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THE JOURNAL OF Organic Chemistry®

VOLUME 36, NUMBER 2

JANUARY 29, 1971

Nucleotide Synthesis. I. Derivatives of Thymidine Containing *p*-Nitrophenyl Phosphate Groups[1a]

R. P. GLINSKI,*[1b] A. B. ASH,[1c] C. L. STEVENS,[1c] M. B. SPORN,[1d] AND H. M. LAZARUS[1d]

Ash Stevens, Inc., Detroit, Michigan 48202, and Chemistry Branch, National Cancer Institute, Bethesda, Maryland 20014

Received April 3, 1970

The synthesis of a number of nucleotide derivatives of thymidine containing *p*-nitrophenyl phosphate groups which have utility as substrates of staphylococcal nuclease is described. Included in this group of compounds are thymidine 3′,5′-di(*p*-nitrophenyl phosphate), derivatives of thymidine 5′-(*p*-nitrophenyl phosphate) substituted at the 3′ position with phosphate and β-cyanoethyl phosphate groups, and derivatives of thymidine 3′-(*p*-nitrophenyl phosphate) substituted at the 5′ position with phosphate, β-cyanoethyl phosphate, methyl- and halomethylphosphonate, and sulfate. The proof of structure of the nucleotides prepared rests on characterization by uv, paper chromatography, and elemental analysis, supplemented by a semimicro method for the determination of pK_a-molecular weight data.

A large amount of data has been accumulated on the physicochemical properties of staphylococcal nuclease.[2] Knowledge of catalytic mechanisms and substrate specificity, however, has been limited by the unavailability of low-molecular-weight substrates of the enzyme. A recent paper[3] describes studies of staphylococcal nuclease with such low-molecular-weight substrates. The synthesis, physical properties, and proof of structure of a number of the nucleotides used in these studies form the subject matter of this paper. Furthermore, one of the nucleotides, thymidine 5′-phosphate-3′-(*p*-nitrophenyl phosphate) (**13**), on catalytic reduction of the *p*-nitrophenyl group, affords an intermediate which has been used in the purification of staphylococcal nuclease by affinity chromatography.[4] Since simple *p*-nitrophenyl compounds have been used successfully in the past as substrates for measuring the activity of many esterases, for example spleen and liver phosphodiesterase,[5] the more complex *p*-nitrophenyl nucleotides described herein may also have potential utility for probing the structure, specificity, and activity of other enzymes. Further, these compounds have activity as active-site-directed inhibitors (at *ca.* 2.5×10^{-2} *M* concentration) or as intermediates in the synthesis of other active-site-directed inhibitors of a nuclear exoribonuclease isolated from mammalian cells.[6]

Thymidine 3′-(*p*-nitrophenyl phosphate) (**3**) and thymidine 5′-(*p*-nitrophenyl phosphate) (**5**) were used as starting materials in the synthesis of the 5′- and 3′-substituted *p*-nitrophenyl nucleotide derivatives. Compound **3** (Scheme I) was prepared from thymidine by tritylation of the 5′-hydroxyl group, followed by *p*-nitrophenyl phosphorylation of the 3′-hydroxyl group and hydrolysis of the 5′-*O*-trityl group. The *p*-nitrophenyl phosphorylation reaction was performed using *p*-nitrophenyl phosphorodichloridate according to the procedure of Turner and Khorana,[7] or using di-*p*-nitrophenyl phosphorochloridate, followed by a mild alkaline hydrolysis. The product, as were most of the nucleotide derivatives prepared, was purified by large-scale preparative paper chromatography. The preparative paper chromatography procedure outlined briefly in the Experimental Section has proved more efficient for gram quantity purification, in our hands, than column chromatography over anion-exchange resins and cellulose with buffer solutions. Compound **5** was prepared by the reaction of 3′-*O*-acetylthymidine (**4**) with di-*p*-nitrophenyl phosphorochloridate, followed by a mild alkaline hydrolysis to remove one *p*-nitrophenyl group and the 3′-*O*-acetyl protection. The product (**5**) was identical with material prepared by a lengthy, more difficult, procedure involving a DCC coupling reaction of excess *p*-nitrophenol with thymidine 5′-phosphate.[8]

(1) (a) A portion of this work has been reported: R. P. Glinski and C. L. Stevens, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., March 1968, N17. (b) To whom correspondence should be addressed: Ash Stevens, Inc. (c) Ash Stevens, Inc. (d) National Cancer Institute.

(2) For a review, see P. Cuatrecasas, H. Taniuchi, and C. B. Anfinsen, *Brookhaven Symp. Biol.*, **21**, 172 (1969).

(3) P. Cuatrecasas, M. Wilchek, and C. B. Anfinsen, *Biochemistry*, **8**, 2277 (1969).

(4) P. Cuatrecasas, M. Wilchek, and C. B. Anfinsen, *Proc. Nat. Acad. Sci. U. S.*, **61**, 636 (1968).

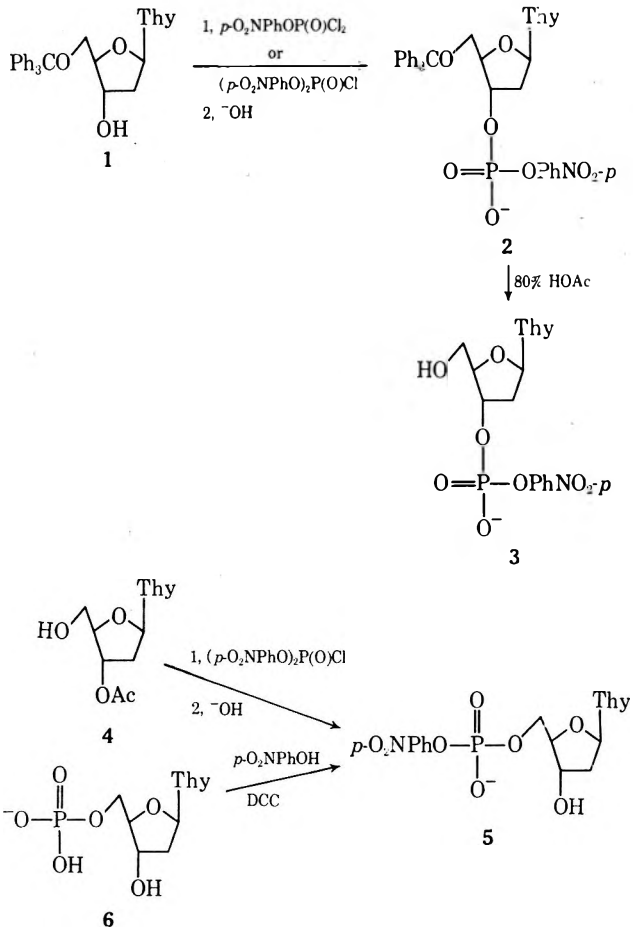
(5) H. G. Khorana, *Enzymes*, **5**, 79 (1961); W. E. Razzell, *Methods Enzymol.*, **6**, 236 (1963).

(6) For a review of the work performed on the isolation, properties, and inhibition of this enzyme, see M. B. Sporn, D. M. Berkowitz, R. P. Glinski, A. B. Ash, and C. L. Stevens, *Science*, **164**, 1408 (1969), and the references cited therein.

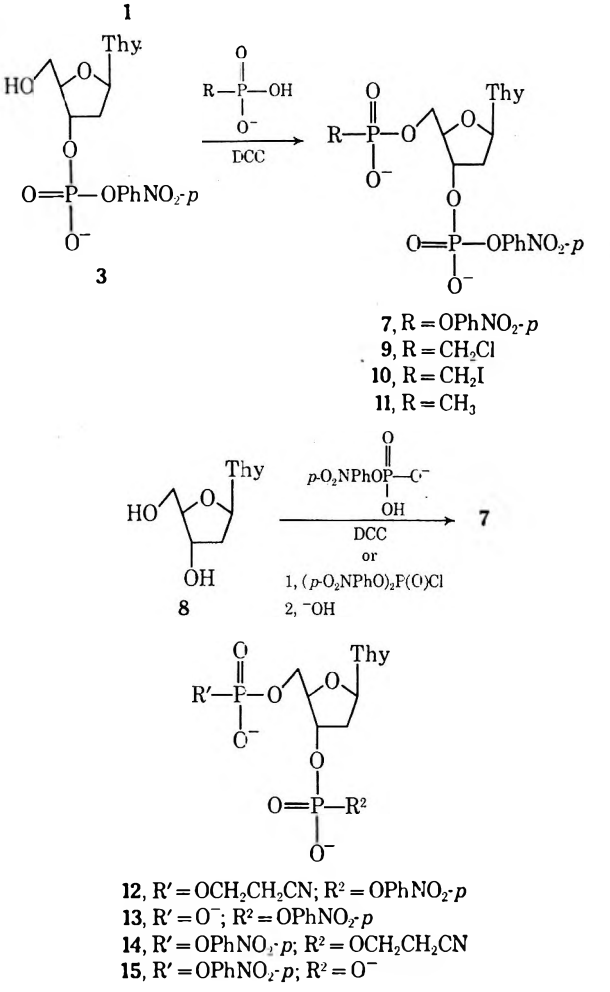
(7) A. F. Turner and H. G. Khorana, *J. Amer. Chem. Soc.*, **81**, 4651 (1959).

(8) W. E. Razzell and H. G. Khorana, *J. Biol. Chem.*, **234**, 2105 (1959).

SCHEME I



SCHEME II



DCC coupling reactions of both thymidine 3′-(*p*-nitrophenyl phosphate) (**3**) and 5′-(*p*-nitrophenyl phosphate) (**5**) were studied. Reaction of compound **3** with β-cyanoethyl phosphate, *p*-nitrophenyl phosphate, methyl-, chloromethyl-, and iodomethylphosphonate, and DCC gave compounds **12**, **7**, **11**, **9**, and **10**, respectively. Thymidine 3′,5′-di(*p*-nitrophenyl phosphate) (**7**) was synthesized also by either a DCC coupling of *p*-nitrophenyl phosphate with thymidine, or by phosphorylation of thymidine with di-*p*-nitrophenyl phosphorochloridate, followed by a basic hydrolysis (Scheme II). The latter procedure is the most convenient and has been used to prepare crystalline compound **7** on a 5–10-g scale, after large-scale preparative paper chromatography.

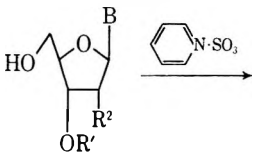
Thymidine 5′-(β-cyanoethyl phosphate)-3′-(*p*-nitrophenyl phosphate) (**12**) was prepared for use as an intermediate in the synthesis of thymidine 3′-(*p*-nitrophenyl phosphate)-5′-phosphate (**13**). Reaction of compound **12** with 1 *N* sodium hydroxide gave a selective β elimination of the β-cyanoethyl ester group in the presence of the 3′-(*p*-nitrophenyl phosphate) group. That this reaction was indeed selective was demonstrated by elemental analysis, pK_a–molecular weight determinations, and the fact that the liberation of *p*-nitrophenol (monitored at 400 mμ) was negligible during the reaction. Higher concentrations of sodium hydroxide or longer reaction times lead to cleavage of the *p*-nitrophenyl group in addition to the β-cyanoethyl group. Thymidine 5′-(*p*-nitrophenyl phosphate) (**5**) was converted into thymidine 3′-(β-cyanoethyl phosphate)-5′-(*p*-nitrophenyl phosphate) (**14**) and thymidine 5′-(*p*-nitrophenyl phosphate)-3′-phosphate (**15**) by the same sequence of reactions used for the preparation of compound **13** with similar results.

Compound **3** was converted also into thymidine 3′-(*p*-nitrophenyl phosphate)-5′-sulfate (**19**). Two model reactions were attempted first. Uridine and thymidine were converted into uridine 2′,3′,5′-trisulfate (**18**) and thymidine 3′,5′-disulfate (**17**), using the pyridine–sulfur trioxide method[9] (Scheme III). The products were isolated in good yield as crystalline barium salts. Similarly, compound **3** afforded crystalline **19** as a barium salt in excellent yield, in which the 5′-hydroxyl group was sulfated in the presence of the 3′-*p*-nitrophenyl phosphate group. It is noteworthy that no difficulty was encountered with compounds containing a sulfatophosphate group;[10] presumably a product containing a sulfatophosphate group would be hydrolyzed to compound **19** during isolation.

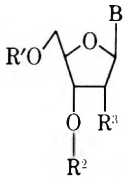
All of the new compounds reported herein were subjected to pK_a–molecular weight determinations (see Experimental Section). The method involves the quantitative conversion of a small, dried sample (7–15 mg) of nucleotide salt into the corresponding free acid by passage of an aqueous solution of the salt through a column of purified Dowex 50 (H^+). The acidic eluate (10 ml) is titrated with dilute sodium hydroxide (0.5–1.5 ml) using a Sargent pH-Stat. A plot of pH *vs.* ml

(9) P. W. Wigler and H. U. Choi, *J. Amer. Chem. Soc.*, **86**, 1636 (1964).
(10) J. Baddiley, J. G. Buchanan, R. Letters, and A. R. Sanderson, *J. Chem. Soc.*, 1731 (1959).

SCHEME III



8, $R' = R^2 = H$; B = thymine
16, $R' = H$; $R^2 = OH$; B = uridine
3, $R' = P(O)OPhNO_2\text{-}p$; $R^2 = H$; R^3 = thymine



17, $R' = R^2 = SO_3^-$; $R^3 = H$; B = thymine
18, $R' = R^2 = SO_3^-$; $R^3 = OSO_3^-$; B = uridine
19, $R' = SO_3^-$; $R^2 = P(O)OPhNO_2\text{-}p$; $R^3 = H$; B = thymine

of titrant gives curves from which pK_a's and molecular weights can be calculated in the usual manner. The determined molecular weights are generally within 2% of the calculated values when 15–30 mg of sample is available or within 5% when 7–15 mg of sample is available.

The method establishes also the degree of substitution on phosphorus. Thus, disubstituted phosphate esters, such as thymidine 3′,5′-di-(*p*-nitrophenyl phosphate) (**7**), give curves with only one inflection and one pK_a. On the other hand, monosubstituted phosphate esters, or mixed monosubstituted and disubstituted esters, such as thymidine 5′-(*p*-nitrophenyl phosphate)-3′-phosphate (**15**), give curves with two inflections and two pK_a values.

Experimental Section

Paper chromatography (pc) was by the descending technique using the following solvent systems: A, 1-butanol–acetic acid–water (5:2:3, v/v); B, 2-propanol–water–concentrated ammonium hydroxide (7:1:2, v/v); C, 2-propanol–aqueous ammonium sulfate (1%) (5:2, v/v); D, ethanol–aqueous ammonium acetate (1%) (5:2, v/v). The nucleotides were detected with ultraviolet light. Analytical pc was performed using Whatman No. 1 and No. 7 paper. Unless stated otherwise, Whatman No. 1 paper was used. Whatman 3MM paper (1–2 g per 20 sheets) was used for the preparative paper chromatography (ppc). The paper was converted into a pulp suspension in water by use of a Waring Blendor. The pulp was washed thoroughly with water (2 l.) in a 2-l. sintered glass filter and was removed by filteration. The filtrate was concentrated to a small volume *in vacuo* below 50° using a Büchi Rotavap (Rinco Instruments). The remaining water was removed by lyophilization to afford a weighable solid.

Thin layer chromatography (tlc) analyses were performed using Eastman chromatogram sheets 6060 (silica gel) impregnated with a fluorescent indicator and Brinkman Instruments' MN-Polygram cel 300 PEI sheets (anion-exchange cellulose). The following tlc systems were used: A, chloroform–ammonium hydroxide (1%) in methanol (3:2, v/v); B, 1% sodium chloride in water. Uv spectra wre recorded using a Hatachi-Coleman 124 spectrophotometer using distilled water as solvent unless stated otherwise. Pyridine was distilled and stored over Linde Molecular Sieves (type 4A). Elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., on all new compounds.

Thymidine 3′-(*p*-Nitrophenyl phosphate) Ammonium Salt (3). A.—The title compound was prepared by a modified literature procedure[7] or by method B. In our hands, compound **3** required purification by ppc using pc solvent system A to remove a very minor faster-migrating impurity, relative to **3**. The yields of chromatographically homogeneous product were *ca.* 70%.

B.—5′-*O*-Tritylthymidine[7] (**1**, 562 mg) was dissolved in anhydrous pyridine (5 ml) and di-*p*-nitrophenyl phosphorochloridate[11] (653 mg) was added. The reaction mixture was allowed to stand at 1° for 16 hr. Water (4 ml) was added and the mixture was frozen (Dry Ice) and concentrated to a gum *in vacuo* (oil pump). Water (7 ml) was added to the gum and the pH of the mixture was adjusted to 8 (pH paper) by the dropwise addition of 1 *N* NaOH with vigorous shaking. The mixture became homogeneous at pH 5–6. The solution was allowed to stand at room temperature overnight. The pH of the reaction mixture was adjusted to 1–2 with 1 *N* hydrochloric acid. The solution was extracted with chloroform (three 10-ml portions). The chloroform extracts were combined and extracted with aqueous 1 *M* pyridine hydrochloride solution (five 10-ml portions). The chloroform solution was dried (Na_2SO_4) and was concentrated *in vacuo* to give a gum. The gum was dissolved in 80% acetic acid (11 ml). The solution was heated in a boiling water bath for 10 min. The reaction mixture was cooled to room temperature and water (15 ml) was added. The resulting heterogeneous mixture was frozen and lyophilized. The resulting solid was suspended in water and the mixture was lyophilized again. Water (20 ml) was added to the residue and the mixture was allowed to stand at 1° for 2 days. The suspension of trityl alcohol was removed by filtration and the solid was washed well with water. The filtrate and washings were combined and lyophilized. The resulting residue was dissolved in a minimum amount of water and the solution was applied to a Dowex 50 (H^+) column (10 ml). The column was eluted with water until the effluent was neutral to pH paper. The acidic effluent was neutralized to pH 7.0 with concentrated NH_4OH and was lyophlized. The residue was purified by ppc using seven sheets of 3MM paper and solvent system A to afford 297 mg (64%) of chromatographically homogeneous product, identical with compound **3** (NH_4^+ salt) by ir (KBr), uv, and pc using four solvent systems.

Thymidine 5′-(*p*-Nitrophenyl phosphate) Lithium Salt (5).— Thymidine 3′-*O*-acetate[12] (**4**, 4.5 g) was dissolved in anhydrous pyridine (50 ml) and di-*p*-nitrophenyl phosphorochloridate[11] (7.5 g) was added. The mixture was stirred at room temperature overnight. The pH of the solution was adjusted to *ca.* 10–11 by the dropwise addition of 1 *N* sodium hydroxide (105 ml). After the addition was complete, the reaction mixture was allowed to stand at room temperature for 20 hr. The reaction mixture was cooled to 0° by the addition of ice and was added to an Amberlite IR-120 (H^+) column (100 ml) which was also cooled to 0° by preliminary elution with ice–water. The column was eluted with ice–water (*ca.* 1 l.). The effluent was concentrated *in vacuo* to *ca.* 200-ml volume. The heterogeneous aqueous phase was extracted with diethyl ether (three 200-ml portions). The resulting homogeneous aqueous phase was percolated through a small Amberlite IR-120 (H^+) column (20 ml). The column was eluted with water until the effluent was neutral. The pH of the total effluent was adjusted to 3.5 with lithium hydroxide solution and the solution was extracted with diethyl ether (three 100-ml portions) to remove additional *p*-nitrophenol. The pH of the aqueous phase was adjusted to 6.0 with lithium hydroxide solution. The neutralized solution was lyophilized to give 9.09 g of crude product **5**. The crude red solid was purified by ppc using pc system A and 120 sheets of 3MM paper to give chromatographically homogeneous compound **5** (4.32 g).

