin with *m*-chlorobenzoic acid and *m*-chloroperbenzoic acid was examined to establish whether **2a** comes from this route. This reaction yielded unidentified, more polar materials but did not give **2a**.

The probable mode of formation of **2a** therefore appears to be *via* the attack of peracid on a Δ^{22}-furostene intermediate **5** formed initially to yield a 23-hydroxy derivative, **6**. Further reaction of the $\Delta^{20(22)}$-furostene **6** with peracid leads to **2a**. The formation of variable quantities of Δ^{22}-furostene derivatives, along with the more usual $\Delta^{20(22)}$-furostenes from the sapogenin ring F opening reactions, has been previously noted.[9]

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer Infracord in Nujol and on a Beckman IR-4 in carbon disulfide solutions (0.0025 *M*). Nmr spectra were obtained on a Varian A-60A instrument using deuteriochloroform as a solvent and tetramethylsilane as an internal standard. Optical rotations were measured in 0.2–0.5% chloroform solutions at 23°. All extracts were dried over anhydrous sodium sulfate and evaporated at reduced pressure.

***m*-Chloroperbenzoic Acid Oxidation of Pseudohecogenin.**—To a solution of 10 g of pseudohecogenin in 1.8 l. of methylene chloride at 0° was added 9.7 g of *m*-chloroperbenzoic acid (80%). The solution was allowed to warm to room temperature and then stored in the dark. After 7 days, the solution was washed with sodium bisulfite and water and evaporated to yield a residue of 12.1 g. To 10 g of the residue in 10 ml of pyridine was added 10 ml of acetic anhydride. After 18 hr, water was added; the product was extracted with ether and washed with sodium bicarbonate and water. The residue was recrystallized from methanol to give 6.12 g of **1b**: mp 261–262°; $[\alpha]D$ −11°; ir ν_{max} 3510 cm^{-1} (OH) (lit.[4] mp 254–259°; $[\alpha]D$ −9°). The mother

(1) Acknowledgment is made for support of this work by Public Health Service Research Grant AI-07397 from the National Institute of Allergy and Infectious Diseases.

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liquor was chromatographed on 300 g of silica gel. Nonpolar material was eluted with 50% benzene–ether to give 1.04 g of **1b**, followed by mixed fractions and, finally, 2.68 g of 3β-(23*R*)-diacetoxy-(20*S*)-hydroxy-(22*R*,25*R*)-5α-spirostan-12-one (**2b**), eluted with 20% chloroform–ether. An analytical sample was recrystallized from methanol: mp 288–289°; $[\alpha]_D$ −21°; ir ν_{max} 3510 cm^{-1} (OH), λ_{max} 2.86 (OH), 5.77, 8.10 ($OCOCH_3$), 5.85 (C=O), spiroketal bands, 10.78 (s), 10.99 (s), 11.10 (w), and 11.41 μ (w); nmr τ 9.22 (d, *J* = 6 Hz, CH_3-27), 9.10 (CH_3-19), 8.80 (CH_3-18), 8.67 (CH_3-21), 8.02 ($OCOCH_3$-3), 7.92 ($OCOH_3$-23), and 5.08 (t, *J* = 2.2 Hz, H-23).

Anal. Calcd for $C_{31}H_{46}O_8$: C, 68.11; H, 8.48. Found: C, 68.49; H, 8.43.

3β-(23*R*)-Diacetoxy-(22*R*,25*R*)-5α-spirost-20(21)-en-12-one (4).—To a solution of 0.5 g of **2b** in 20 ml of pyridine at 0° was added 2.5 ml of thionyl chloride, dropwise with stirring. The mixture was allowed to stand at room temperature for 2 hr, poured over ice, extracted with ether, and washed with sodium bicarbonate and water. The residue was recrystallized from methanol to give 0.45 g of **4**: mp 281–283°; $[\alpha]_D$ −1.0°; ir λ_{max} 5.77, 8.10 ($OCOCH_3$), 5.85 (C=O), spiroketal bands, 10.81 (w), 10.91 (s), 11.02 (s), 11.14 (m), and 11.49 μ (m); nmr τ 9.20 (d, *J* = 6 Hz, CH_3-27), 9.09 (CH_3-19), 8.89 (CH_3-18), 8.01, ($OCOCH_3$-3), 7.92, ($OCOCH_3$-23), 5.08 (t, *J* = 2.2 Hz, H-23), and 4.58 (m, =CH_2-21).

Anal. Calcd for $C_{31}H_{44}O_7$: C, 70.43; H, 8.39. Found: C, 70.86; H, 8.58.