Compound **5** was prepared also on small scale by the method of Razzell and Khorana[8] which involved a DCC coupling of excess *p*-nitrophenol and thymidine 5′-phosphate. The products obtained by both routes were identical by pc and uv spectroscopy, and the analytical data were in agreement with reported values.[8]

Thymidine 3′ 5′-Di(*p*-nitrophenyl phosphate) Barium Salt (7). A.—Thymidine 3′-(*p*-nitrophenyl phosphate) ammonium salt (**3**, 750 mg) and *p*-nitrophenylphosphoric acid (750 mg) were dissolved in anhydrous pyridine (15 ml). DCC (5 g) was added to the magnetically stirred solution. The reaction mixture was allowed to stand at room temperature for 24 hr. The pyridine was removed *in vacuo*. Water (25 ml) was added to the residue. The resulting heterogeneous mixture was stirred at room temperature for 2 hr. The solid was removed by filtration and was

(11) T. Ukita and H. Hayatsu, *J. Amer. Chem. Soc.*, **84**, 1879 (1962).
(12) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 951 (1953).

washed well with water. The filtrate and washings were combined and were passed through a Dowex 50 (H^+) column (50 ml). The column was eluted with water until the effluent was neutral. The effluent was neutralized with concentrated NH_4OH and was lyophilized to afford crude compound **7**. The major nucleotide band migrating slightly slower than **3** was separated by ppc using pc systems A and C in succession to give chromatographically homogeneous compound **7** (250 mg, diammonium salt) as a hygroscopic solid. The diammonium salt was converted into the barium salt by passage through a Dowex 50 (H^+) column and neutralization with $Ba(OH)_2$ solution to give compound **7** (230 mg) as an amorphous yellow solid. The amorphous solid was fractionally precipitated from water–2-propanol mixtures. The first fractions yielded highly colored solids and gums. The latter fractions crystallized to afford analytically pure compound **7** (130 mg) after drying at 110° (10^{-3} mm) for 2 hr: mp 264° dec; R_f values in systems A, B, C, and D were 0.61, 0.69, 0.79, and 0.79, respectively: uv max (H_2O) 275 mμ (ε 21,000), 250–260 (0.64), 260–270 (0.77), 270–280 (0.99); pK_a = 2.79; mol wt 798 (found) *vs.* 798 (calcd).

Anal. Calcd for $C_{22}H_{20}N_4O_{15}P_2 \cdot Ba \cdot H_2O$: C, 33.12; H, 2.78; N, 7.02; P, 7.77. Found: C, 33.11; H, 3.38; N, 7.23; P, 7.49.

Similarly, thymidine was coupled with excess *p*-nitrophenyl phosphate to give a low yield of product **7**.

B.—Thymidine (**8**, 5.0 g) was dissolved in anhydrous pyridine (125 ml). The solution was cooled to 0° and stirred. Di-*p*-nitrophenyl phosphorochloridate (22.5 g) was added portionwise. The reaction mixture was allowed to stand at 0° for 3 days. Sodium hydroxide, 1 *N* (175 ml), was added over 30 min with stirring. The reaction mixture was allowed to warm to room temperature and was allowed to stand at room temperature for 2 hr. Additional 1 *N* sodium hydroxide (5 ml) was added and the mixture was stirred at room temperature for an additional 16 hr. The reaction mixture was cooled with ice and added to a Dowex 50 (H^+) column (900 ml). The column was eluted with water. The total effluent was neutralized to pH 3.5 (pH paper) with 1 *N* sodium hydroxide. The solution (2 l.) was concentrated *in vacuo* to *ca.* 100-ml volume. The concentrated solution was extracted with ethyl ether (five 100-ml portions). The aqueous phase was adjusted to *ca.* pH 6.5 and lyophilized to yield 21.6 g of crude **7**. Compound **7** was purified by ppc (134 sheets of 3MM paper) using pc system A to give chromatographically homogeneous solid (9.8 g). The solid was dissolved in water and applied to a Dowex 50 (H^+) column (180 ml). The column was eluted with water until the effluent was neutral. The effluent was extracted with ethyl ether (twice) and stirred with a small amount of charcoal at room temperature for 1 hr. The charcoal treatment was repeated. The charcoal was removed by filtration. The pH of the filtrate was adjusted to pH 6.5 with $Ba(OH)_2$ solution. The solution was concentrated *in vacuo* and was adjusted to pH 7.0 with $Ba(OH)_2$ solution. The neutralized solution was stirred at room temperature for 3 hr with a small amount of charcoal. The charcoal was removed by filtration. The filtrate was lyophilized to yield amorphous compound **7** (9.64 g). The amorphous solid was dissolved in a minimum amount of warm water. The solution was cooled to room temperature and diluted with 2-propanol to the point of turbidity. The mixture was centrifuged. This treatment was repeated several times. The supernatant was transferred to a 125 ml flask, diluted to the point of turbidity, and seeded with crystalline compound **7**. A brown gum formed over a period of several hours. The supernatant was decanted away from the gum and the above procedure was repeated five times with similar results before crystallization occurred. 2-Propanol was added daily to the point of turbidity as crystallization continued. After *ca.* 1 week, 7.45 g (45%) of crystalline compound **7** was obtained. An additional 1.0 g (6%) of pure **7** was obtained by purification of the residue (obtained by evaporation of mother liquors) by ppc using pc system C and 30 sheets of 3MM paper. A sample was recrystallized from water–2-propanol mixtures and dried *in vacuo* as before for analysis.

Anal. Calcd for $C_{22}H_{20}N_4O_{15}P_2 \cdot Ba \cdot H_2O$: C, 33.12; H, 2.78; N, 7.02; P, 7.77. Found: C, 33.09; H, 3.03; N, 7.26; P, 8.25.

Preparations of **7** by both routes were identical by pc (four systems), uv, melting point, and mixture melting point determinations.

Thymidine 5′-Chloromethylphosphonate-3′-(*p*-nitrophenyl phosphate) Diammonium Salt (9).—Thymidine 3′-(*p*-nitrophenyl phosphate) ammonium salt (**3**, 300 mg) and anhydrous chloromethylphosphonic acid were dissolved in anhydrous pyridine (8 ml). DCC (1.3 g) was added and the heterogeneous mixture was stirred at room temperature for 16 hr. The solvent was removed *in vacuo*. Water (5 ml) was added to the residue. The mixture was stirred vigorously for 5 min. The dicyclohexylurea was removed by filtration and was washed thoroughly with water (four 5-ml portions). The brown filtrate and washings were combined and were passed through a Dowex 50 (H^+) column (25 ml). The column was eluted with water until the effluent was neutral. The yellow effluent was neutralized with dilute ammonium hydroxide and was lyophilized to give 350 mg of crude **9**. Compound **9** was purified by ppc (six 3MM sheets) using solvent systems C and A in succession to afford 213 mg (56%) of chromatographically homogeneous product **9**. An analytically pure sample was prepared by fractional precipitation from water–methanol–ethyl ether mixtures, followed by drying at room temperature (5×10^{-3} mm) over P_2O_5 for 48 hr: R_f values (Whatman No. 7 paper) using solvent systems A, B, C, and D were 0.58, 0.62, 0.76, and 0.75, respectively; uv max 272 mμ (ε 14,300), 250–260 (0.63), 260–270 (0.82), 270–280 (1.09); pK_a = 2.83; mol wt 558 (found) *vs.* 590 (calcd).

Anal. Calcd for $C_{17}H_{18}ClN_3O_{12}P_2$: Cl, 6.01. Found: Cl, 6.00.

Thymidine 5′-Iodomethylphosphonate-3′-(*p*-nitrophenyl phosphate) Barium Salt (10).—Thymidine 3′-(*p*-nitrophenyl phosphate) ammonium salt (**3**, 500 mg) and iodomethylphosphonic acid[13] were dissolved in anhydrous pyridine (5 ml). DCC (2.2 g) was added and the solution was stirred at room temperature for 24 hr. Using experimental procedures similar to those described for the preparation of compound **9**, 900 mg of crude **10** (barium salt) was obtained as a light yellow solid. The solid was dissolved in water (5 ml) and ethanol was added. A precipitate of barium iodomethylphosphonate (190 mg, identified by a pK_a–molecular weight determination) resulted immediately. The mother liquor was concentrated *in vacuo* to afford 700 mg of **10**. Compound **10** was chromatographically homogeneous at this point using four pc systems and Whatman No. 1 paper. Using Whatman No. 7 paper and solvent system A, however, a minor faster migrating impurity was evident. A sample (200 mg) was purified by ppc (Whatman No. 7 paper, 20 mg per sheet) using system A to give 105 mg of chromatographically homogeneous compound **10**. Compound **10** was purified further for analysis by fractional precipitation from water–ethanol mixtures. The first and last crops were discarded and the intermediate fractions were dried at 110° (5×10^{-3} mm) for 2 hr: R_f values (Whatman No. 7 paper) in systems A, B, C, and D were 0.62, 0.63, 0.76, and 0.75, respectively; uv max 272 mμ (ε 15,200), 250–260 (0.65), 260–270 (0.82), 270–280 (1.09); pK_a = 2.77; mol wt 690 (found) *vs.* 783 (calcd).

Anal. Calcd for $C_{17}H_{18}IN_3O_{12}P_2 \cdot Ba$: I, 16.21. Found: I, 16.50.

Thymidine 5′-(Methylphosphonate)-3′-(*p*-nitrophenyl phosphate) Dilithium Salt (11).—Thymidine 3′-(*p*-nitrophenyl phosphate) pyridinium salt (**3**), prepared from the diammonium salt (250 mg), was dissolved in anhydrous pyridine (6 ml) containing DCC (1.1 g). Methylphosphonic acid (80 mg) was added with stirring. The reaction mixture was allowed to stand at room temperature for 20 hr. Isolation, in a manner similar to that described for the preparation of compound **9**, gave crude compound **11** (lithium salt, 350 mg) which was essentially homogeneous by pc. Crude **11** was subjected to ppc using pc system A to give 191 mg of chromatographically homogeneous material. An analytically pure sample was obtained by fractional precipitation from methanol–diethyl ether mixtures, followed by drying at room temperature (5×10^{-3} mm) for 24 hr over P_2O_4: R_f values in pc systems A, B, C, and D were 0.42, 0.46, 0.49, and 0.55; pK_a = 2.9; mol wt 555 (found) *vs.* 597 (calcd); uv max 271 mμ (ε 15,250); uv max *ca.* 305 mμ, shoulder (ε 6900), 250–260 (0.63), 260–270 (0.84), 270–280 (1.11), 280–290 (1.35).

Anal. Calcd for $C_{17}H_{19}N_3O_{12}P_2 \cdot 2Li \cdot 2CH_3OH$: C, 38.21; H, 4.55; N, 7.04; P, 10.37. Found: C, 38.58; H, 4.72; N, 6.68; P, 10.42.

Thymidine 5′-Phosphate-3′-(*p*-nitrophenyl phosphate) Trilithium Salt (13).—Thymidine 3′-(*p*-nitrophenyl phosphate) pyridinium salt (**3**), prepared from the amonium salt (750 mg), was dissolved in pyridine (18 ml) containing DCC (3.35 g).

(13) P. C. Crofts and G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **75**, 5738 (1953).

β-Cyanoethyl phosphate pyridine salt[14] (665 mg) was dissolved in anhydrous pyridine (9.3 ml) and the solution was added slowly, with stirring. The reaction mixture, processed in a manner similar to that described for the preparation of compound **9**, gave crude thymidine 5′-(β-cyanoethyl phosphate)-3′-(*p*-nitrophenyl phosphate) dilithium salt (**12**, 969 mg). Crude **12**, without purification by ppc, was dissolved in 1 *N* NaOH solution (2 ml) and the solution was allowed to stand at room temperature for 1 hr. The solution was applied to a Dowex 50 (H^+) column (15 ml). The column was eluted with water (250 ml). The effluent was stirred with charcoal (*ca.* 50 mg) at room temperature for 15 min. The charcoal was removed by filtration using a Celite bed. The filtrate was neutralized with lithium hydroxide solution, concentrated *in vacuo* (aspirator pressure) to a small volume, and lyophilized to yield crude compound **13** (870 mg). Analytical pc indicated that the hydrolysis was incomplete. The mixture was dissolved in 1 *N* sodium hydroxide (3 ml) and the solution was allowed to stand at room temperature for 1.5 hr. Processing the reaction mixture as before yielded essentially chromatographically homogeneous compound **13** (750 mg). Purification of compound **13** by ppc using pc system A afforded chromatographically homogeneous **13** (628 mg, 66%). Compound **13** was purified for elemental analysis by fractional precipitation from water–2-propanol mixtures. Six fractions were collected, the first five as gums. The sixth fraction, a solid (210 mg), was dried at room temperature (5×10^{-3} mm) for 24 hr over P_2O_5: R_f values in systems A, B, C, and D were 0.42, 0.22, 0.39, and 0.48, respectively; uv max 270 mμ (ε 14,900), 300 shoulder (8100), 260–270 (0.87), 270–280 (1.12), 280–290 (1.32); pK_{a^1} = 2.8, pK_{a^2} = 7.0; mol wt$_1$ 6.06, mol wt$_2$ 617 (calcd 586).

Anal. Calcd for $C_{16}H_{16}N_3O_{13}P_2 \cdot 3Li \cdot 2.5H_2O$: C, 32.79; H, 3.61; N, 7.17; P, 10.57. Found: C, 32.87; H, 3.92; N, 6.81; P, 10.45.

Thymidine 3′-Phosphate-5′-(*p*-nitrophenyl phosphate) Trilithium Salt (**15**).—Thymidine 5′-(*p*-nitrophenyl phosphate) pyridinium salt (**5**, 362 mg) was dissolved in anhydrous pyridine (4 ml) containing DCC (0.715 mg). β-Cyanoethyl phosphate (290 mg),[14] dissolved in anhydrous pyridine (4 ml), was added slowly with stirring. The reaction mixture was processed in a manner similar to that described for the preparation of compound **13**. The yield of chromatographically homogeneous compound **15**, after ppc using pc system A, was 333 mg (76%). Compound **15** was purified for elemental analysis by fractional precipitation from wet methanol–2-propanol mixtures and drying at room temperature (5×10^{-3} mm) for 24 hr over P_2O_5: R_f values in pc systems A, B, C, and D were 0.45, 0.19, 0.35, and 0.40, respectively; uv max 270 mμ (ε 15,420) *ca.* 305 mm, shoulder (7000), 260–270 (0.87), 270–280 (1.16), 280–290 (1.35); pK_{a^1} = 3.0, pK_{a^2} = 6.7; mol wt$_1$ 634, mol wt$_2$ 637 (calcd 637).

Anal. Calcd for $C_{16}H_{16}N_3O_{13}P_2 \cdot 3Li \cdot 3CH_3OH$: C, 35.81; H, 4.43; N, 6.59; P, 9.72. Found: C, 35.97; H, 4.80; N, 6.86; P, 9.69.

Alternatively, compound **15** (730 mg, purified by ppc) was suspended in methanol (20 ml). The insoluble material was removed by centrifugation. The supernatant was concentrated *in vacuo* to give a gel. The gel was dissolved in methanol (5 ml) and the solution was diluted with 2-propanol (5 ml) and *n*-pentane (10 ml). The resulting gelantinous precipitate was removed by centrifugation, ans washed with 2-propanol and *n*-pentane. The residue was dissolved in water and the water was removed *in vacuo* (water pump). This procedure was repeated three times. The residue was dissolved in water again and lyophilized to give 280 mg.

Anal. Calcd for $C_{16}H_{16}N_3O_{13}P_2 \cdot 3Li \cdot 4H_2O$: C, 31.34; H, 3.95; N, 6.85; P, 10.10. Found: C, 31.55; H, 3.84; N, 7.02; P, 9.93.

Thymidine 3′,5′-Disulfate Barium Salt (**17**).—Thymidine (1.21 g) and pyridine–sulfur trioxide complex[7] (4.0 g) were stirred in pyridine (90 ml) at room temperature for 48 hr. Water (90 ml) was added and the pH was adjusted to 10.5 (pH paper) with 1.3 *N* NaOH. The solvent was removed *in vacuo*, the residue was suspended in hot methanol (100 ml), and the suspension was cooled to 4°. The Na_2SO_4 was removed by filtration and the filtrate was concentrated *in vacuo* to yield a brown solid. The solid was dissolved in water and converted into the barium salt by passage of an aqueous solution through Dowex 50 (H^+), followed by neutralization of the water eluate with $Ba(OH)_2$ solution. The water solution was lyophilized. The resulting white salt was crystallized from aqueous ethanol to yield 2.21 g of the crystalline polyhydrate of **17** with mp 164–166° dec. A sample was dried at 110° (5×10^{-3} mm) for 2 hr to afford the dihydrate compound **17** with mp 200° dec: uv max (H_2O) 266.5 (ε 10,300),[15] 250–260 (0.65), 260–270 (0.94), 270–280 (1.55); pK_a = 2.69; mol wt 591 (found) *vs.* 576 (calcd).

Anal. Calcd for $C_{10}H_{12}N_2O_{11}S_2Ba \cdot 2H_2O$: C, 20.94; H, 2.80; S, 11.18. Found: C, 21.09; H, 2.98; S, 11.00.

Uridine 2′,3′,5′-Trisulfate Barium Salt (**18**).—Title compound **18** was prepared from uridine (1.0 g) in the same manner that compound **17** was prepared from thymidine. The yield of chromatographically homogeneous compound **18** before crystallization was 2.0 g. A small sample (500 mg) was purified by crystallization from aqueous ethanol to give a polyhydrate of **18** (380 mg) with mp 173° dec. The sample was dried at 80° (5×10^{-3} mm) for 16 hr to give compound **18** monohydrate with mp 235° dec: R_f values in systems A, B, C, and D were 0.11, 0.45, 0.53, and 0.72, respectively; uv max (H_2O) 260 mμ (ε 10,000), 250–260 (0.81), 260–270 (1.28), 270–280 (2.78); pK_a = 2.84; mol wt 738 (found) *vs.* 705 (calcd).

Anal. Calcd for $C_9H_9N_2O_{15}S_3Ba_{1.5} \cdot H_2O$: C, 15.32; H, 1.57; N, 3.97; S, 13.64. Found: C, 15.33; H, 1.83; N, 4.30; S, 12.66.

Thymidine 5′-Sulfate-3′-(*p*-nitrophenyl phosphate) Barium Salt (**19**).—Thymidine 3′-(*p*-nitrophenyl phosphate) ammonium salt (**3**, 1.0 g) and pyridine–sulfur trioxide complex[7] (0.90 g) were stirred in dry pyridine at room temperature for 36 hr. After 24 hr, the reaction was complete by pc. The pyridine was removed *in vacuo* to afford a gum. The gum was dissolved in water and passed through a column of Dowex 50 (H^+), eluting with water. The highly acidic effluent was adjusted to pH 8 with $Ba(OH)_2$ and the insoluble $BaSO_4$ was removed by filtration. The filtrate was lyophilized to afford 1.3 g (theory, 1.43 g) of a white solid. Analytically pure, crystalline **19** monohydrate was obtained after four recrystallizations of a sample from water–alcohol mixtures and drying at 110° (10^{-3} mm) for 2 hr: mp 235° dec; uv max (H_2O) 272 mμ (ε 15,300), 250–260 (0.63), 260–270 (0.82), 270–280 (1.1); pK_a = 2.37; mol wt 687 (found) *vs.* 697 (calcd).

Anal. Calcd for $C_{16}H_{16}N_3O_{13}PS \cdot Ba \cdot H_2O$: C, 28.39; H, 2.68; N, 6.21; P, 4.58; S, 4.74. Found: C, 28.65; H, 3.06; N, 5.97; P, 4.70; S, 4.45.

Registry No.—**3**, 26886-08-8; **5**, 26886-09-9; **7**, 26886-10-2; **9**, 26886-11-3; **10**, 26886-12-4; **11**, 26963-85-9; **13**, 26886-13-5; **15**, 26886-14-6; **17**, 26886-15-7; **18**, 28594-70-9; **19**, 28594-71-0.

Acknowledgment.—This work was supported by NIH Contract PH4366-929.

(14) G. M. Tener, *J. Amer. Chem. Soc.*, **83**, 159 (1961).

(15) The uv data given for compound **17** (barium salt) are in agreement with that reported for the corresponding disodium salts: G. Kowollik and P. Langen, *Chem. Ber.*, **99**, 2725 (1966).

Synthesis of Some Pyrimidine 2′-Amino-2′-deoxynucleosides

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Contribution No. 78 from the Institute of Molecular Biology, Syntex Research, Palo Alto, California 93404

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The reaction of 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil with lithium azide in hexamethylphosphoramide at 150° gives 2′-azido-2′-deoxyuridine in 50% yield. Catalytic reduction of the latter compound gives 2′-amino-2′-deoxyuridine (**3**), the first such pyrimidine nucleoside to be described. The dichloroacetyl derivative of the 2′-amino group was prepared by conventional methods. Acetylation of **3** followed by reaction with phosphorus pentasulfide and amination of the resulting 4-thiouracil derivative gave 2′-amino-2′-deoxycytidine (**8**). The latter compound was also obtained directly by reaction of 3′,5′-di-*O*-acetyl-2′-azido-2′-deoxyuridine (**9**) with phosphorus pentasulfide in pyridine followed by treatment with methanolic ammonia. Reaction of **9** with *N*-iodosuccinimide gave the 5-iodo derivative and subsequent reduction of the azido group with sodium borohydride gave 2′-amino-2′-deoxy-5-iodouridine.

Spurred largely through the presence of the 3′-amino-3′-deoxy-β-D-ribofuranose moiety in the antibiotic puromycin,[1] considerable effort has been devoted to the synthesis of other amino sugar nucleosides. Thus, synthetic routes leading to purine ribofuranosyl nucleoside analogs containing 5′-amino-5′-deoxy-,[2] 2′-amino-2′-deoxy-,[3] and 3′-amino-3′-deoxy[4]-β-D-ribofuranosyl moieties have been described. Also syntheses leading to 5′-amino-5′-deoxy-,[5] 3′-amino-3′-deoxy-,[5a] 3′-amino-2′,-3′-dideoxy-,[6] and 3′-amino-2′,3′-dideoxy-2′-thio[7]-β-D-ribofuranosylpyrimidines have been described. The methods of synthesis have involved both transformations of preformed nucleosides[2,5b,6,7] and condensations of derivatives of suitable amino sugars with the purine or pyrimidine bases.[3,4,5a]

The notably missing member in the above series is the pyrimidine 2′-amino-2′-deoxyribonucleosides and in this paper we describe the synthesis of two such compounds, namely 1-(2-amino-2-deoxy-β-D-ribofuranosyl)-uracil (**3**) and 1-(2-amino-2-deoxy-β-D-ribofuranosyl)-cytosine (**8**).

While it has previously been shown that the anhydro bridge of 2,3′-anhydro-1-(2-deoxy-β-D-threopentofuranosyl)thymine can be opened by nucleophiles such as phthalimide anion,[6a] it has been stated by both Brown, *et al.*,[8] and by Horwitz, *et al.*,[5b] that 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil (**1a**) was resistant to reaction with azide ion in acetonitrile or dimethylformamide. In both cases, the attempted displacement reaction was actually done upon 5′-*O*-acetyl-2′-*O*-tosyluridine and the reaction led only to the formation of the anhydronucleosides (**1a** and **1b**) which resisted further attack. A comparable reaction between **1b** and iodide ion led, however, to 5′-*O*-acetyl-2′-deoxy-2′-iodouridine.[8] It thus seemed to be of interest to investigate the opening of such anhydronucleosides in other aprotic dipolar solvents known to favor nucleophilic attack.

The preparation of **1a** was done essentially according to Hampton[9] with the exception that the reaction of uridine with diphenyl carbonate was carried out in hexamethylphosphoramide (HMPT) rather than in dimethylformamide (DMF). This modification somewhat reduced the reaction time and substantially increased the yield of crystalline product to 88%. It is interesting to note that tlc of the crude product from this reaction in either DMF or HMPT showed the presence of two products with the characteristic ultraviolet spectrum of **1**. During work-up of the reaction, the more polar of these disappeared with exclusive formation of **1a**. It is possible that this very polar product is the unstable 3′-hemicarbonate of **1a** arising directly from opening of uridine 2′,3′-carbonate by the C_2-carbonyl of the uracil ring.[10]

In our initial efforts to react **1a** with lithium azide we used dimethyl sulfoxide (DMSO) as the solvent. Since nucleophilic opening of anhydronucleosides is known to be acid catalyzed,[11] trial experiments were carried out at 100° in the presence of benzoic acid, methanesulfonic acid, or ammonium chloride and in the absence of added acid. In no case was there any significant reaction during 2 hr at 100,° but at 150° all reactions rapidly turned dark and tlc showed the presence of a less polar compound with a uridine spectrum. The reactions containing acid appeared to be less colored and somewhat cleaner and subsequent studies were done using benzoic acid. The desired reaction product 2′-azido-2′-deoxyuridine (**2**) proved to be water soluble and work-up necessitated evaporation of the DMSO to dryness prior to chromatography. Nevertheless, **2** was isolated in modest yield from such a reaction. A notable improvement was achieved by conducting the reaction in HMPT rather than in DMSO.[12] At 150° in this solvent the reaction of **1a** with lithium azide was much more rapid than in DMSO and was essentially complete within 15 min. A second advantage of the use of HMPT lies in the selective extraction of this otherwise very polar solvent into chloroform *via* complex formation.[12] Subsequent chromatography of the reaction mixture on silicic acid led to the isolation of **2** as a chromatographically and analytically pure syrup in 50% yield. Subsequent reduction of **2** in the presence of a palladium catalyst rapidly gave 2′-amino-2′-deoxyuridine (**3**) that was obtained in crystalline form in 98% yield. Titration of **3** indicated pK_a values of 9.2 and 6.2 which

(1) For a review, see J. J. Fox, K. A. Watanabe, and A. Block in *Progr. Nucl. Acid Res. Mol. Biol.*, **5**, 251 (1966).

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(3) M. L. Wolfrom and M. W. Winkley, *J. Org. Chem.*, **32**, 1823 (1967).

(4) (a) B. R. Baker, R. E. Schaub, and H. M. Kissman, *J. Amer. Chem. Soc.*, **77**, 5911 (1955); (b) H. M. Kissman, A. S. Hoffman, and M. J. Weiss, *J. Med. Chem.*, **6**, 407 (1963); (c) L. Goldman and J. M. Marsico, *ibid.*, **6**, 413 (1963).

(5) (a) H. M. Kissman and M. J. Weiss, *J. Amer. Chem. Soc.*, **80**, 2575 (1958); (b) J. P. Horwitz, J. A. Tomson, J. A. Urbanski, and J. Chua, *J. Org. Chem.*, **27**, 3045 (1962).

(6) (a) N. Miller and J. J. Fox, *ibid.*, **29**, 1772 (1964); (b) J. P. Horwitz, J. Chua, and M. Noel, *ibid.*, **29**, 2076 (1964).

(7) T. Sekiya and T. Ukita, *Chem. Pharm. Bull.*, **15**, 1503 (1967).

(8) D. M. Brown, D. B. Parihar, and Sir A. Todd, *J. Chem. Soc.*, 4242 (1958).

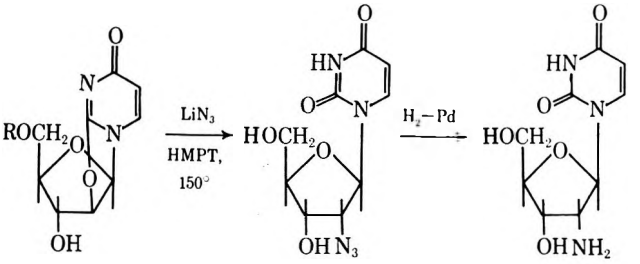
(9) A. Hampton and A. W. Nichol, *Biochemistry*, **5**, 2076 (1966).

(10) K. K. Ogilvie and D. Iwacha, *Can. J. Chem.*, **47**, 495 (1969).

(11) J. J. Fox and N. C. Miller, *J. Org. Chem.*, **28**, 936 (1963).

(12) See H. Normant, *Bull. Soc. Chim. Fr.*, 791 (1968), for a review on the utilities of HMPT.

are in good agreement with those of uridine (pK_a = 9.2)[13] and of various 2′-amino-2′-deoxy sugars (pK's = 6.1–7.7).[14]



1a, R = H
b, R = Ac

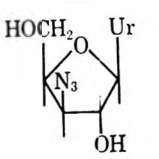
2

3

Brown, *et al.*,[15] have shown that the reaction of **1a** with sodium ethyl sulfide gives 1-(3-deoxy-3-ethylthio-β-D-xylofuranosyl)uracil rather than the desired 2′-2′-deoxy-2′-ethylthiouridine, this result presumably arising from intervention of the 2′,3′-*ribo*-epoxide. Accordingly, it was of importance to prove that the introduction of azide led to the desired compound **2** rather than to the 3′-azide-3′-deoxyxylo epimer (**4**). Confirmation of the proposed structures was provided by nmr spectroscopy. Thus, the acyl derivatives of **2** (**9**) showed extensive deshielding of C_3′H relative to that of C_2′H. The spectrum of the 5′-*O*-trityl derivative of **2** (to be described as part of a separate study) in DMSO-d_6 was even more convincing since C_3′H (4.44 ppm, q, 1, $J_{2',3'} = J_{3',4'} = J_{H,OH}$ = 6 Hz) could be readily shown to be spin coupled to the 3′-hydroxyl group (5.97 ppm, d, 1, $J_{H,OH}$ = 6 Hz). The assignments of sugar proton resonances were confirmed by spin decoupling experiments. These results are compatible only with the presence of a free 3′-hydroxyl group in **2** and exclude the alternative structure **4**.

The amino alcohols **3** and **8** were also found to be rapidly oxidized by periodate, 0.8 equiv of oxidant being consumed within 7 sec at pH 6.4. While some uncertainty attends the definitive assignment of configuration to cyclic amino alcohols by periodate oxidation,[16] this very rapid oxidation also supports the cis configuration for **3** and **8**. Under similar conditions, the periodate oxidation of 9-(3-amino-3-deoxy-β-D-arabinofuranosyl)adenine, a nucleoside containing a 2′,3′-*trans*-amino alcohol moiety kindly provided by Dr. Elmer Reist and the Cancer Chemotheraphy National Service Center, was slower, consumption of 0.65 and 0.9 equiv of oxidant requiring 10 and 100 min, respectively. This, once again, strongly supports our assigned configuration.

The availability of this amino alcohol **3** made it attractive to attempt to combine several of the structural features of the antibiotics puromycin and chloramphenicol by preparation of 2′-dichloroacetamideo-2′-deoxyuridine (**5**). The latter compounds was readily formed and isolated in 74% yield by heating a solution of **3** and excess methyl dichloroacetate in ethanol.



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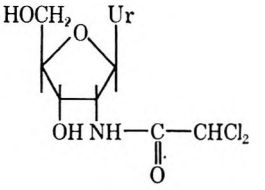
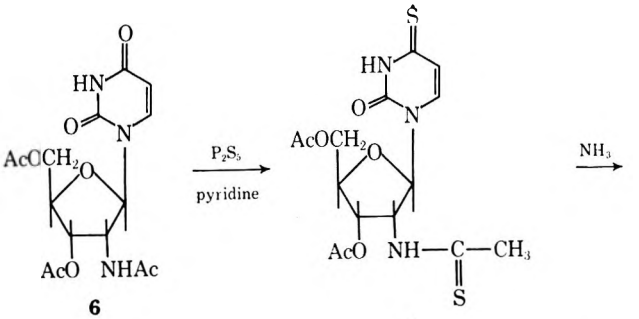


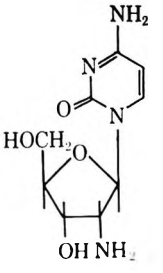
5

Conversion of **3** into the related 2′-amino-2′-deoxycytidine (**8**) was accomplished by the general thiation–amination procedure of Fox, *et al.*[17] Thus, acetylation of **3** gave the crystalline triacetate **6** in 90% yield. Subsequent reaction with phosphorus pentasulfide in refluxing anhydrous pyridine led to thiation of both the uracil ring and of the 2′-acetamido function. This reaction, or the following chromatography, was, however, accompanied by partial loss of one of the *O*-acetyl groups as shown by tlc and infrared spectroscopy. This crude material was satisfactory for subsequent steps but in order to characterize the dithio compound **7** the mixture was reacetylated, giving **7** as a chromatographically homogeneous and analytically pure, amorphous, yellow solid. It is interesting to note that the presence of a 2′-acylamido function has a rather striking effect upon the conformation of the furanose sugar ring. Thus, while the nmr spectra of most simple uridine derivatives show values of $J_{1',2'}$ ranging from 0 to 6 Hz the 2′-acetamido compound **6**, the 2′-dichloroacetamido compound **4**, and the 2′-thioacetamido **7** show $J_{1',2'}$ values of 8.5, 8, and 9 Hz, respectively. We have previously noted[18] that the 1′,2′ coupling constants of certain 2′- and 3′-*O*-trityluridines are also as large as 8 Hz but we are not aware of values as large as 9 Hz as in **7**. Treatment of crude **7** with methanolic ammonia at 120° both converted the thiouracil ring to a cytosine derivative and cleaved the *O*-acetyl and the 2′-thioacetamide groups with formation of the desired 2′-amino-2′-deoxycytidine (**8**). A similar cleavage of a thioacetamide has previously been described by Watanabe, *et al.*, in the case of a 3′-thioacetamido-β-D-glucopy-



6

7



8

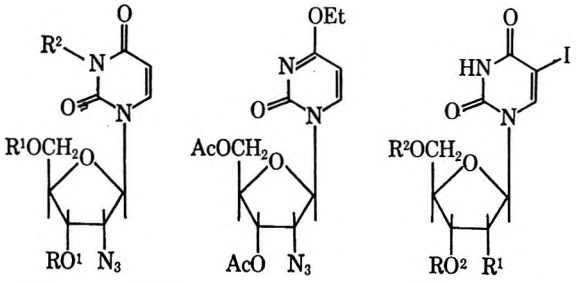
(13) P. A. Levene and H. S. Simms, *J. Biol. Chem.*, **65**, 519 (1925).
(14) (a) C. B. Barlow, R. D. Guthrie, and A. M. Prior, *Carbohyd. Res.*, **10**, 481 (1969); (b) S. Inouye, *Chem. Pharm. Bull.*, **16**, 1134 (1968).
(15) D. M. Brown, D. B. Parihar, Sir A. Todd, and S. Varadarajan, *J. Chem. Soc.*, 3028 (1958).
(16) G. E. McCasland and D. A. Smith, *J. Amer. Chem. Soc.*, **73**, 5164 (1951).
(17) J. J. Fox, D. Van Praag, I. Wempen, I. L. Doerr, L. Cheong, J. E. Knoll, M. L. Eidinoff, A. Bendich, and G. B. Brown, *ibid.*, **81**, 178 (1959).
(18) A. F. Cook and J. G. Moffatt, *ibid.*, **89**, 2697 (1967).

ranosyl nucleoside.[19] In this way, crystalline **8** was obtained in 24% overall yield from **6** and was characterized by elemental analysis and spectral properties.

As a possible alternative route to **8** and to 2′-azido-2′-deoxycytidine we have also reacted 3′,5′-di-*O*-acetyl-2′-azido-2′-deoxyuridine (**9a**) with thionyl chloride and a catalytic amount of DMF in chloroform according to the general method of Žemlicka and Sŏrm.[20] While the starting material disappeared with formation of the intermediate 4-*O*-chlorodimethylaminomethyl adduct as judged by its tlc behavior and ultraviolet spectrum,[20] the desired 4-chloro-1,2-dihydro-2-pyrimidinone nucleoside was isolated. The only crystalline compound isolated in low yield was 4-ethoxy-1-(3,5-di-*O*-acetyl-2-azido-2-deoxy-β-D-ribofuranosyl)-2(1*H*)-pyrimidinone (**10**) which must have arisen from the presence of traces of ethanol used as stabilizer in the chloroform. Further treatment of the crude product with ethanol raised the yield of **10** to 19%. While aminolysis of **10** would doubtless lead to the desired 2′-azido-2′-deoxycytidine we have not explored this route further.

The reaction of **9a** with phosphorus pentasulfide and pyridine led not only to thiation of the uracil ring but also to reduction of the azido function, probably due to the presence of hydrogen sulfide which is known to effect such reduction.[21] Subsequent amination of the crude thiation product led directly to 2′-amino-2′-deoxycytidine (**8**) in an overall yield of 39% from **9a**. This, thus, becomes the most direct route to **8**.

Reaction of **2** with benzoyl chloride did not give the desired 2′,3′-di-*O*-benzoyl derivative **9b** but rather a tribenzoyl derivative, presumably **9c** that would not be suitable for further transformation to the cytosine series. It did, however, prove possible to selectively remove the *N*-benzoyl group by brief treatment with hot pyridine containing 2% water giving the desired **9b**. This simple procedure may well prove to be useful during benzoylation of other uridine derivatives.



9a, R¹ = Ac; R² = H
b, R¹ = Bz; R² = H
c, R¹ = R² = Bz

10

11a, R¹ = N₃; R² = Ac
b, R¹ = NH₂; R² = H

Since it was of interest to introduce various substituents into the 5 position of the pyrimidine ring of **3**, we wished to prepare, as a common intermediate, a 2′-amino-2′-deoxy-5-halouridine. Direct halogenation of **3** appeared to be difficult due to side reactions of the amino group and so we preferred to attempt halogenation of the azidonucleoside **9a**. Preliminary experiments on the reaction of **9a** in chloroform with *N*-bromosuccinimide in the presence of benzoyl peroxide[22] indeed gave a mixture of two 5-bromonucleosides in 35% yield as shown by nmr and ultraviolet spectra. Since this mixture could be completely reduced to a mixture of **3** and its 5-bromo derivative with sodium borohydride (see below) one of the products was presumably the consequence of some side reaction with the azido function. Iodination of **9a** using *N*-iodosuccinimide in the presence of a catalytic amount of di-*n*-butyl disulfide,[23] however, was more effective and the pure 5-iodonucleoside **11a** was obtained in 51% yield. Selective catalytic reduction of the azido group of **11a** did not seem possible due to concomitant hydrogenolysis of the iodo group and attempted reduction of **2** with diborane, which has been used successfully with aliphatic α-iodoazides[24] led only to a product showing end absorption in its ultraviolet spectrum. Reduction of **2** using sodium borohydride in hot isopropyl alcohol[25] did, however, give crystalline **3** in 42% yield and encouraged us to apply the same reaction to **11a**. Here the reaction was less effective and even after prolonged reaction unreacted azido compounds remained and considerable loss of the 5-iodo function occurred. The desired crystalline 2′-amino-2′-deoxy-5-iodouridine (**11b**) was obtained in only 18% yield.