3β-Acetoxy-(22*R*,25*R*)-5α-spirost-20(21)-en-12-one (3).—The same procedure as the preparation of **4** was followed, using 0.5 g of **1b**, 20 ml of pyridine, and 2.5 ml of thionyl chloride. The residue was recrystallized from methanol to give 0.23 g of **3**: mp 229–232°; $[\alpha]_D$ +19°; ir λ_{max} 5.77, 8.10 ($OCOCH_3$), 5.85 (C=O), spiroketal bands, 10.22 (s), 10.95 (m), 10.87 (m), 11.04 (s) and 11.55 μ (m); nmr τ 9.20 (d, *J* = 6 Hz, CH_3-27), 9.09 (CH_3-19), 9.04 (CH_3-18), 8.00 ($OCOCH_3$-3), and 5.76 (m, =CH_2-21).

Anal. Calcd for $C_{29}H_{42}O_5$: C, 74.01; H, 8.99. Found: C, 73.79; H, 8.77.

Treatment of 3β-Acetoxy-(20*S*)-hydroxy-(22*R*,25*R*)-5α-spirostan-12-one with Peracid.—A solution of 0.4 g of **1a**, 0.4 g of *m*-chloroperbenzoic acid, and 0.4 g of *m*-chlorobenzoic acid in 50 ml of methylene chloride was stirred at room temperature, in the dark, for 5 days. The reaction was quenched by washing with a saturated sodium bisulfite solution, saturated sodium bicarbonate, and water. The residue (0.43 g) was acetylated in 2 ml of acetic anhydride and 10 ml of pyridine. The resulting acetate was recrystallized from methanol to afford 0.18 g of **1b**. The mother liquor was chromatographed on 15 g of silica gel. Upon elution with benzene–40% ether, 0.02 g of **1b** was obtained. Then 0.07 g of a mixed fraction was obtained, followed by 0.05 g of an unknown substance eluted with 20% chloroform–ether.

Registry No.—**2b,** 23405-42-7; **3,** 23405-43-8; **4,** 23405-44-9.

Thermal Decomposition of β-Hydroxy Esters. Ethyl-3-hydroxy-3-methylbutanoate

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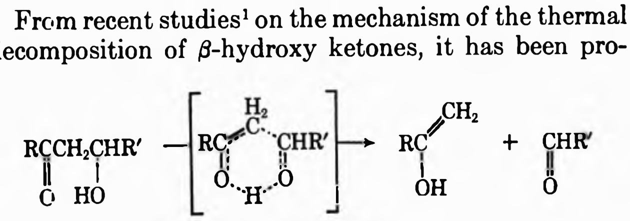
Received September 3, 1969

From recent studies[1] on the mechanism of the thermal decomposition of β-hydroxy ketones, it has been proposed that the reaction involves a cyclic six-membered transition state.



An obvious extension to this work would be to examine the thermal decomposition of β-hydroxy esters to see if they decompose by a similar mechanism. If such is the case, it would be predicted that the β-hydroxy ester ethyl 3-hydroxy-3-methylbutanoate would pyrolyze to acetone and ethyl acetate.

$$(CH_3)_2C(OH)CH_2CO_2Et \longrightarrow (CH_3)_2C{=}O + CH_3CO_2Et$$

A literature search has indicated that, as far as can be ascertained, the thermal decomposition of β-hydroxy esters has not previously been studied. Accordingly, a study has been carried out on the thermal decomposition of ethyl 3-hydroxy-3-methylbutanoate, which was prepared by a Reformatsky reaction between ethyl bromoacetate and acetone.[2] The pyrolyses were carried out in xylene solution in sealed glass tubes that had been carefully washed to remove all traces of acid or base, and the products of the reaction were analysed by gas chromatography, using a 5-ft column of SE-30 on Chromosorb W.

It was found that in xylene solution ethyl 3-hydroxy-3-methylbutanoate did indeed decompose at temperatures of 180–250° to give acetone and ethyl acetate in yields of 90–95%. The products of the reaction were characterized both by their glpc retention times and in the case of acetone by the formation of a 2,4-dinitrophenylhydrazone, mp 127–8° (after crystallization), from the products of pyrolysis. (The reported melting point of the 2,4-dinitrophenylhydrazone of acetone is 128°.[3]) In the gas chromatography of the products of pyrolysis apart from the solvent peak (xylene) only peaks due to acetone and ethyl acetate were observed. The yields were calculated using glpc by comparison of the peak areas of the products of pyrolysis with those of a known mixture of ethyl acetate and acetone in xylene using benzene as an internal standard. In tubes that were not carefully washed some dehydration occurred as evidenced by the appearance of a new peak due to water in the gas chromatograph of the pyrolysis products.

The kinetics of the decomposition were followed by the methods used in the earlier study.[1a] The reaction was followed to at least two half-lives at 217.8 and 206.0° and one half-life at 191.4 and 179.4°. Good first-order kinetics were observed, the first-order plots being linear for all the periods during which the reaction was followed. The rate constants obtained are listed in Table I, and were found to be reproducible to within ±5%. Equal rate constants were obtained when the reaction was followed by the rate of appearance of the

TABLE I

RATE CONSTANTS FOR THE PYROLYSIS OF ETHYL 3-HYDROXY-3-METHYLBUTANOATE

	Temperature, °C			
	179.4	191.4	206.0	217.8
$k \times 10^6$, sec^{-1}	0.269	0.812	2.76	6.88

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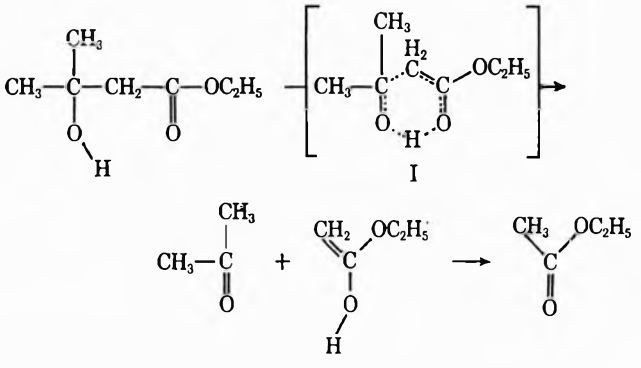
acetone and of the ethyl acetate as well as by the rate of disappearance of the β-hydroxy ester. In the gas chromatography of the products of the reaction no peak due to ethylene was observed indicating that a possible side reaction, the pyrolysis of the ester involving the OC_2H_5 group, takes place to a negligible degree at the temperature of the reaction.

Varying the initial ester concentration over 1, 2, 4, and 8% by volume did not affect the velocity of the pyrolysis as evidenced by observed rate constants at 206.0° of 2.65, 2.80, 2.76, and 2.62 × 10^{-6} sec^{-1}. Packing the reaction tubes with glass wool which increased the surface area by a factor of at least 15 gave a rate constant of 2.60 × 10^{-6} at 206.0°, compared to 2.76 × 10^{-6} sec^{-1} in an unpacked vessel.

These results indicate that the reaction is homogeneous and of first-order. This taken together with the products of the reaction and the negative entropy of activation, which is typical of those reactions that are thought to involve cyclic transition states,[4] suggests that the pyrolysis of ethyl 3-hydroxy-3-methylbutanoate involves the cyclic six-membered transition state I.



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Furthermore, the fact that the pyrolysis of ethyl 3-hydroxy-3-methylbutanoate has proved to follow the course predicted from the results obtained from the work on the β-hydroxy ketones strongly suggests that a similar mechanism is involved in the pyrolysis of both types of compounds. A comparison of the rate of pyrolysis in xylene solution of ethyl 3-hydroxy-3-methylbutanoate with that of the analogously substituted β-hydroxy ketone, 4-hydroxy-4-methyl-2-pentanone, reveals however that the β-hydroxy ester tends to pyrolyze more slowly than the β-hydroxy ketone, the respective rates at 206.0° being 2.76 × 10^{-6} and 1.00 × 10^{-3} sec^{-1}. This could perhaps reflect the greater difficulty of formation of the enol form of ethyl acetate than that of acetone.[5] It is interesting that in the analogous case of ester pyrolysis, in which reaction an intermediate enol form is not required, carbonates ($ROCOOCH_2CH_2R$) tend to pyrolyze more rapidly than the corresponding ester ($RCOOCH_2CH_2R$).[6]

The results of the present study would thus seem to indicate that the pyrolysis of β-hydroxy esters involves a cyclic six-membered transition state similar to those proposed for various other thermal decomposition reactions, for example, the pyrolysis of esters,[4] β-hydroxy olefins,[7] β,γ-unsaturated acids,[8] and β-hydroxy ketones.[4]

Registry No.—Ethyl 3-hydroxy-3-methylbutanoate, 18267-36-2.

Acknowledgments.—The authors wish to thank the Fund for Overseas Grants and Education (FORGE) and the Comite de Investigaciones of the Universidad del Valle for support of this work.