Further transformations of this compound await the development of a more efficient and selective method for reduction of the azido group. The preparation and some biological properties of further compounds derived from 2′-amino-2′-deoxy pyrimidine nucleosides will be described at a later date.

Experimental Section

General Methods.—Thin layer chromatography (tlc) was carried out on 0.25-mm layers of Merck silica gel GF and products were visualized by ultraviolet absorption or by spraying with a 5% solution of ammonium molybdate in 10% sulfuric acid followed by heating at 150°. Preparative tlc was done on 20 × 100 cm glass plates coated with a 1.3-mm layer of Merck silica gel HF and column chromatography on Merck silica with 0.05–0.20-mm particles. Nuclear magnetic resonance (nmr) spectra were determined using a Varian HA-100 spectrometer and are reported in parts per million downfield from an internal standard of TMS. The assignments of sugar proton resonances were confirmed by spin-decoupling experiments. Mass spectra were obtained using an Atlas CH-4 spectrometer with a direct inlet system. Optical rotatory dispersion spectra were obtained with a Jasco ORD/UV-5 instrument. Instrumental analyses are by the staff of the Analytical Laboratory of Syntex Research. We are particularly grateful to Dr. M. L. Maddox and Miss J. Tremble and to Dr. L. Tokes for their cooperation with nmr and mass spectrometry, respectively. Periodate oxidations were followed spectrophotometrically at 310 mμ.[26] Elemental analyses were obtained from Dr. A. Bernhardt, Mülheim, Germany, and from the Analytical Laboratories of the University of California, Berkeley. Melting points are corrected.

2,2′-Anhydro-1-(β-D-arabinofuranosyl)uracil[1] (**1a**).—Uridine (38 g) and diphenyl carbonate (44.4 g) were dissolved in hexamethylphosphoramide (150 ml) and, after addition of sodium bicarbonate (1.0 g), the mixture was heated at 150° for 20 min. Tlc (ethyl acetate–methanol, 1:1) then showed essentially only **1a** and a slightly slower spot with a uv spectrum similar to **1a**'s. The mixture was cooled, added to water (1.2 l.), and extracted

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three times with chloroform. The aqueous phase was evaporated to dryness and the residue crystallized from methanol giving 31.0 g (88%) of pure **1a** with mp 238–240° and spectral properties identical with that of an authentic sample.[9]

2′-Azido-2′-deoxyuridine (2).—A suspension of **1a** (2.26 g, 10 mmol) and lithium azide (3.50 g, 71 mmol) in anhydrous hexamethylphosphoramide (40 ml) was rapidly stirred in a 150° oil bath until most of the solid dissolved. Benzoic acid (1.22 g, 10 mmol) was then added and heating was continued for 15 min during which time the solution became very dark. The mixture was rapidly cooled, diluted with water (80 ml), and extracted with chloroform (200 ml). The chloroform extracts were back-extracted twice with water (80 ml each) and the combined aqueous solutions were extracted three times with chloroform and then evaporated to dryness leaving 8.0 g of a dark oil. This was dissolved in a mixture of acetone (80 ml) and methanol (30 ml), filtered, and applied to a 12.5 × 12.5 cm column of silicic acid. Elution with acetone followed by charcoal treatment gave 1.34 g (50%) of **2** as a colorless, tlc homogeneous (ethyl acetate–acetone, 1:1) syrup that has not been obtained crystalline: λ_{max}^{MeOH} 260 mμ (ε 9500); ν_{max}^{KBr} 2120 cm^{-1}; nmr (DMSO-d_6) 3.62 (m, 2, $C_{5'}H_2$), 3.89 (m, 1, $C_{4'}H$), 4.03 (t, 1, $J_{1',2'} = J_{2',3'} =$ 5.5 Hz, $C_{2'}H$), 4.31 (t, 1, $J_{2',3'} = J_{3',4'} =$ 5.5 Hz, $C_{3'}H$), 5.67 (d, 1, $J_{5,6} =$ 8 Hz, C_5H), 5.90 (d, 1, $J_{1',2'} =$ 5.5 Hz, $C_{1'}H$), 7.90 ppm (d, 1, $J_{5,6} =$ 8 Hz, C_6H).

Anal. Calcd for $C_9H_{11}N_5O_5$: C, 40.15; H, 4.12; N, 26.01. Found: C, 39.97; H, 4.41; N, 26.15.

2′-Amino-2′-deoxyuridine (3).—A solution of **2** (1.34 g, 5 mmol) in methanol was vigorously stirred in a hydrogen atmosphere with 10% palladium-on-carbon catalyst (700 mg) for 40 min. The mixture was filtered and evaporated leaving 1.18 g (98%) of crystalline **3** with mp 192–193°. A sample recrystallized twice from ethanol had mp 197–198°: $\lambda_{max}^{H_2O}$ 261 mμ (ε 9500); ORD (H_2O) positive Cotton effect with a peak at 275 mμ (Φ −2000°), and a trough at 242 (Φ −8600°); nmr (DMSO-d_6) 3.62 (m, 2, $C_{5'}H_2$), 3.90 (br q, 1, $J_{4',5'} \simeq$ 4 Hz, $J_{3',4'} =$ 5 Hz, $C_{4'}H$), 4.03 (t, 1, $J_{1',2'} = J_{2',3'} =$ 5.5 Hz, $C_{2'}H$), 4.31 (br t, 1, $J_{2',3'} =$ 5.5 Hz, $J_{3',4'} =$ 5 Hz, $C_{3'}H$), 5.67 (d, 1, $J_{5,6} =$ 8 Hz, C_5H), 5.90 (*d*, 1, $J_{1',2'} =$ 5.5 Hz, $C_{1'}H$), 7.90 ppm (d, 1, $J_{5,6} =$ 8 Hz, C_6H).

Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.39; N, 17.28. Found: C, 44.33; H, 5.44; N, 17.44.

2′-Dichloroacetamido-2′-deoxyuridine (5).—A solution of **3** (243 mg, 1 mmol) and methyl dichloroacetate (1 ml) in methanol (10 ml) was heated under reflux for 6 hr. Upon cooling, crystalline **5** was obtained and after recrystallization from ethanol the yield was 260 mg (74%) with mp 246–247°: $\lambda_{max}^{H_2O}$ 262 mμ (ε 9300); ORD (H_2O) positive Cotton effect with a peak at 277 mμ (Φ +14,700°), crossover at 258 mμ, and a trough at 240 mμ (Φ −16,400°); nmr (pyridine-d_5) 3.97 (q, 1, $J_{gem} =$ 12 Hz, $J_{4',5'a} =$ 3 Hz, $C_{5'a}H$), 4.12 (q, 1, $J_{gem} =$ 12 Hz, $J_{4',5'b} =$ 3 Hz, $C_{5'b}H$), 4.50 (br s, 1, $C_{4'}H$), 4.86 (br d, 1, $J_{2',3'} =$ 5.5 Hz, $J_{2',4'} \simeq$ 1 Hz, $C_{3'}H$), 5.32 (br h, 1, $J_{1',2'} = J_{2',NH} =$ 8 Hz, $J_{2',3'} =$ 5.5 Hz, $C_{2'}H$), 5.73 (d, 1, $J_{5,6} =$ 8 Hz, C_5H), 6.83 (d, 1, $J_{1',2'} =$ 8 Hz, $C_{1'}H$), 6.83 (s, 1, $COCHCl_2$), 8.37 (d, 1, $J_{5,6} =$ 8 Hz, C_6H), 9.60 ppm (br d, 1, $J_{2'NH} =$ 8 Hz, $NHCOCHCl_2$).

Anal. Calcd for $C_{11}H_{13}N_3O_6Cl_2$: C, 37.30; H, 3.70; N, 11.86; Cl, 20.03. Found: C, 37.40; H, 3.91; N, 11.61; Cl, 19.41.

2′-Acetamido-3′,5′-di-*O*-acetyl-2′-deoxyuridine (6).—A solution of **3** (850 mg, 3.5 mmol), acetic anhydride (4 ml), and pyridine (2 ml) in anhydrous dimethylformamide (20 ml) was stored overnight at room temperature. After addition of methanol the solution was evaporated to dryness and the residue was reevaporated with methanol giving a crystalline residue that was recrystallized from methanol giving 1.16 g (90%) of **6** with mp 199–200°: λ_{max}^{MeOH} 259 mμ (ε 9600); ν_{max}^{KBr} 1755, 1710, 1685 cm^{-1}; nmr (DMSO-d_6) 1.81 (s, 3, NAc), 2.06 and 2.12 (s, 3, OAc), 4.26 (s, 3, $C_{4'}H$ and $C_{5'}H_2$), 4.73 (q, 1, $J_{1',2'} =$ 8.5 Hz, $J_{2',3'} =$ 6 Hz, $C_{2'}H$), 5.12 (br d, 1, $J_{2',3'} =$ 6 Hz, $J_{3',4'} =$ 1 Hz, $C_{3'}H$), 5.74 (d, 1, $J_{5,6} =$ 8 Hz, C_5H), 5.90 (d, 1, $J_{1',2'} =$ 8.5 Hz, $C_{1'}H$), 7.70 (d, 1, $J_{5,6} =$ 8 Hz, C_6H), 9.18 (br d, 1, $J_{2',NH} =$ 9 Hz, NHAc), 11.37 ppm (br s, 1, N^3H).

Anal. Calcd for $C_{15}H_{19}N_3O_8$: C, 48.78; H, 5.18; N, 11.37. Found: C, 48.88; H, 5.31; N, 11.48.

3′,5′-Di-*O*-acetyl-2′-deoxy-2′-thioacetamido-4-thiouridine (7).—Phosphorus pentasulfide (440 mg, 2 mmol) and **6** (370 mg, 1 mmol) were dissolved in anhydrous pyridine and heated under reflux for 80 min. After cooling, the red solution was decanted from some insoluble material and evaporated to dryness. The residue was dissolved in chloroform and washed with water, 0.2 *N* sulfuric acid, and sodium bicarbonate prior to preparative tlc using ethyl acetate. Elution of the major fast-moving band gave 300 mg (~80%) of a yellow foam that was shown by tlc to have partially lost one of the *O*-acetyl groups. Reacetylation with acetic anhydride in pyridine for 1 hr gave homogeneous **7** as a noncrystalline yellow solid: λ_{max}^{MeOH} 268 mμ (ε 12,400), 330 (17,500); ν_{max}^{KBr} 1750, 1715, 1625 cm^{-1}; nmr ($CDCl_3$) 2.19 and 2.21 (s, 3, OAc), 2.54 (s, 3, CH_3CSNH), 4.40 (m, 3, $C_{4'}H$ and $C_{5'}H_2$), 5.55 (m, 1, $C_{2'}H$), 6.45 (d, 1, $J_{1',2'} =$ 9 Hz, $C_{1'}H$), 6.49 (d, 1, $J_{5,6} =$ 8 Hz, C_5H), 7.40 (d, 1, $J_{5,6} =$ 8 Hz, C_6H), 8.23 (br d, 1, $J_{2',NH} =$ 8 Hz, $NHCSCH_3$), 8.65 ppm (br s, 1, N^3H).

Anal. Calcd for $C_{15}H_{19}N_3O_6S_2$: C, 44.87; H, 4.76; N, 10.46; S, 15.97. Found: C, 44.61; H, 4.94; N, 9.82; S, 15.58.

2′-Amino-2′-deoxycytidine (8). A.—Thiation of **6** (1.11 g, 3 mmol) was carried out exactly as above and the crude, washed chloroform solution was evaporated to dryness. The residue was dissolved in saturated methanolic ammonia and heated in a stainless steel bomb at 120° for 40 hr. After filtration and evaporation of the solvent, the residue was dissolved in water (50 ml), stirred with Dowex AG-1 (OH^-) resin (15 ml), and filtered. Evaporation of the filtrate left a colorless syrup that crystallized giving 200 mg (24% from **6**) of **8**. After recrystallization from ethanol the melting point was 196–197°: $\lambda_{max}^{pH\ 2}$ 276 mμ (ε 11,900); $\lambda_{max}^{pH\ 12}$ 270 mμ (8200), 230 (7600); ORD (0.01 *N* HCl) positive Cotton effect with a peak at 290 mμ (Φ +6200°), crossover at 274 mμ, and a trough at 225 mμ (Φ −7400°); nmr (DMSO-d_6) 3.23 (q, 1, $J_{1',2'} =$ 7 Hz, $J_{2',3'} =$ 5 Hz, $C_{2'}H$), 3.55 (br s, 2, $C_{5'}H_2$), 3.85 (m, 2, $C_{3'}H$ and $C_{4'}H$), 5.67 (d, 1, $J_{1',2'} =$ 7 Hz, $C_{1'}H$), 5.71 (d, 1, $J_{5,6} =$ 7.5 Hz, C_5H), 7.12 (br s, 2, NH_2), 7.76 ppm (d, 1, $J_{5,6} =$ 7.5 Hz, C_6H).

Anal. Calcd for $C_9H_{14}N_4O_4$: C, 44.44; H, 6.21; N, 23.00. Found: C, 44.65; H, 6.01; N, 22.90.

B.—A solution of **9a** (0.45 mmol) and phosphorus pentasulfide (120 mg) in pyridine (20 ml) was heated under reflux for 3 hr. The mixture was evaporated, dissolved in ethyl acetate, washed with water, and evaporated to dryness. The residue was treated in a steel bomb with saturated methanolic ammonia at 120° for 2 days and worked up as in A giving 42 mg (39%) of **8**.

3′,5′-Di-*O*-acetyl-2′-azido-2′-deoxyuridine (9a).—A solution of **2** (135 mg, 0.5 mmol) in dimethylformamide (5 ml) was treated overnight with acetic anhydride (1 ml) and pyridine (0.5 ml). The solvent was evaporated and a solution of the residue in chloroform was washed with water, dried, and purified by preparative tlc using ethyl acetate–ether (1:1). Elution of the main band gave 130 mg (73%) of **9a** as a white foam: λ_{max}^{MeOH} 259 mμ (ε 9200); ORD (MeOH) positive Cotton effect with a peak at 280 mμ (Φ +4200°), crossover at 268 mμ, and a trough at 245 mμ (Φ −9400°); nmr ($CDCl_3$) 2.11 and 2.18 (s, 3, OAc), 4.37 (m, 4, $C_{2'}H$, $C_{4'}H$ and $C_{5'}H_2$), 5.21 (m, 1, $C_{3'}H$), 5.78 (d, 1, $J_{5,6} =$ 8 Hz, C_5H), 5.88 (d, 1, $J_{1',2'} =$ 4.5 Hz, $C_{1'}H$), 7.48 ppm (d, 1, $J_{5,6} =$ 8 Hz, C_6H).

Anal. Calcd for $C_{13}H_{15}N_5O_7$: C, 44.19; H, 4.28; N, 19.82. Found: C, 44.06; H, 4.16; N, 19.63.

4-Ethoxy-1-(3,5-di-*O*-acetyl-2-azido-2-deoxy-β-D-ribofuranosyl)-2(1*H*)-pyrimidinone (10).—A solution of **9a** (354 mg, 1 mmol) in a mixture of chloroform (unpurified, 5 ml), dimethylformamide (0.05 ml), and thionyl chloride (0.8 ml) was heated under reflux for 6 hr at which point tlc (ethyl acetate–ether, 1:1) showed disappearance of the starting material and formation of a main, fast-moving product. Preparative tlc of the evaporated mixture using the above solvent gave a syrup (110 mg) that was crystallized from chloroform–hexane giving 25 mg (7%) of **10** with mp 109–110°. The mother liquors were then heated under reflux with ethanol for 7 hr, evaporated, and purified by tlc as above giving a further 45 mg (12%) of crystalline **10**: λ_{max}^{MeOH} 275 mμ; nmr ($CDCl_3$) 1.36 (t, 3, $J =$ 6.5 Hz, OCH_2CH_3), 2.10 and 2.16 (s, 3, OAc), 4.40 (m, 6, $C_{2'}H$, $C_{4'}H$, $C_{5'}H_2$, and OCH_2CH_3), 5.88 (d, 1, $J_{5,6} =$ 7.5 Hz, C_5H), 5.89 (d, 1, $J_{1',2'} =$ 3 Hz, $C_{1'}H$), 7.78 ppm (d, 1, $J_{5,6} =$ 7.5 Hz, C_6H).

Anal. Calcd for $C_{15}H_{19}N_5O_7$: C, 47.24; H, 5.02; N, 18.36. Found: C, 46.95; H, 4.83; N, 18.02.

3′,5′-Di-*O*-acetyl-2′-azido-2′-deoxy-5-iodouridine (11a).—A solution of **9a** (700 mg, 2 mmol) in DMSO (20 ml) containing di-*n*-butyl disulfide (0.1 ml) was added slowly to a solution of *N*-iodosuccinimide (1.8 g, 8 mmol) in DMSO (20 ml) and kept at 20° for 24 hr. Tlc (chloroform–acetone, 4:1) showed incomplete reaction, and, after 24 and 48 hr, further portions of *N*-iodosuccinimide (1.8 g) and di-*n*-butyl disulfide (0.1 ml) were added. After dilution with ethyl acetate the solution was extracted with saturated aqueous sodium chloride, sodium bicarbonate, and

sodium thiosulfate. Preparative tlc using the above solvent gave 490 mg (51%) of 11 as a homogeneous syrup: λ_{max}^{MeOH} 282 mμ (ε 7500), 215 (9700); ν_{max}^{KBr} 2120 cm^{-1} (N_3); nmr ($CDCl_3$) 2.21 and 2.25 (s, 3, OAc), 4.33 (q, 1, $J_{1',2'}$ = 4 Hz, $J_{2',3'}$ = 6 Hz, C_2'H), 4.41 (m, 3, C_4'H and C_5'H_2), 5.23 (m, 1, C_3'H), 5.93 (d, 1, $J_{1',2'}$ = 4 Hz, C_1'H), 7.97 ppm (s, 1, C_6H); mass spectrum (70 eV) *m/e* 479 (M^+), 451 (M − N_2), 409 (M − N_2 − C_2H_2O), 391 (M − AcOH), 242 (M − base), 238 (base + H), 214 (sugar − N_2), 172 (sugar − N_2 − C_2H_2O).

Anal. Calcd for $C_{13}H_{14}N_5O_7I$: C, 32.58; H, 2.94. Found: C, 32.95; H, 3.11.

2'-Amino-2'-deoxy-5-iodouridine (11b).—A solution of 11a (420 mg, 0.87 mmol) and sodium borohydride (300 mg) in 2-propanol (60 ml) was heated under reflux for 3 days. After evaporation of the solvent the residue was dissolved in water, brought to pH 6 with acetic acid, evaporated, and repeatedly coevaporated with methanol. The final residue was dissolved in water and passed through a column containing Dowex 50 (H^+) resin (60 ml). The eluate and washings contained 2250 optical density units (262 mμ) of 2'-azidonucleosides. Elution with 1 *N* ammonium hydroxide gave 2000 optical density units (273 mμ) of 2'-aminonucleosides. After evaporation to dryness, this material (200 mg) was purified by preparative tlc using acetone giving two main bands. The slower band (70 mg) consisted of 2'-amino-2'-deoxyuridine, while the faster band contained 60 mg (18%) of 12 which was crystallized from methanol with mp 204.5–205.5°: $\lambda_{max}^{H_2O}$ 287 mμ (ε 7200), 216 (11,900); $\lambda_{max}^{pH\ 13}$ 277 mμ (ε 5500); ORD (H_2O) multiple Cotton effect with a peak at 280 mμ (Φ +3700°) a trough at 250 mμ (Φ +3200°), a peak at 217 mμ (Φ 14,400°), and crossover at 205 mμ; nmr (pyridine-d_5) 4.01 (q, 1, $J_{1',2'}$ = 6.5 Hz, $J_{2',3'}$ = 5 Hz, C_2'H), 4.07 (AB of ABM, 2, J_{gem} = 14 Hz, C_5'H_2), 4.62 (br q, 1, $J_{4',5'a}$ = $J_{4',5'b}$ = $J_{3',4'}$ = 3 Hz, C_4'H), 4.77 (q, 1, $J_{2',3'}$ = 5 Hz, $J_{3',4'}$ = 5 Hz, $J_{3',4'}$ = 3 Hz, C_3'H), 6.52 (d, 1, $J_{1',2'}$ = 6.5 Hz, C_1'H), 9.10 ppm (s, 1, C_6H).

Anal. Calcd for $C_9H_{12}N_3O_5I$: C, 29.28; H, 3.28; N, 11.38. Found: C, 28.86; H, 3.33; N, 11.29.

2'-Azido-3',5'-di-*O*-benzoyl-2'-deoxyuridine (9b).—A solution of 2 (950 mg, 3.5 mmol) and benzoyl chloride (1.4 g, 10 mmol) in pyridine (10 ml) was kept for 16 hr at 23°. After addition of water, the solution was diluted with ethyl acetate, extracted with sodium bicarbonate, dried, and evaporated leaving a brown syrup. Purification by preparative tlc using benzene–ethyl acetate (9:1) gave 1.22 g (60%) of the N^2,3'-*O*,5'-*O*-tribenzoate (9b) as a homogeneous foam with λ_{max} 250 mμ (sh), 232, and unchanged in alkali: nmr ($CDCl_3$) 4.4–4.8 (m, 4, C_2', C_3', and C_5'H's), 5.60 (t, 1, $J_{2',3'}$ = $J_{3',4'}$ = 5.5 Hz, C_3'H), 5.66 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.97 (d, 1, $J_{1',2'}$ = 4 Hz, C_1'H), 7.4–7.7 and 7.9–8.2 ppm (m, 16, aromatic and C_6H).

This compound (1.2 g) was dissolved in pyridine (10 ml) containing 2% water and heated under reflux for 1 hr. Evaporation to dryness, preparative tlc using ether–hexane (85:15) and crystallization from chloroform–hexane gave 735 mg (75%) of 9b with mp 153–154°: λ_{max}^{MeOH} 256 mμ (ε 11,900), 231 (28,800); nmr ($CDCl_3$) 4.49 (q, 1, $J_{1',2'}$ = 4 Hz, $J_{2',3'}$ = 6 Hz, C_2'H), 4.6–4.8 (m, 3, C_4'H and C_5'H_2), 5.63 (t, 1, $J_{2',3'}$ = $J_{3',4'}$ = 6 Hz, C_3'H), 5.64 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.04 (d, 1, $J_{1',2'}$ = 4 Hz, C_1'H), 7.4–7.7 and 8.0–8.2 ppm (m, 11, aromatic and C_6H).

Anal. Calcd for $C_{23}H_{19}N_5O_7$: C, 57.86; H, 4.01; N, 14.66. Found: C, 57.77; H, 4.06; N, 14.80.

Registry No.—**2**, 26929-65-7; **3**, 26889-39-4; **5**, 26889-40-7; **6**, 26889-41-8; **7**, 26929-67-9; **8**, 26889-42-9; **9a**, 26889-43-0; **9b**, 26889-44-1; **10**, 26889-45-2; **11a**, 26889-46-3; **11b**, 26889-47-4.

Macrocyclic Polyether Sulfides

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Macrocyclic polyether sulfides have been synthesized and some of their properties have been determined. These compounds contain two to four oxygen atoms and two to four sulfur atoms in the polyether–polysulfide ring. Formation of complexes of the macrocyclic polyether sulfides with alkali, alkaline earth, and silver cations is reported.

The preparation and properties of a number of macrocyclic polyethers derived from aromatic vicinal diols have been previously reported.[1] It was shown that certain of these compounds, particularly those containing five to ten oxygen atoms in the polyether ring, form stable complexes with cations including those of the alkali and alkaline earth metals and silver. In a continuation of this work, some macrocyclic polyethers in which two to four –O– linkages are replaced by –S– linkages were synthesized in order to determine the effects of this change on the complexing of cations. Differences were to be expected because oxygen is a smaller atom than sulfur, the C–O–C bond angle is greater than the C–S–C bond angle, and the electronegativity of oxygen is higher than that of sulfur which makes the C–S bond less ionic than the C–O bond. It is the purpose of this paper to report on the preparation of the macrocyclic polyether sulfides and to give a brief description of some of their properties.

4,7,10-Trioxa-1-thiacyclododecane, 4,10-dioxa-1,7-dithiacyclododecane, 4,7,13,16-tetraoxa-1,10-dithiacyclooctadecane, and 4,7,10,16,19,22-hexaoxa-1,13-dithiacyclotetracosane,[2] 1,3,5,7,9-oxatetrathiacyclodecane, and 1,3,5,7,9,11-oxapentathiacyclododecane[3] have been previously described, but their tendency to form complexes with cations is not mentioned.

The code letters and the structural formulas of the compounds described in this paper are shown in Figure 1. The digits within the diagrams indicate the total number of atoms in the polyether ring. The full names of the compounds and their preparation are given in the Experimental Section.

Results and Discussion

In general, the compounds were prepared by refluxing in 1-butanol under nitrogen cyclic vicinal mercaptophenol or dithiols with equivalent proportions of terminally substituted ether dichlorides and sodium hydroxide. The yields, melting points, and analytical data are shown in Table I. No attempt was made to maximize the yields or develop methods of recovery.

The infrared spectra of the compounds showed the

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absence of OH and the presence of the appropriate ether linkages. The nmr spectra were consistent with the proposed structures. The ultraviolet spectra of the compounds which absorb in the region of 220–400 mμ are summarized in Table II, as well as the changes induced in them by the addition of excess silver nitrate.

The ultraviolet spectra of the macrocyclic polyethers in methanol show a single absorption peak at about 275 mμ with an extinction coefficient approximately 2100–2600 per aromatic ring.[1] The spectra of the aromatic macrocyclic polyether sulfides having at least one sulfur atom attached to the aromatic ring have a strong peak at about 255 mμ and another, often evident as a shoulder, in the region of 280–300 mμ. The spectra of such compounds, B, C, E, F, and G, are profoundly affected by the addition of silver nitrate. The aromatic macrocyclic polyether sulfide, D, and sulfite, J, with no sulfur attached to the aromatic ring have spectra like those of the aromatic cyclic polyethers, and the effect of silver nitrate is also similar.

The ultraviolet spectra of all these compounds are little affected by the addition of an excess of the salts of the alkali and alkaline earth elements, suggesting that the interaction between the compounds and the cations of these salts in methanol is not strong.[1]

Crystalline complexes of silver nitrate with E and H were obtained. However, no crystalline complex of potassium thiocyanate and E was formed when an attempt was made to prepare it by the method which gave the crystalline complex of potassium thiocyanate with the macrocyclic polyether dibenzo-18-crown-6.[1]

The extraction method described below is a convenient way of comparing the relative complexing powers of organic compounds for different cations. This method has these advantages over the previously employed spectral method[1]: complexing efficiencies can be ranked numerically, and saturated compounds which do not absorb in the region of 220–400 mμ can also be evaluated.

When an aqueous solution of an alkali metal hydroxide or salt containing a very low concentration of the picrate of the same cation is mixed with an equal volume of an immiscible organic solvent, nearly all the picrate is present in the yellow aqueous phase and the organic phase remains substantially colorless. If a complexing agent is added to the system (by dissolving in the organic solvent), the complexed picrate transfers to the organic phase, the extent depending on the effectiveness of the polyether as a complexing agent for the cation (assuming no complication due to lack of solubility). If the additive is ineffective, the organic phase will be colorless; if the complexing agent is very powerful, most of the color will be in the organic phase, the intensity of which can be quantitatively determined spectrophotometrically by means of the picrate absorption band. The efficiencies of the complexing agents will lie between these two limits and can be expressed as percentage extracted. The stoichiometry of the extractable complex is 1:1 in respect to a univalent cation and picrate anion, hence, the maximum extraction is limited by the component present at the lowest concentration. For this reason, per cent extraction always means per cent of the extractable maximum.

The results obtained with some of the macrocyclic polyether sulfides are shown in Table III. For the pur-

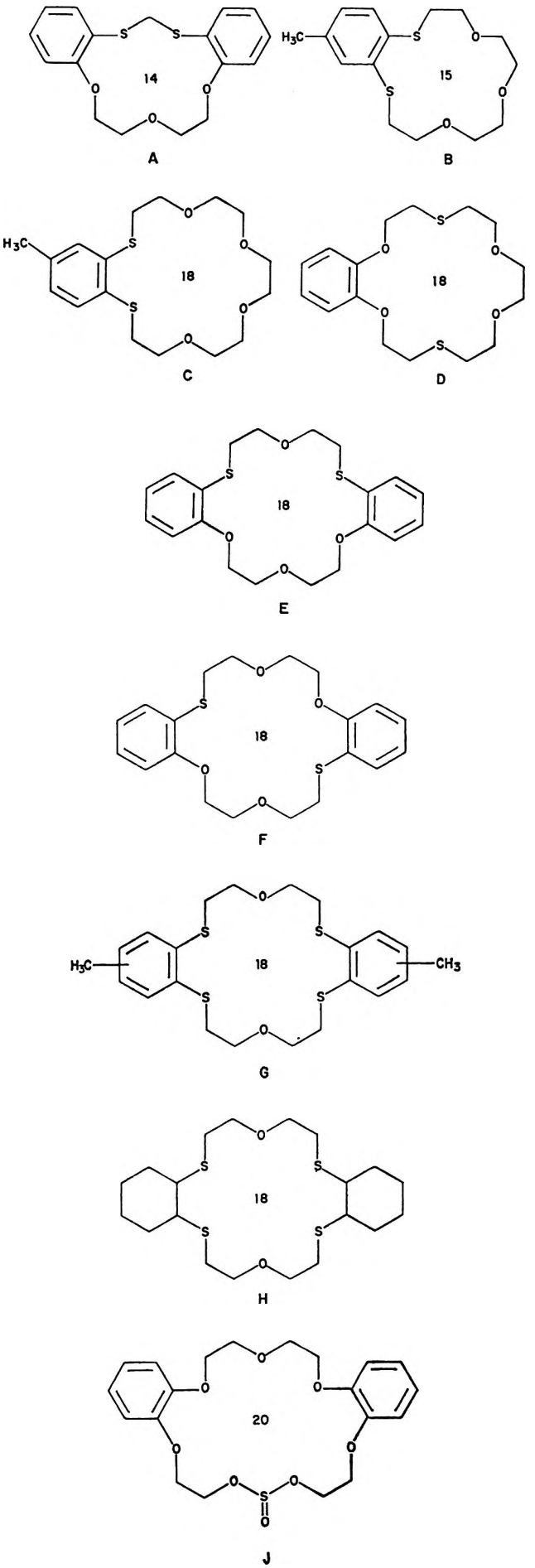

Figure 1.—Structural formulas and codes.

TABLE I

YIELDS AND ANALYTICAL DATA

Compd	Formula	Yield, %	Mp, °C[a]	Carbon, % Found	Carbon, % Calcd	Hydrogen, % Found	Hydrogen, % Calcd	Sulfur, % Found	Sulfur, % Calcd	Mol wt Found	Mol wt Calcd
A	$C_{17}H_{18}O_3S_2$	3	150–153	60.9	61.0	5.4	5.4	19.7	19.2		334
B	$C_{15}H_{22}O_3S_2$	30	Viscous oil	57.0	57.3	7.1	7.0	19.8	20.4	333	314
C	$C_{17}H_{26}O_4S_2$	56	Viscous oil	56.5	57.0	7.3	7.3	17.9	17.9	382	358
D	$C_{16}H_{24}O_4S_2$	1	91	55.0	55.8	7.1	7.0	17.4	18.6		344
E	$C_{20}H_{24}O_4S_2$	15	143–144	61.3	61.2	6.1	6.1	16.3	16.3	384	392
F	$C_{20}H_{24}O_4S_2$	5	114–115	61.3	61.2	6.0	6.1	16.3	16.3	357	392
G	$C_{22}H_{28}O_2S_4$	6	147	58.7	58.4	6.0	6.2	27.6	28.3	462	452
H	$C_{20}H_{36}O_2S_4$	24	Viscous oil	56.7	55.0	7.8	8.3	28.8	29.4	432	436
J	$C_{20}H_{24}O_8S$	33	133	56.7	56.6	5.8	5.7	7.0	7.5		424

[a] Melting points were determined on a Fisher-Johns apparatus and are uncorrected.

TABLE II

ULTRAVIOLET SPECTRA IN METHANOL

Compd	Without any salt: Peaks, mμ[b]	Without any salt: Ext coeff	With silver nitrate[a]: Peaks, mμ[b]	With silver nitrate[a]: Ext coeff
A	286.5	6,800	[c]	[c]
	292	6,700		
B	256	10,500	249	13,400
	(*ca.* 294)	1,700	(*ca.* 292)	1,200
C	254	11,300	(*ca.* 258)[d]	4,300
	(292)	2,000	(*ca.* 288)	1,900
D	277	3,000	275	3,100
			(280.5)	2,600
E	254	9,600	252	12,400
	282.5	6,100	282	7,400
	288	6,200		
F	255	9,100	(*ca.* 247)[d]	10,000
	282	6,100	282	5,700
	288.5	6,000		
G	256	22,000	(*ca.* 259)[d]	3,800
	(*ca.* 300)	2,300	297	1,400
J	276	4,600	...[c]	...[c]

[a] Silver nitrate was added in about 50-fold excess, and its effects on the spectra of the compounds (without any salt) are indicated by the changed values of the peaks and the extinction coefficients. [b] Parentheses indicate shoulders rather than peaks. [c] Little change on addition of silver nitrate. [d] The peak nearly disappears on addition of silver nitrate and is replaced by a slight shoulder on the sloping curve with a peak at 224 mμ.

TABLE III

EXTRACTION DATA. WATER–METHYLENE CHLORIDE[a]

Compd	Concn × 10^5 *M*	Salt	Concn, *M*	Extracted, %[b]
B	7.0	KNO_3	0.1	2.4
B	7.0	$AgNO_3$	0.1	52
C	7.0	KNO_3	0.1	3.2
C	7.0	$AgNO_3$	0.1	77
E[c]		KCl		Poor
E[c]		$AgNO_3$		Good
F[c]		KCl		Poor
F[c]		$AgNO_3$		Good
G	7.0	KNO_3	0.1	5.5
G	7.0	$AgNO_3$	0.1	92
H	6.4	NaOH	0.125	2.2
H	6.4	$AgNO_3$	0.059	68
K[d]	25.4	NaOH	0.125	<1
K[d]	25.4	$AgNO_3$	0.059	10
XXXI[e]	7.0	KNO_3	0.1	69
XXXI[e]	7.0	$AgNO_3$	0.1	63

[a] Equal volumes of water and methylene chloride, and picric acid at 7.0 × 10^{-5} *M*. [b] The cation of the listed salt. [c] Not run quantitatively. [d] Di(*n*-octadecyl) sulfide. [e] Dicyclohexyl-18-crown-6, see ref 1.

pose of comparison, the extraction data for dicyclohexyl-18-crown-6 (XXXI)[1] and di(*n*-octadecyl) sulfide, K, are included. Of the previously studied polyethers, XXXI is the best complexing agent for potassium and also, in general, the most effective for the other cations.

It is evident that, as a group, the macrocyclic polyether sulfides are poorer complexing agents for sodium and potassium than the oxygen analogs (compare H with XXXI), but they are, at least, as good for complexing silver. B, C, G, and H were also tested with the other alkali metal and alkaline earth metal salts with similar results. Cursory tests indicated that the macrocyclic polyether sulfides are good complexing agents for gold, but the valence of the complexed gold was not determined.

A comparison of K with any other sulfur compound suggests that the macrocyclic polyether sulfides are very much better complexing agents for silver than the open-chain sulfide. It does not seem likely, however, that different types of coordination are involved in the two cases, but the great advantage accrues from chelation and the more favorable steric environment in the case of macrocyclic complexing agents.

The strong complexing power of the macrocyclic polyethers for the alkali and alkaline earth cations is destroyed by substituting –S– for –O–, probably because the symmetrical distribution of the negative charge around the "hole" of the polyethers is disturbed due to the larger size of the sulfur atom, its lower electronegativity, and the different bond angles involving the sulfur atom.

Experimental Section

The following instruments were used: Varian Model A-60 for nmr spectra, Perkin-Elmer Infracord Model 137 for infrared spectra, and Perkin-Elmer ultraviolet–visible spectrophotometer Model 202 for ultraviolet spectra. All inorganic compounds were reagent grade, and all solvents and available organic materials were commercial products used without purification.

Preparation of 2,3,7,8-Dibenzo-1,9,12-trioxa-4,6-dithiacyclotetradeca-2,7-diene (A).—To a mixture of 24.7 g (0.0936 mol) of bis(*o*-hydroxyphenylmercapto)methane, 200 ml of 1-butanol, and 7.5 g (0.188 mol) of sodium hydroxide dissolved in 10 ml of water was added dropwise 13.4 g (0.0936 mol) of bis(2-chloroethyl)ether diluted with 50 ml of 1-butanol. The mixture was refluxed overnight.

The solvent was distilled off while the volume was kept constant by the addition of water, and the aqueous mixture was extracted with 200 ml of chloroform and washed twice with 100 ml of aqueous 5% sodium hydroxide. (There was trouble due to emulsion.) The chloroform solution was evaporated and the residue, 20.3 g of very viscous material, was recrystallized from *n*-heptane. The desired compound was obtained as white crystals, 1.0 g.

Preparation of 2,3-(4′-Methylbenzo)-1,4-dithia-7,10,13-trioxacyclopentadeca-2-ene (B).—A mixture of 17.3 g (0.111 mol) of toluene-3,4-dithiol, 400 ml of 1-butanol, 25.6 g (0.111 mol) of

1,11-dichloro-3,6,9-trioxaundecane, and 8.9 g (0.222 mol) of sodium hydroxide dissolved in 10 ml of water was refluxed with good agitation for 6.5 hr (temperature 104°). The warm reaction mixture was filtered, the insoluble material was washed with 100 ml of 1-butanol, and the filtrate and the washing were concentrated. The residue, 17.5 g of viscous oil, was placed on a column (1.75 × 8 in.) of acid-washed, 200 mesh alumina, and the portion which came off with a mixture of 600 ml of benzene and 600 ml of chloroform, 10.5 g of viscous oil, was the desired compound.

Preparation of 2,3-(4'-Methylbenzo)-1,4-dithia-7,10,13,16-tetraoxacyclooctadeca-2-ene (C).—This compound was synthesized in the same way as the previous compound, B. The elution from the alumina column was effected, however, with benzene (20.1 g of product as a viscous oil).