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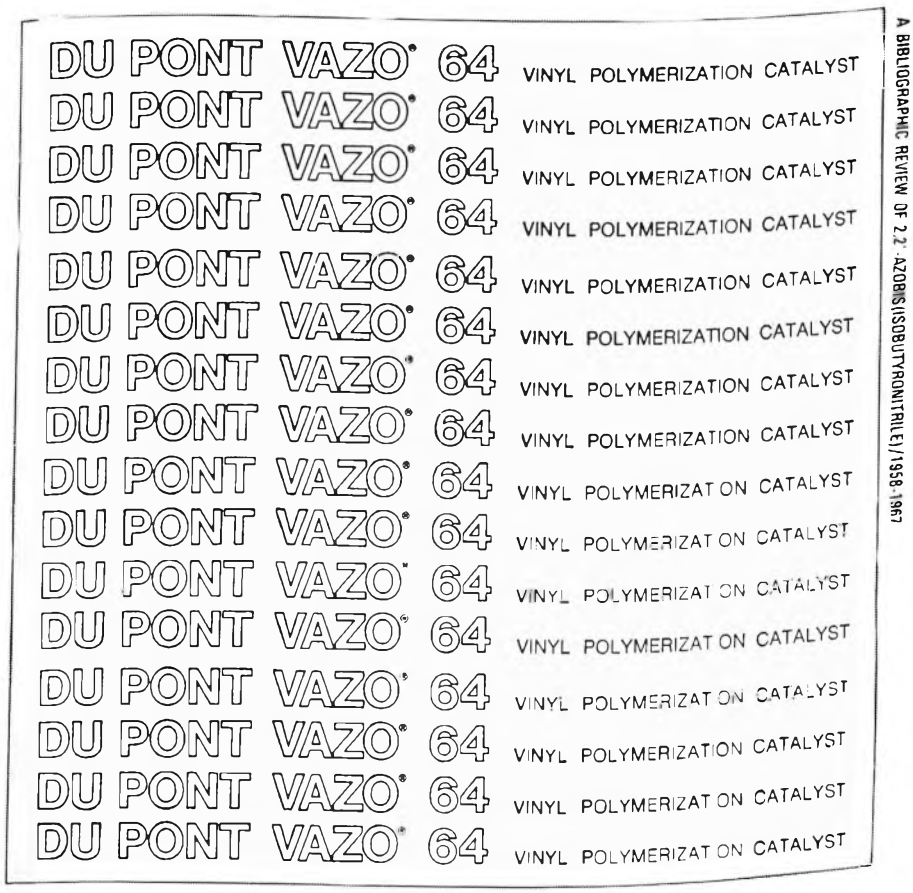

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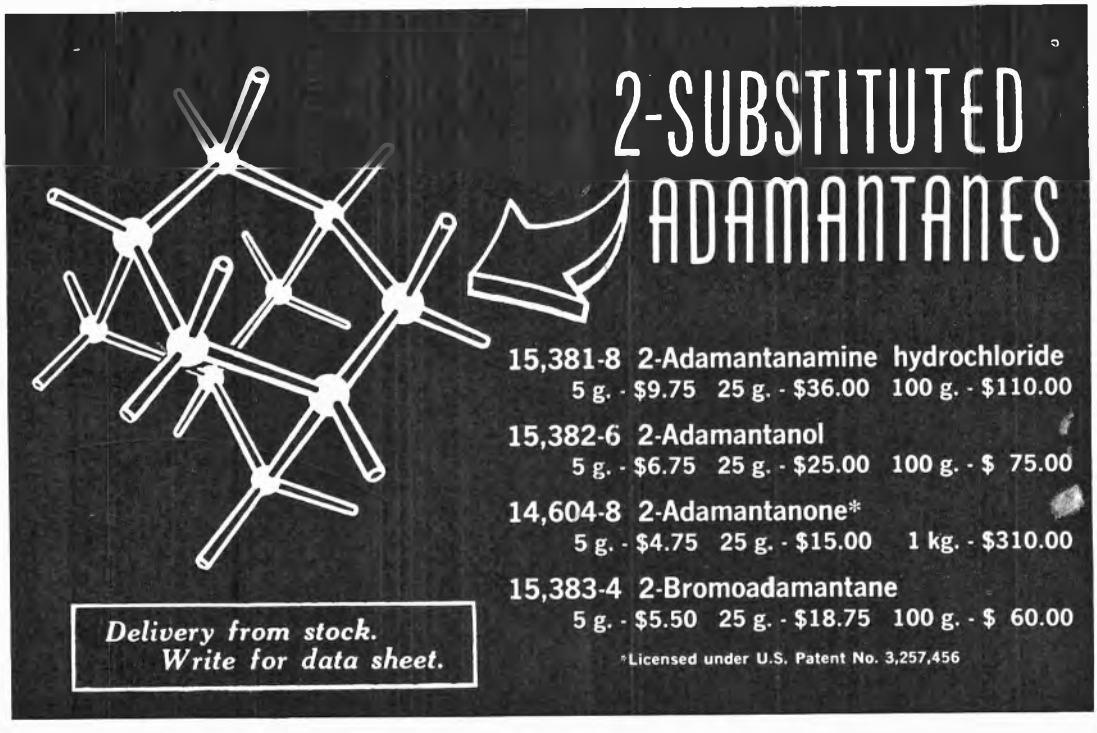

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