Preparation of 2,3-Benzo-1,4,10,13-tetraoxa-7,16-dithiacyclooctadeca-2-ene (D).—To a boiling mixture of 900 ml of ethyl alcohol, 900 ml of water, and 6.4 g (0.06 mol) of anhydrous sodium carbonate was added dropwise in 1 hr 100 ml of ethyl alcohol containing 14.0 g (0.06 mol) of 1,2-bis(β-chloroethoxy)-benzene and 11.0 g (0.06 mol) of 1,2-bis(β-mercaptoethoxy)-ethane. The mixture was refluxed overnight, cooled, filtered, and evaporated. The residue, 9.4 g of brownish paste, was placed on a porous plate and 0.16 g of white fibrous crystals was obtained. No attempt was made to recover more product from the residue.

Preparation of 2,3,11,12-Dibenzo-1,7,13,16-tetraoxa-4,10-dithiacyclooctadeca-2,11-diene (E).—To a boiling mixture of 126 g (1 mol) of o-mercaptophenol, 1000 ml of 2-butanol, and 40 g (1 mol) of sodium hydroxide was added dropwise in 2 hr 74 g (0.52 mol) of bis(2-chloroethyl) ether diluted with 50 ml of 2-butanol. The mixture was cooled to 87°, 40 g of sodium hydroxide was added, and it was refluxed for 30 min (96°). Bis(2-chloroethyl)ether (74 g) diluted with 50 ml of 2-butanol was then added dropwise in 2 hr and the mixture was refluxed for 16 hr.

The mixture ws acidified with 30 ml of concentrated hydrochloric acid diluted with 200 ml of water, and the solvent was distilled off while making up the volume with water until the vapor temperature had risen to 100°. The pasty solids were filtered off, washed with water, and sucked as dry as possible. It was then mixed with 500 ml of acetone, filtered, and washed with 500 ml of acetone, and dried. The desired product, 60.4 g, was obtained as fibrous crystals.

Preparation of 2,3,11,12-Dibenzo-1,7,10,16-tetraoxa-4,13-dithiacyclooctadeca-2,11-diene (F).—To a mixture of 70.6 g (0.56 mol) of o-mercaptophenol, 460 ml of 1-butanol, and 22.4 g (0.56 mol) of sodium hydroxide in 25 ml of water was added rapidly 160 g (1.12 mol) of bis(2-chloroethyl) ether dissolved in 340 ml of 1-butanol and refluxed for 2 hr. The mixture was distilled while 1 l. of water was being added until about 1600 ml of distillate had been removed and the temperature was 104°. To the residue in the flask was added dropwise 22.4 g of sodium hydroxide in 25 ml of water which was then diluted with 400 ml of 1-butanol, and refluxed for 20 hr (97°).

The mixture was cooled, acidified with 29 ml of concentrated hydrochloric acid, and distilled while 1200 ml of water was added until about 1150 ml of distillate had been removed and the temperature was 105°. The mixture was extracted with 500 ml of chloroform and washed twice with 400 ml of water containing 20 g of sodium hydroxide. The chloroform solution was evaporated and gave 29.7 g of yellow oil. This was placed on a column of alumina and eluted with benzene. The residue from the eluate, 23.6 g, was extracted with n-hexane and gave the desired compound as white crystals.

Preparation of 2,3,11,12-Bis(4'- and/or 5'-methylbenzo)-1,4,10,13-tetrathia-7,16-dioxacyclooctadeca-2,11-diene (G).—A mixture of 48.8 g (0.313 mol) of toluene-3,4-dithiol, 500 ml of 1-butanol, and 20.7 g (0.313 mol) of 85% potassium hydroxide was heated to reflux temperature (114°) and to it was added dropwise in 2 hr 22.5 g (0.157 mol) of bis(2-chloroethyl) ether diluted with 50 ml of 1-butanol, and refluxed for 1 hr. The temperature was lowered to 76°, potassium hydroxide (20.7 g of 85%) was added, the temperature was raised to reflux, and to the mixture was added dropwise in 1 hr 22.5 g of bis(2-chloroethyl)ether diluted with 50 ml of 1-butanol. Then the refluxing was continued for 4 hr more.

After acidifying with 3 ml of concentrated hydrochloric acid, 1-butanol was distilled off while the volume of the mixture was kept constant by the addition of water. The pinkish paste which separated from the aqueous phase was dissolved in 600 ml of chloroform and extracted with 400 ml of 5% aqueous sodium hydroxide. The chloroform solution was dried with calcium chloride and evaporated. The residue, 67.2 g of very thick, sticky paste, was extracted with n-heptane and then with acetone. From these extracts, 4.2 g of white, shiny crystals of the desired compound were recovered. It is probable that the yield of the product was considerably higher, but an efficient method of recovery had not been developed.

Preparation of 2,8,15,21-Tetrathia-5,18-dioxatricyclo[20.4.0.-$0^{9,14}$]hexacosane (H).—To a mixture of 57.4 g (*ca.* 0.37 mol) of crude *trans*-1,2-cyclohexanedithiol,[4] 500 ml of air-free 1-butanol, and 14.6 g (0.365 mol) of sodium hydroxide in 20 ml of water, all at 60°, was added dropwise in 54 min 26.1 g (0.182 mol) of bis(2-chloroethyl)ether diluted with 70 ml of 1-butanol, and it was refluxed for 30 min. The mixture was cooled to 95°. Sodium hydroxide (14.6 g) in 20 ml of water was added, and then 26.1 g of bis(2-chloroethyl)ether diluted with 70 ml of 1-butanol was added dropwise in 57 min.

The mixture was filtered and evaporated (39.5 g of residue). This was dissolved in 200 ml of methylene chloride, washed with 200 ml of aqueous 5% sodium hydroxide (there was trouble due to emulsion), and evaporated. The residue, 31.5 g of brownish oil, was placed on a 1.75 × 6 in. column of alumina and eluted with benzene. The first 200 ml of eluate contained 18.9 g of the desired compound.

Preparation of 2,3,13,14-Dibenzo-1,4,7,9,12,15,18-heptaoxa-8-thiacycloeicosa-2,13-diene 8-Oxide (J).—1,17-Dihydroxy-4,5,13,-14-dibenzo-3,6,9,12,15-pentaoxaheptadeca-4,13-diene (1.89 g, 0.005 mol) dissolved in 200 ml of dry benzene was treated with 3.14 g (0.04 mol) of pyridine and 1.2 g (0.01 mol) of thionyl chloride, and warmed on a steambath for 1 hr. The mixture was filtered, and the filtrate was washed with 150 ml of water containing 5 ml of concentrated hydrochloric acid, dried, and evaporated. The residue was crystallized from a mixture of cyclohexane and benzene and yielded white crystals of the desired compound.

Preparation of Crystalline Silver Nitrate Complex of E.—A clear solution obtained by warming a mixture of 1.96 g (0.005 mol) of E, 50 ml of methanol, and 0.86 g (0.0051) mol of silver nitrate was cooled to room temperature and left in an open beaker protected from light. Large, off-white crystals were obtained melting at 197–203°. *Anal.* Calcd : C, 42.7; H, 4.3; S, 11.4; Ag, 19.2. Found: C, 42.8; H, 4.2; S, 11.5; Ag, 19.2.

On treating the above complex with sodium bromide in methanol, yellowish, fibrous crystals were recovered with a melting point above 210°. *Anal.* Calcd: Br, 13.8; Ag, 18.6. Found: Br, 12.7; Ag, 17.3

Registry No.—A, 26736-17-4; B, 26736-18-5; C, 26736-19-6; D, 26850-07-7; E, 26736-20-9; F, 26736-21-0; G, 26778-70-1; H, 26736-22-1; J, 26736-23-2.

Acknowledgments.—The author thanks Rudolph Pariser for advice and encouragement, and Bradbury Emerson for technical assistance.

(4) *trans*-1,2-Cyclohexanedithiol was prepared according to C. C. J. Culvenor, W. Davies, and K. H. Pausacker, *J. Chem. Soc.* (*London*), 1050 (1946).

Synthesis of α-Azidovinyl Ketones from the Iodine Azide Adducts of α,β-Unsaturated Ketones[1a]

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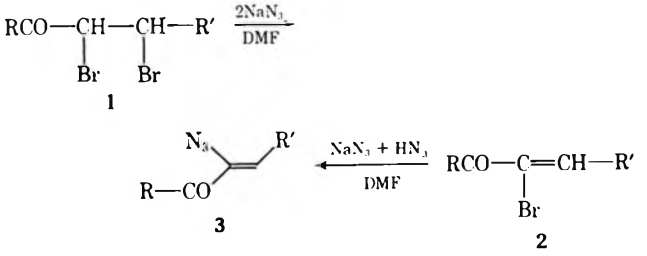
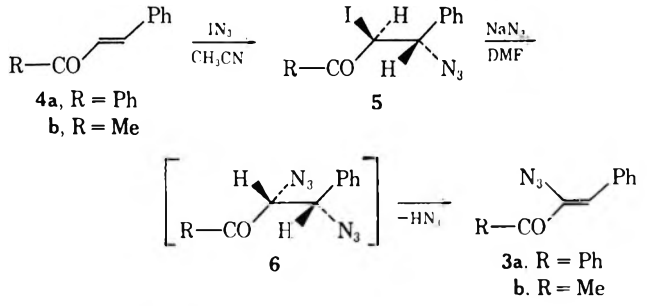
A synthetic approach to α-azidovinyl ketones is provided by the reaction of the iodine azide adducts of α,β-unsaturated ketones with sodium azide in DMF at room temperature. α-Azidochalcone (**3a**), α-azidobenzylideneacetone (**3b**), and α-azidoethylideneacetophenone (**3c**) were prepared in good yields and subsequently converted to the corresponding iminophosphoranes on treatment with triphenylphosphine. The mechanism of the synthetic method, which involves in part transposition of an azide function, is discussed, as is the regiochemistry of IN_3 additions to unsaturated carbonyl compounds.

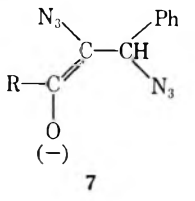
α-Azidovinyl ketones (**3**), which are regioisomeric[1b] with the readily available β-azidovinyl ketones,[2] were obtained recently by two synthetic methods developed in this laboratory.[3] The first method consists of reacting the dibromides of α,β-unsaturated ketones (**1**) with 2 equiv of sodium azide in DMF at room temperature. The second method involves treatment of the α-bromovinyl ketones (**2**) with an equimolar mixture of sodium azide and hydrazoic acid in DMF.



We now wish to report a third facile approach to this rare class of vinyl azides.[4] Treatment of the *trans*-α,β-unsaturated ketones, **4a** and **4b**, with iodine azide in acetonitrile solution yields the *erythro*-iodo azides, **5a** and **5b**, in high yields. The latter are smoothly converted by sodium azide in DMF to the azidovinyl ketones, **3a** and **3b**. The reaction can be rationalized by an S_N2

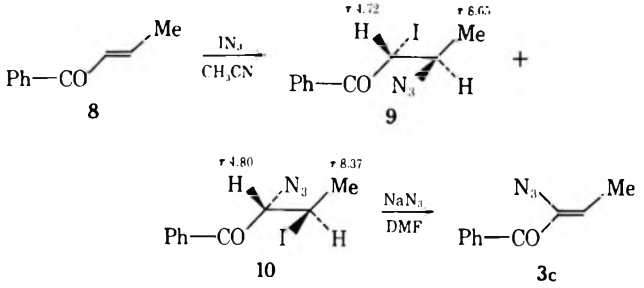


attack of the azide ion on the iodine bearing carbon of **5** to give the bisazide **6** which on elimination of hydrazoic acid yields the *trans*-vinyl azide (**3**). Step **6** → **3** can either be considered an anti elimination of hydrazoic acid, or it can involve the loss of a proton from **6** under the basic reaction conditions (NaN_3 in DMF) to give intermediate **7** which is subsequently transformed to the thermodynamically most stable *trans*-vinyl azide

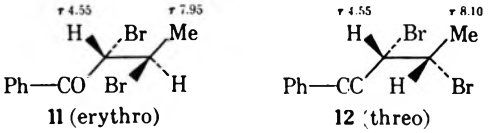


(**3**). Bisazides of type **6** are unstable and have never been isolated in the pure state, but their presence can be inferred from the nmr spectra, as described elsewhere.[3]

When *trans*-ethylideneacetophenone (**8**) was treated with iodine azide in acetonitrile, a mixture of two products in a ratio of 40:60 was obtained which analyzed correctly for the IN_3 adducts. We assign the regioisomeric structures **9** and **10** to these components on the basis of the nmr data. One other possibility, namely an



erythro–threo mixture, is most unlikely in view of the chemical shift values and coupling constants observed. For comparison, we prepared the *erythro*- and *threo*-dibromides of ethylideneacetophenone (**11** and **12**) by the method of Lutz[5] and observed that the α-hydrogen



atoms exhibit the same chemical shifts (τ 4.55) but sharply different coupling constants (J = 10.5 Hz for **11** and J = 7 Hz for **12**) as expected for different dihedral angles. On the contrary, the α-hydrogen atoms of the

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(1) (a) Steveochemistry. LIX. For paper LVIII, see G. L'abbé, M. J. Miller, and A. Hassner, *Chem. Ind. (London)*, 1321 (1970). (b) Regio is used to describe directional preference in bond making or breaking: A. Hassner, *J. Org. Chem.*, **33**, 2684 (1968).

(2) Review: M. I. Rybinskaya, A. N. Nesmeyanov, and N. K. Kochetkov, *Russ. Chem. Rev.*, **38**, 961 (in Engl. 433) (1969).

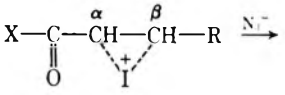
(3) A. Hassner, G. L'abbé, and M. J. Miller, *J. Amer. Chem. Soc.*, in press.

(4) After our research had been completed, Knittel, Hemetsberger, and Weidmann [*Monatsh. Chem.*, **101**, 157 (1970)], reported a fourth synthetic method for α-azidovinyl ketones by the condensation of azidoacetophenone with substituted benzaldehydes.

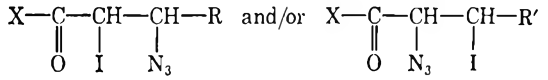
(5) R. E. Lutz, D. F. Hinkley, and R. H. Jordan, *J. Amer. Chem. Soc.*, **73**, 4647 (1951).

iodine azide adducts **9** and **10** show the same coupling constants (J = 9 Hz) but different chemical shifts (τ 4.72 for **9** and 4.80 for **10**) in accordance with expectations. In addition, the widely separated methyl absorptions at τ 8.65 and 8.37 are consistent with the regioisomeric structures **9** and **10** rather than with diastereomers. Ionic addition of BrN_3 to **8** also afforded two regioisomers (the Br analogs of **9** and **10**) in which the α protons absorb at τ 4.88 and 5.02, respectively, and the methyl absorption occurs at τ 8.65 and 8.43.[3]

The formation of **9** and **10** deserve comment. The regiochemistry of IN_3 additions to olefins has been shown to be dependent on electronic and steric factors operating during the opening of the iodonium ion intermediate (*e.g.*, **13**).[6] Since a carbonyl group is known to



13

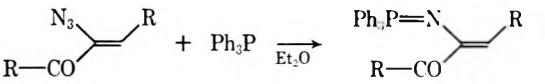


14 **15**

destabilize an adjacent incipient positive charge, opening of **13** would be expected to occur at the β-carbon atom leading to regioisomer **14**. However, opening of **13** can also be viewed as an S_N2 displacement which is known to occur with ease in α-halo ketones and esters. A β-phenyl group in vinyl ketones and a β-methyl group in vinyl esters (see **13**, R = Ph or Me, respectively) are sufficient to counteract the latter effect, so that **13** is opened exclusively at the β carbon. If, on the contrary, the β substituent cannot substantially contribute to the stabilization of a positive charge on the β-carbon atom, displacement occurs at the α and the β position and both regioisomers, **14** and **15**, are obtained. Thus methyl acrylate on IN_3 addition gave a mixture of **14** and **15** (X = OMe, R = H) in a ratio of 12:88,[6b] and vinyl ketone **8** is likewise converted into both isomers **9** and **10**.

For the synthesis of the vinyl azide **3c**, no further separation of **9** and **10** is necessary since both isomerr are cleanly converted into **3c** upon treatment with sodium azide in DMF. Interestingly, the vinyl azide **3c** is also obtained when the mixture of **9** and **10** is treated with sodium acetate, a base of similar basicity as sodium azide. While the conversion of **10** into **3c** by a base is unexceptional, the transformation of **9** into **3c** by sodium acetate requires explication. Elimination of hydrazoic acid from adduct **9** by sodium acetate occurs to some extent and provides the necessary azide ions for the conversion of the remaining **9** into **3c** *via* **6**. Evidence for this interpretation is provided by the nmr spectrum of the crude reaction product which shows, in addition to the vinyl azide **3c**, the α-iodovinyl ketone (vinyl H at τ 3.28) derived from **9** in *ca.* 5–10% yield.[7]

The three α-azidovinyl ketones prepared in this work react readily with triphenylphosphine with nitrogen evolution to give the vinyliminophosphoranes **16** in high yield. The mechanism of this general reaction for azides has been recently reviewed.[8]



3

16a, R = Ph; R′ = Ph
b, R = Me; R′ = Ph
c, R = Ph; R′ = Me

Experimental Section

All-melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 457 spectrophotometer. Nmr spectra were recorded with a Varian A-60-A spectrometer using tetramethylsilane as an internal standard. The elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Addition of Iodine Azide to the α,β-Unsaturated Ketones.—The IN_3 adducts were prepared by treating the respective α,β-unsaturated ketones with iodine azide (reaction time, 1 day) according to the general procedure described elsewhere.[6a]

1-Phenyl-1-azido-2-iodo-3-phenyl-3-propanone (**5a**) was obtained from chalcone in nearly quantitative yield: mp 104–104.5° (reported[6a] 100–102°); nmr ($CDCl_3$) τ 1.75–2.10 (m, 2 H), 2.3–2.8 (m, 3 H), 2.57 (s, 5 H), 4.48 (d, 1 H, J = 11 Hz), 4.70 (d, 1 H, J = 11 Hz).

1-Phenyl-1-azido-2-iodo-3-methyl-3-propanone (**5b**) was obtained from benzylideneacetone in 85% yield and recrystallized from ethanol: mp 86–87°; nmr ($CDCl_3$) τ 2.60 (s, 5 H), 4.97 (d, 1 H, J = 11 Hz), 5.38 (d, 1 H, J = 11 Hz), 7.50 (s, 3 H). *Anal.* Calcd for $C_{10}H_{10}IN_3O$ (315): C, 38.10; H, 3.17; N, 13.33. Found: C, 37.92; H, 3.02; N, 13.42.

Adducts 9 and 10.—When **8** was treated with iodine azide and worked up in the usual manner, a brown oil was obtained whose nmr spectrum showed, among other impurities, the two regioisomeric adducts **9** and **10** in a ratio of about 40:60. The oil was chromatographed on silica gel with petroleum ether–benzene as the eluent, and gave a pure mixture of **9** and **10** in 23% yield: nmr ($CDCl_3$) τ 1.8–2.8 (two multiplets), 4.72 (d, J = 9 Hz), 4.80 (d, J = 9 Hz), 5.5–6.1 (octet), 8.37 (d, J = 6.5 Hz), 8.65 (d, J = 6.5 Hz). *Anal.* Calcd for $C_{10}H_{10}N_3IO$: C, 38.10; H, 3.17; N, 13.33. Found: C, 38.41; H, 3.24; N, 13.03.

Reaction of the Iodine Azide Adducts with Sodium Azide.—The IN_3 adduct (0.02 mol) was allowed to react with sodium azide (0.02 mol) in 100 ml of DMF (dried over molecular sieves, type 4A) at room temperature for the appropriate reaction time (1 hr for **5a**, 2 hr for **5b**, and 0.5 hr for **9**–**10**). The solution was then poured into a mixture of water–ether, and the ether layer was washed several times with water and dried ($MgSO_4$). After removing the ether under vacuum the α-azidovinyl ketones were obtained as follows.

α-Azidochalcone (**3a**) was isolated as a red oil and was purified by passing through a small column of neutral aluminum oxide using petroleum ether–50% benzene as the eluent. The yellow fraction was collected and gave, after removal of the solvent, the pure azide in 60–72% yield, mp 63.5–64° (from petroleum ether, bp 20–40°). When the reaction was carried out with 2 equiv of sodium azide, the α-azidochalcone was obtained pure in 68% yield.

α-Azidobenzylideneacetone (**3b**) was obtained as a crude yellow solid and recrystallized from petroleum ether (bp 20–40°) in 67% yield, mp 79.5–80.0°.

α-Azidoethylideneacetophenone (**3c**) was obtained as a pure yellow liquid in 83% yield and did not need further purification. When the reaction was carried out with 1 equiv of sodium acetate instead of sodium azide, the vinyl azide **3c** was obtained crude in 85% yield. The nmr spectrum indicated the presence of a small amount of the α-iodoethylideneacetophenone (τ 3.28, q, J = 6.5 Hz; τ 7.92, d, J = 6.5 Hz). The latter compound was also obtained in *ca.* 10% yield (in addition to starting material) when the reaction was carried out with 2 equiv of silver acetate for 2 hr. Chromatography on silica gel failed to lead to the isolation of this labile vinyl iodide.

(6) (a) F. W. Fowler, A. Hassner, and L. A. Levy, *J. Amer. Chem. Soc.*, **89**, 2077 (1967); (b) A. Hassner and F. W. Fowler, *J. Org. Chem.*, **33**, 2686 (1968).

(7) A referee suggested that another possible reaction course could be the displacement of iodine ion from **9** by acetate, followed by loss of hydrazoic acid. This should result in the formation of α-acetoxyethylideneacetophenone which has not been observed.

(8) Review: G. L'abbé, *Ind. Chim. Belge*, **34**, 519 (1969).

All three α-azidovinyl ketones were identified by comparison with authentic samples prepared by the two other methods.[3]

Reaction of the α-Azidovinyl Ketones with Triphenylphosphine.—The azidovinyl ketone (0.01 mol) was allowed to react with 0.01 mol of triphenylphosphine in 50 ml of ether at room temperature. Nitrogen evolution was observed and the iminophosphorane precipitated partly from the mixture. After 1 day the solution was cooled, and the precipitate was filtered, washed with petroleum ether, and dried.

α-(Triphenylphosphinimino)chalcone (16a) was obtained as a yellow crystalline product in 87–93% yield and was recrystallized from carbon tetrachloride–petroleum ether: mp 163–163.5°; nmr ($CDCl_3$) τ 1.6–2.9 (three multiplets), 3.75 (d, 1 H, J = 7 Hz). *Anal.* Calcd for $C_{33}H_{26}NOP$ (483): C, 77.50; H, 5.09. Found: C, 77.65; H, 5.29.

α-(Triphenylphosphinimino)benzylideneacetone (16b) was obtained in 88% yield and recrystallized from carbon tetrachloride–petroleum ether: mp 166–166.5°; nmr ($CDCl_3$) τ 1.5–3.0 (three multiplets), 3.38 (d, 1 H, J = 8 Hz), 7.72 (s, 3 H). *Anal.* Calcd for $C_{28}H_{24}NOP$ (421): C, 79.81; H, 5.70. Found C, 80.08; H, 5.92.

α-(Triphenylphosphinimino)ethylideneacetophenone (16c) was obtained in 86% yield and recrystallized from carbon tetrachloride: mp 146–147°; nmr ($CDCl_3$) τ 1.9–2.9 (two multiplets), 4.2–4.7 (dq, 1 H), 7.92 (dd, 3 H, J = 7 and 1 Hz). *Anal.* Calcd for $C_{28}H_{24}NOP$ (421): C, 79.81; H, 5.70. Found: C, 79.76; H, 5.78.

The ir spectra (KBr) of the iminophosphoranes showed the expected C=O bands at 1630–1600 and C—P bands at 1410–1430, 1120, and 990–1000 cm^{-1}.

Registry No.—**3a**, 26309-08-0; **3b**, 26309-09-1; **3c**, 26309-10-4; **5b**, 26309-13-7; **9**, 26309-11-5; **10**, 26309-12-6; **16a**, 26309-14-8; **16b**, 26309-15-9; **16c**, 26309-16-0.

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The Nature of the Ortho Effect. VI. Polarographic Half-Wave Potentials

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Twenty-seven sets of polarographic half-wave potentials and related data for ortho-substituted benzene derivatives have been correlated with the equations $Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + \varphi r_V + h$ and $Q_X = \alpha\sigma_{I,X} + \beta\sigma_{E,X} + h$. Significant correlations were obtained with 18 of the sets correlated with the former, and 22 of the sets correlated with the latter equation. The results obtained for correlations with the former equation show that, in general, ψ is not significant. As successful correlations were obtained with the latter equation in most cases, there is no steric effect exerted by ortho substituents in the majority of the sets studied. Their effect is generally purely electrical in nature. The magnitude and composition of the electrical effect seems to be independent of the medium but strongly dependent on the group being reduced.

In continuation of our interest in the nature of the ortho effect, it seemed worthwhile to extend our investigations to polarographic half-wave potentials. The problem seems to have first been studied by Bennett and Elving,[1] who reported a correlation of $E_{0.5}$ values for 2-substituted nitrobenzenes with the Taft σ_o^* constants by means of the simple Hammett equation

$$Q_X = \rho\sigma_X + h \quad (1)$$

Zuman[2] has studied the correlation of $E_{0.5}$ values for ortho-substituted benzene derivatives with the equation

$$\Delta E_{0.5,X} = \rho\sigma_{o,X}^* + \delta E^\circ_{S,X} \quad (2)$$

in an attempt to determine the presence or absence of steric effects. Hussey and Diefenderfer[3] have correlated $E_{0.5}$ values for 2-substituted phenyl bromides and iodides with the simple Hammett equation using σ_o constants defined by the expression

$$\sigma_o = 2.4\sigma_I + (1 - \text{S.F.})\sigma_R \quad (3)$$

where S.F. is a steric hindrance factor defined as the fraction of overlap between the reaction site radius and the substituent radius. The radii were obtained from data on the resolution of diphenyls. As we have recently shown[4] that the E_S° values proposed by Taft[5] as a measure of the steric effect of ortho substituents are in fact electrical effect parameters, it seemed useful to investigate the correlation of $E_{0.5}$ values with the aim of determining whether or not a steric effect is present.

It is convenient at this point to review our method for ascertaining the presence or absence of steric effects. There are several possible cases to consider,[6] of which four are of major interest to us. They are (1) the steric effect obeys a linear free-energy relationship.[5] Then, if a suitable steric effect parameter is available, we may write a linear free-energy relationship including electrical and steric terms. For a steric effect parameter we have chosen the van der Waals radius of that atom or group of atoms of the substituent which is bonded to the benzene ring. Then, in this case, we write the linear free-energy relationship[4,7,8]

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + \psi r_{V,X} + h \quad (4)$$

(2) The steric effect does not obey a linear free-energy relationship. In this case, we may write for any particular datum in the set

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + S_X + h \quad (5)$$

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(1) C. E. Bennett and P. J. Elving, *Collect. Czech. Chem. Commun.*, **25**, 3213 (1960).

(2) P. Zuman, *ibid.*, **27**, 648 (1962); "Substituent Effects in Organic Polarography," Plenum Publishing Co., New York, N. Y., 1967, p 75.

(3) W. W. Hussey and A. J. Diefenderfer, *J. Amer. Chem. Soc.*, **89**, 5359 (1967).

(4) M. Charton, *ibid.*, **91**, 615 (1969).

(5) R. W. Taft in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 565.

(6) M. Charton, *J. Org. Chem.*, **34**, 278 (1969).

(7) M. Charton, *J. Amer. Chem. Soc.*, **91**, 619 (1969).

(8) M. Charton, *ibid.*, **91**, 624 (1969).

TABLE I

1. $E_{0.5}$ 2-XC_6H_4I, 66% EtOH–H_2O, 0.01 *M* Et_4NBr, 25°[a]

I	OH	Br	NH_2	Cl		Me	Ph	H
1.235	1.49	1.30	1.56	1.34	1.683	1.48	1.65	

2. $E_{0.5}$ 2-XC_6H_4I, 90% EtOH–H_2O, 0.06 *M* LiCl, 0.2 *M* KOAc, 0.013 *M* AcOH, 25°[b]

H	Cl	Br	Me	MeO	EtO	OH[c]	CO_2H	Ph
1.68	1.56	1.50	1.70	1.60	1.64	1.55	1.47	1.61

3. $E_{0.5}$ 2-XC_6H_4I, H_2O, 1.0 *M* $LiClO_4$[d]

H	Me	Et	Ph	NH_2	OH	OMe	OEt
1.655	1.688	1.685	1.570	1.565	1.535	1.567	1.587

F	Cl	Br	CF_3
1.374	1.375	1.322	1.343

4. $E_{0.5}$ 2-XC_6H_4I, H_2O, 0.1 *M* Me_4NCl[d]

H	Me	Et	Ph	NH_2	OH	OMe	OEt
1.467	1.495	1.478	1.327	1.416	1.391	1.393	1.405

F	Cl	Br	CF_3
1.205	1.203	1.153	1.190

5. $E_{0.5}$ 2-XC_6H_4Br, H_2O, 0.1 *M* Me_4NCl[d]

H	Me	NH_2	OH	OMe	OEt	CF_3	F	Cl
2.07	2.12	2.01	1.97	1.93	1.99	1.67	1.69	1.69

6. $E_{0.5}$ 2-XC_6H_4OTs, Me_2NCHO, 0.05 *M* Et_4NI, 25°[e]

F	Cl	NH_2	OMe	Me	NMe_2	NO_2[b]
1.332	1.337	1.422	1.431	1.420	1.740	1.118, 1.330

H
1.429

7. $E_{0.5}$ 2-XC_6H_4OTs, Me_2SO, 0.05 *M* Et_4NI, 25°[e]

F	Cl	NH_2	OMe	Me	NMe_2	NO_2[b]	H
1.452	1.436	1.501	1.527	1.497	1.608	1.484	1.491

8. $E_{0.5}$ 2-XC_6H_4OTs, MeCN, 0.05 *M* Et_4NI, 25°[e]

F	Cl	NH_2	OMe	Me	NMe_2	NO_2[c]	H
1.409	1.407	1.441	1.508	1.510	1.455	1.378	1.463

9. $E_{0.5}$ 2-XC_6H_4OTs, C_5H_5N, Et_4NI, 25°[f]

Cl	F	NH_2	NMe_2	OMe	Me	H
1.313	1.328	1.398	1.388	1.427	1.400	1.415

10. $E_{0.5}$ 2-XC_6H_4OTs, PhCN, Et_4NI, 25°[g]

Cl	F	NH_2	NMe_2	Me	OMe	H
1.414	1.427	1.450	1.440	1.475	1.468	1.452

11. $E_{0.5}$ 2-XC_6H_4OTs, equimolar C_5H_5N–Me_2NCHO, Et_4NI, 25°[g]

Cl	F	NH_2	NMe_2	Me	OMe	H
1.297	1.313	1.392	1.379	1.387	1.409	1.381

12. $E_{0.5}$ 2-XC_6H_4CHO, 66% EtOH–H_2O, 0.01 *M* Et_4NBr, 25°[a]

H	I	Cl	MeO	OH	Me
1.506	1.248	1.331	1.494	1.504	1.493

13. $E_{0.5}$ 2-XC_6H_4CHO, 60% EtOH–H_2O, pH 1.73, 25°[a]

H	I	Cl	MeO	OH	Me
1.000	0.827	0.868	0.960	1.050	0.962

14. $E_{0.5}$ 2-XC_6H_4CHO, 60% EtOH–H_2O, pH 2.25, 25°[a]

H	I	Cl	MeO	OH	NH_2[c]	Me
1.022	0.850	0.895	0.994	1.070	1.030	0.990

15. $E_{0.5}$ 2-XC_6H_4CHO, 60% EtOH–H_2O, pH 2.59, 25°[a]

H	I	Cl	MeO	OH	Me
1.051	0.876	0.918	1.020	1.098	1.018

16. $E_{0.5}$ 2-XC_6H_4CHO, 60% EtOH–H_2O, pH 3.16, 25°[a]

H	I	Cl	OH	NH_2[c]	Me
1.088	0.914	0.970	1.134	1.090	1.062

17. $E_{0.5}$ 2-XC_6H_4CHO, H_2O, pH 0, 20°[h]

H	OH	OMe	Me	Cl	Br	I	NHAc
0.780	0.850	0.775	0.720	0.693	0.698	0.707	0.765

CHO	CO_2H	NH_2[c]	CO_2Me
0.465,[i] 0.776	0.684	0.843	0.722

18. $E_{0.5}$ 2-XC_6H_4CHO, H_2O, pH 13, 20°[h]

H	OH[c]	OMe	Me	Cl	Br	I	NHAc
1.40	1.62	1.62	1.38	1.39	1.264	1.197	1.247

CO_2H[c]	NH_2	CHO
1.34	1.555	1.317,[i] 1.462

19. $E_{0.5}$ 2-XC_6H_4CHO, H_2O, pH 13, 20°, second wave[h]

H	OH[c]	OMe	Me	Cl	Br	I	NHAc
1.23	1.22	1.245	1.16	1.043	1.066	1.117	1.05

CO_2Me
1.097

20. $E_{0.5}$ 2-$XC_6H_4NO_2$, 66% EtOH–H_2O, 0.01 *M* Et_4NBr, 25°[a]

H	I	Br	Cl	OH	NH_2	Ph	Me
0.935	0.816	0.860	0.866	0.990	1.030	0.928	1.005

CO_2H	CO_2Et	CHO	NO_2
0.526, 0.968	0.826	0.640	0.570

21. $E_{0.5}$ 2-$XC_6H_4NO_2$, 60% EtOH–H_2O, pH 1.73, 25°[a]

H	I	Br	Cl	OH	NH_2	Ph	Me
0.326	0.204	0.263	0.256	0.246	0.372	0.290	0.358

CO_2H	CHO	CO_2Et	NO_2
0.304	0.228	0.282	0.134

22. $E_{0.5}$ 2-$XC_6H_4NO_2$, 60% EtOH–H_2O, pH 2.25, 25°[a]

H	I	Br	Cl	OH	NH_2	Ph	Me
0.366	0.232	0.294	0.306	0.284	0.422	0.341	0.390

CO_2H	CHO	CO_2Et	NO_2
0.340	0.286	0.313	0.168

23. $E_{0.5}$ 2-$XC_6H_4NO_2$, 60% EtOH–H_2O, pH 3.16, 25°[a]

H	I	Br	Cl	OH	NH_2	Ph	Me
0.430	0.306	0.396	0.410	0.362	0.488	0.412	0.525

CO_2H	CHO	CO_2Et	NO_2
0.420	0.346	0.400	0.230

24. E_S 2-$XC_6H_4NO_2$, 50% MeOH–H_2O, pH 12.5, 26°[j]

Cl	OMe	NH_2	OH[c]	Me	H
−0.81	−0.90	−0.95	−0.88	−0.93	−0.83

25. $E_{0.5}$ 2-$XC_6H_4NO_2$, 50% MeOH–H_2O, pH 12.5, 46°[j]

Cl	OMe	NH_2	OH[c]	Me	H
−0.91	−0.97	−1.08	−1.09	−1.07	−1.06

26. E_S 2-$XC_6H_4NO_2$, 50% MeOH–H_2O, pH 12.5, 46°[j]

Cl	OMe	NH_2	OH[c]	Me	H
−0.81	−0.89	−0.96	−0.91	−0.91	−0.84

27. $E_{0.5}$ 2-$XC_{11}H_4C_{10}H_{11}Fe$, MeCN, 0.2 *M* $LiClO_4$, 25°[k]

MeO	EtO	Me	F	Cl	Br	I	NO_2
0.292	0.295	0.340	0.359	0.386	0.388	0.389	0.444

CO_2Me	CH_2OH	Ph	H	CO_2H
0.380	0.352	0.340	0.343	0.373

[a] E. Gergeley and T. Iredale, *J. Chem. Soc.*, 3226 (1953). [b] E. L. Colichman and S. K. Liu, *J. Amer. Chem. Soc.*, **76**, 913 (1954). [c] Excluded from correlation. [d] Reference 3. [e] V. M. Maremae, *Org. Reactiv.*, **4**, 573 (1967). [f] V. M. Maremae, *ibid.*, **5**, 943 (1968). [g] V. M. Maremae, *ibid.*, **5**, 953 (1968). [h] L. Holleck and H. Marsen, *Z. Elektrochem.*, **57**, 944 (1953). [i] Value used in correlation. [j] S. Hashimoto, J. Sunamoto, and I. Shinkai, *Kogyo Kagaku Zasshi*, **68**, 1017 (1965). [k] W. F. Little, C. N. Reilley, J. D. Johnson, K. N. Lynn, and A. P. Sanders, *J. Amer. Chem. Soc.*, **86**, 1376 (1964).

where S_X is the steric effect of the substituent and does not obey a linear free-energy relationship.

(3) The steric effect is constant. Then

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + h' \quad (6)$$

where

$$h' = h + S_X \quad (7)$$

(4) The steric effect is nonexistent. Then

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + h \quad (8)$$

Obviously eq 7 and 8 are equivalent. To determine the presence or absence of a steric effect, the data are correlated with eq 4 and 8.

The data used are set forth in Table I. The presence of a significant steric effect will not be indicated by a successful correlation with eq 4. Although this is a necessary condition for the existence of a steric effect, in case 1 it is not sufficient. The conclusive evidence for the existence of such a steric effect is provided by the confidence level of ψ, the coefficient of the Van der

TABLE II

Set	α	β	ψ	h	R^a	F^b	$r_{12}{}^c$	$r_{13}{}^c$	$r_{23}{}^c$
1A	−0.631	−0.0432	−0.174	1.88	0.966	18.34[i]	0.068	0.584	0.145
1B	−0.753	−0.0719		1.61	0.944	20.52[h]	0.068		
2A	−0.355	−0.0722	−0.0293	1.70	0.855	4.537[m]	0.235	0.453	0.140
2B	−0.371	−0.0783		1.66	0.853	8.00[k]	0.235		
3A	−0.584	−0.0454	−0.0996	1.81	0.965	36.34[g]	0.151	0.295	0.439
3B	−0.625	−0.0870		1.64	0.955	46.65[g]	0.151		
4A	−0.529	−0.0872	−0.0951	1.59	0.959	30.71[g]	0.151	0.295	0.439
4B	−0.568	−0.127		1.44	0.948	40.14[g]	0.151		
5A	−0.789	−0.118	−0.0706	2.17	0.974	31.32[h]	0.049	0.384	0.381
5B	−0.825	−0.141		2.06	0.971	49.14[g]	0.049		
$6A_1$	−0.310	−0.272	−0.0454	1.46	0.803	1.810[n]	0.096	0.223	0.149
$6A_2$	−0.230	−0.120	−0.0369	1.47	0.960	3.943[n]	0.681	0.249	0.205
$6B_1$	−0.318	−0.269		1.39	0.801	3.568[n]	0.096		
$6B_2$	−0.236	−0.118		1.41	0.947	8.765[n]	0.681		
$7A_1$	−0.144	−0.117	−0.0283	1.52	0.872	3.163[n]	0.096	0.223	0.149
$7A_2$	−0.179	−0.161	−0.0253	1.52	0.974	6.275[n]	0.681	0.249	0.205
$7B_1$	−0.149	−0.115		1.48	0.867	6.063[m]	0.096		
$7B_2$	−0.183	−0.159		1.48	0.963	12.78[m]	0.681		
$8A_1$	−0.134	0.0128	0.0362	1.43	0.715	1.046[n]	0.096	0.223	0.149
$8A_2$	−0.264	−0.182	0.0374	1.42	0.991	18.41[n]	0.681	0.249	0.205
$8B_1$	−0.128	0.0103		1.49	0.699	1.908[n]	0.096		
$8B_2$	−0.257	−0.185		1.47	0.978	22.24[l]	0.681		
$9A_1$	−0.148	−0.0204	−0.0631	1.50	0.851	2.622[n]	0.096	0.223	0.149
$9A_2$	−0.240	−0.163	−0.0631	1.49	0.972	5.660[m]	0.681	0.249	0.205

Set	$s_{est}{}^d$	$s_\alpha{}^d$	$s_\beta{}^d$	$s_\psi{}^d$	$s_h{}^d$	$t_\alpha{}^e$	$t_\beta{}^e$	$t_\psi{}^e$	$t_h{}^e$	n^f
1A	0.0563	0.130	0.0813	0.112	0.179	4.853[i]	0.531[q]	1.552[o]	10.52[g]	8
1B	0.0638	0.118	0.0896		0.0407	6.396[i]	0.803[p]		39.39[g]	8
2A	0.0509	0.117	0.0767	0.106	0.166	3.032[l]	0.942[p]	0.276[q]	10.24[g]	9
2B	0.0468	0.0929	0.0676		0.0286	3.994[i]	1.157[p]		57.98[g]	9
3A	0.0411	0.0663	0.0536	0.0658	0.112	8.817[g]	0.848[p]	1.515[o]	16.12	12
3B	0.0440	0.0648	0.0492		0.0229	9.654[g]	1.767[o]		71.55[g]	12
4A	0.0411	0.0662	0.0536	0.0657	0.112	7.991[g]	1.629[o]	1.446[o]	14.25[g]	12
4B	0.0435	0.0641	0.0487		0.0227	8.868[g]	2.605[l]		63.35[g]	12
5A	0.0497	0.0969	0.0652	0.0848	0.139	8.147[g]	1.807[o]	0.833[p]	15.66[g]	9
5B	0.0484	0.0849	0.0573		0.0325	9.711[g]	2.469[l]		63.46[g]	9
$6A_1$	0.116	0.217	0.142	0.270	0.406	1.427[p]	1.919[o]	0.168[r]	3.593[l]	7
$6A_2$	0.0283	0.0748	0.0876	0.0659	0.0994	3.073[p]	1.370[p]	0.560[q]	14.78[l]	5
$6B_1$	0.101	0.185	0.122		0.0723	1.720[o]	2.199[m]		19.24[g]	7
$6B_2$	0.0229	0.0599	0.0709		0.0173	3.945[m]	1.658[p]		81.55[g]	5
$7A_1$	0.0389	0.0729	0.0476	0.0904	0.136	0.1971[o]	2.455[m]	0.313[q]	11.19[i]	7
$7A_2$	0.0164	0.0434	0.0508	0.0382	0.0576	4.125[o]	3.167[o]	0.662[q]	26.35[l]	5
$7B_1$	0.0342	0.0627	0.0415		0.0245	2.369[m]	2.767[m]		60.37[g]	6
$7B_2$	0.0139	0.0364	0.0430		0.0105	5.043[l]	3.701[m]		140.8[g]	5
$8A_1$	0.0414	0.0776	0.0507	0.0963	0.145	1.732[o]	0.253[r]	0.375[q]	9.882[i]	7
$8A_2$	0.0135	0.0357	0.0418	0.0314	0.0474	7.394[m]	4.361[o]	1.191[p]	29.90[l]	5
$8B_1$	0.0367	0.0672	0.0445		0.0263	1.909[o]	0.232[r]		56.49[g]	7
$8B_2$	0.0148	0.0387	0.0459		0.0112	6.636[l]	4.024[m]		131.2[g]	5
$9A_1$	0.0324	0.0608	0.0397	0.0754	0.114	2.434[m]	0.0513[q]	0.0837[p]	13.20[g]	7
$9A_2$	0.0247	0.0653	0.0764	0.0575	0.0868	3.679[o]	2.124[p]	1.097[p]	17.14[l]	5

Set	α	β	ψ	h	R	F	r_{12}	r_{13}	r_{23}
$9B_1$	−0.159	−0.0160		1.41	0.812	3.872[n]	0.096		
$9B_2$	−0.251	−0.158		1.39	0.937	7.162[n]	0.681		
$10A_1$	−0.0736	0.00441	0.00799	1.45	0.760	1.366[n]	0.096	0.223	0.149
$10A_2$	−0.137	−0.0924	0.00803	1.44	0.9995	345.1[l]	0.681	0.249	0.205
$10B_1$	−0.0723	0.00386		1.46	0.757	2.684[n]	0.096		
$10B_2$	−0.135	−0.0930		1.45	0.997	187.3[i]	0.681		
$11A_1$	−0.151	−0.0378	−0.0326	1.43	0.854	2.701[n]	0.096	0.223	0.149
$11A_2$	−0.243	−0.179	−0.0327	1.42	0.981	8.516[n]	0.681	0.249	0.205
$11B_1$	−0.157	−0.0355		1.38	0.844	4.941[m]	0.096		
$11B_2$	−0.249	−0.177		1.37	0.971	16.24[m]	0.681		
12A	−0.379	−0.235	−0.157	1.70	0.987	25.77[l]	0.333	0.556	0.060
12B	−0.509	−0.281		1.46	0.942	11.89[l]	0.333		
13A	−0.226	−0.196	−0.135	1.16	0.962	8.370[n]	0.333	0.556	0.060
13B	−0.338	−0.236		0.954	0.900	6.416[m]	0.333		
14A	−0.230	−0.202	−0.130	1.18	0.975	13.00[m]	0.333	0.556	0.060
14B	−0.339	−0.240		0.979	0.917	7.900[m]	0.333		
15A	−0.239	−0.203	−0.131	1.21	0.975	12.84[m]	0.333	0.556	0.060
15B	−0.348	−0.242		1.01	0.918	8.032[m]	0.333		

TABLE II (*Continued*)

Set	α	β	ψ	h	R	F	r_{12}	r_{13}	r_{23}
16A	−0.230	−0.239	−0.139	1.26	0.998	88.88[m]	0.341	0.580	0.032
16B	−0.344	−0.271		1.05	0.931	6.522[n]	0.341		
17A	−0.141	−0.230	−0.0789	0.846	0.708	2.339[n]	0.010	0.614[m]	0.163
17B	−0.201	−0.241		0.730	0.696	3.753[m]	0.010		
18A	−0.436	−0.336	−0.0405	1.41	0.952	16.08[i]	0.090	0.627	0.111
18B	−0.466	−0.338		1.35	0.951	28.07[o]	0.090		

Set	s_{est}	s_α	s	s_ψ	s_h	t_α	t_β	t_ψ	t_h	n
$9B_1$	0.0312	0.0571	0.0378		0.0224	2.778[m]	0.422[q]		62.87[o]	5
$9B_2$	0.0259	0.0677	0.0802		0.0196	3.709[m]	1.975[o]		71.11[o]	5
$10A_1$	0.0198	0.0372	0.0243	0.0462	0.0696	1.977[o]	0.181[r]	0.173[r]	20.86[o]	7
$10A_2$	0.00163	0.00430	0.00503	0.00379	0.00571	31.76[l]	18.36[l]	2.122[p]	252.6[i]	5
$10B_1$	0.0173	0.0317	0.0210		0.0124	2.282[m]	0.184[r]		118.0[o]	7
$10B_2$	0.00270	0.00705	0.00834		0.00204	19.18[i]	11.15[i]		713.2[o]	5
$11A_1$	0.0314	0.0588	0.0384	0.0730	0.110	2.573[m]	0.983[p]	0.446[q]	13.00[o]	7
$11A_2$	0.0191	0.0506	0.0592	0.0446	0.0672	4.800[o]	3.025[p]	0.0735[q]	21.09[l]	5
$11B_1$	0.0281	0.0514	0.0341		0.0201	3.052[l]	1.043[p]		68.61[o]	7
$11B_2$	0.0168	0.0439	0.0519		0.0127	5.666[l]	3.409[m]		107.8[o]	5
12A	0.0280	0.0811	0.0567	0.0598	0.0927	4.668[l]	4.136[m]	2.623[o]	18.37[i]	6
12B	0.0482	0.110	0.0927		0.0345	4.611[j]	3.031[m]		42.39[o]	6
13A	0.0356	0.103	0.0722	0.0760	0.118	2.191[o]	2.722[o]	1.771[p]	9.829[i]	6
13B	0.0466	0.107	0.0897		0.0334	3.165[m]	2.635[m]		28.56[o]	6
14A	0.0287	0.0830	0.0581	0.0611	0.0948	2.776[o]	3.472[m]	2.132[o]	12.41[i]	6
14B	0.0423	0.0969	0.0815		0.0303	3.494[l]	2.949[m]		32.27[o]	6
15A	0.0294	0.0851	0.0595	0.0627	0.0972	2.813[o]	3.411[m]	2.092[o]	12.41[i]	6
15B	0.0428	0.0981	0.0824		0.0307	3.551[l]	2.934[m]		32.82[o]	6
16A	0.0110	0.0318	0.0250	0.0236	0.0365	7.255[m]	9.561[m]	5.881[o]	34.41[j]	5
16B	0.0463	0.107	0.103		0.0332	3.223[m]	2.631[o]		31.54[i]	5
17A	0.0814	0.197	0.109	1.64	0.246	0.716[p]	2.112[m]	0.483[q]	3.445[j]	11
17B	0.0774	0.146	0.101		0.0500	1.370[p]	2.386[l]		14.62[o]	11
18A	0.0533	0.126	0.0734	0.108	0.163	3.470[j]	4.583[i]	0.376[q]	8.642[o]	9
18B	0.0493	0.0910	0.0678		0.0336	5.117[i]	4.992[i]		40.17[o]	9

Set	α	β	ψ	h	R	F	r_{12}	r_{13}	r_{23}
19A	−0.236	−0.106	−0.0762	1.30	0.751	1.725[n]	0.210	0.616	0.010
19B	−0.296	−0.118		1.18	0.729	2.841[n]	0.210		
$20A_1$	−0.446	−0.326	0.0787	0.780	0.865	7.943[i]	0.283	0.350	0.099
$20A_2$	−0.402	−0.760	−0.0866	1.04	0.893	7.856[k]	0.121	0.307	0.423
$20B_1$	−0.421	−0.326		0.904	0.861	12.90[h]	0.283		
$20B_2$	−0.431	−0.699		0.901	0.888	13.08[h]	0.121		
$21A_1$	−0.259	−0.0263	0.0203	0.308	0.856	7.305[k]	0.283	0.350	0.099
$21A_2$	−0.245	−0.0265	0.00943	0.323	0.865	5.917[l]	0.121	0.307	0.423
$21B_1$	−0.253	−0.0263		0.340	0.854	12.13[h]	0.283		
$21B_2$	−0.242	−0.0331		0.338	0.864	10.32[i]	0.121		
$22A_1$	−0.262	−0.326	0.0131	0.360	0.854	7.160[k]	0.283	0.350	0.099
$22A_2$	−0.245	−0.0345	0.000108	0.378	0.867	6.047[l]	0.121	0.307	0.423
$22B_1$	−0.258	−0.0326		0.381	0.853	12.01[h]	0.283		
$12B_2$	−0.245	−0.0346		0.378	0.867	10.58[i]	0.121		
$23A_1$	−0.301	−0.0311	0.0686	0.361	0.823	5.589[k]	0.283	0.350	0.099
$23A_2$	−0.278	−0.107	0.0284	0.421	0.828	4.367[m]	0.121	0.307	0.423
$23B_1$	−0.279	−0.0311		0.469	0.807	8.386[i]	0.283		
$23B_2$	−0.269	−0.127		0.465	0.826	7.510[k]	0.121		
24A	0.253	0.143	−0.122	−0.687	0.986	11.73[n]	0.231	0.431	0.207
24B	0.201	0.153		−0.865	0.905	4.542[n]	0.231		
25A	0.351	0.0631	0.00841	−1.06	0.975	6.288[n]	0.231	0.431	0.207
25B	0.355	0.0624		−1.05	0.974	18.67[m]	0.231		
26A	0.230	0.155	−0.0749	−0.751	0.9997	498.6[l]	0.231	0.431	0.207
26B	0.198	0.161		−0.860	0.968	14.86[m]	0.231		
27A	0.121	0.120	0.0251	0.302	0.935	20.94[o]	0.057	0.159	0.158
27B	0.125	0.124		0.343	0.928	30.90[o]	0.057		

Set	s_{est}	s_α	s_β	s_ψ	s_h	t_α	t_β	t_ψ	t_h	n
19A	0.0687	0.175	0.143	0.140	0.213	1.352[p]	0.745[p]	0.543[q]	6.097[i]	8
19B	0.0637	0.126	0.131		0.0428	2.346[m]	0.906[p]		27.66[o]	8
$20A_1$	0.0995	0.155	0.111	0.164	0.264	2.872[l]	2.940[j]	0.481[q]	2.959[j]	12
$20A_2$	0.0899	0.145	0.253	0.175	0.279	2.771[l]	3.008[l]	0.494[q]	3.718[i]	10
$20B_1$	0.0951	0.140	0.106		0.0545	3.010[j]	3.074[j]		16.61[o]	12
$20B_2$	0.0849	0.126	0.208		0.0488	3.425[j]	3.355[j]		18.46[o]	10
$21A_1$	0.0402	0.0628	0.0447	0.0661	0.107	4.132[i]	0.588[q]	0.308[q]	2.893[l]	12
$21A_2$	0.0395	0.0639	0.111	0.0771	0.123	3.833[i]	0.238[r]	0.122[r]	2.635[l]	10

TABLE II (*Continued*)

Set	s_{est}	s_α	s_β	s_ψ	s_h	t_α	t_β	t_ψ	t_h	n
$21B_1$	0.0381	0.0560	0.0424		0.0218	4.512[i]	0.620[q]		15.60[g]	12
$21B_2$	0.0367	0.0543	0.0900		0.0211	4.451[i]	0.368[q]		16.03[g]	10
$22A_1$	0.0419	0.0654	0.0466	0.0688	0.111	4.011[i]	0.700[q]	0.191[r]	3.245[j]	12
$22A_2$	0.0397	0.0641	0.112	0.0775	0.123	3.826[i]	0.309[q]	0.139[r]	3.068[l]	10
$22B_1$	0.0396	0.0581	0.0440		0.0226	4.437[i]	0.741[p]		16.82[g]	12
$22B_2$	0.0368	0.0545	0.0903		0.0211	4.504[i]	0.383[q]		17.87[g]	10
$23A_1$	0.0518	0.0809	0.0577	0.0852	0.137	3.721[i]	0.539[q]	0.806[k]	2.627[l]	12
$23A_2$	0.0543	0.0876	0.153	0.106	0.168	3.172[j]	0.699[q]	0.269[q]	2.501[l]	10
$23B_1$	0.0508	0.0747	0.0565		0.02913	3.738[i]	0.549[q]		16.13[g]	12
$23B_2$	0.0506	0.0749	0.124		0.0290	3.588[i]	1.020[p]		16.01	10
24A	0.0204	0.0545	0.0343	0.0520	0.0773	4.638[o]	4.172[o]	2.351[k]	8.881[m]	5
24B	0.0369	0.0902	0.0614		0.0272	2.232[o]	2.487[o]		31.75[g]	5
25A	0.0335	0.0893	0.0561	0.0853	0.127	3.934[o]	1.125[p]	0.099[r]	8.405[m]	5
25B	0.0238	0.0581	0.0396		0.0175	6.109[l]	1.578[p]		59.95[g]	5
26A	0.00305	0.00812	0.00510	0.00775	0.0115	28.29[l]	30.34[l]	9.663[m]	65.18[j]	5
26B	0.0209	0.0511	0.0348		0.0154	3.880[m]	4.624[l]		55.73[g]	5
27A	0.0167	0.0224	0.0218	0.0251	0.0417	5.430[g]	5.491[g]	1.001[p]	7.243[g]	13
27B	0.0167	0.0220	0.0215		0.00849	5.684[g]	5.743[g]		40.37[g]	13

[a] Multiple correlation coefficient. [b] F test for significance of regression. [c] Partial correlation coefficients of σ_I on σ_R, σ_I on r_V, and σ_R on r_V, respectively. [d] Standard errors of the estimate, α, β, ψ, and h. [e] "Student's t tests" for significance of α, β, ψ, and h. [f] Number of points in set. [g] 99.9% confidence level (cl). [h] 99.5% cl. [i] 99.0% cl. [j] 98.0% cl. [k] 97.5% cl. [l] 95.0% cl. [m] 90.0% cl. [n] <90.0% cl. [o] 80.0% cl. [p] 50% cl. [q] 20% cl. [r] <20% cl.

Waals radius term in eq 4. This confidence level is obtained by means of a "Student's t test" of ψ.

If ψ is not significant, this implies either (a) the existence of cases 2, 3, or 4, or (b) the choice of a steric parameter was incorrect. The data are now correlated with eq 8. If the correlations with eq 4 and 8 are both unsuccessful, this implies either case 1 and an incorrect steric parameter or case 2. It is not possible to distinguish between these situations at the present time. If the data are well correlated by eq 8, cases 1 and 2 may be ruled out, as the data in these cases must include a variable steric term which is not accounted for by eq 8. Thus lack of significance of ψ in correlations with eq 4 coupled with successful correlation with eq 8 indicates the existence of case 3 or case 4. These cases may be distinguished by comparing the experimentally observed value of h (that data point for which X = H), with the calculated value obtained from the correlation. In case 3, $h_{obsd} \neq h_{calcd}$, whereas in case 4 $h_{obsd} = h_{calcd}$.

The σ_I constants used in these correlations are from our compilation;[9] the σ_R constants were obtained from the equation

$$\sigma_R = \sigma_p - \sigma_I \qquad (9)$$

using the σ_p values of McDaniel and Brown.[10] Values of r_V were taken from the collection of Bondi[11] or were group values calculated by us.[4] The correlations were carried out by multiple linear regression analysis.[12]

In several of the sets studied, ionizable substituents were excluded[13] because at the pH of the medium in which the $E_{0.5}$ values were determined, these groups are ionized to some extent. Results for sets 6–11 are considerably improved by exclusion of the values for the amino and dimethylamino groups. These groups seemed to deviate considerably in correlations of the $E_{0.5}$ values for the corresponding meta- and para-substituted phenyl tosylates in some of the sets. The nitro group was excluded from sets 6–8 as it is reportedly reduced by a mechanism differing from that common to the other groups in the set.[14] Sets 20–23 were correlated both including and excluding the values for the hydroxy and amino groups as it has been suggested that they are reduced by a mechanism differing from that which is observed for the other substituents.[15]

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(13) Reference 2, p 49.

Results

Results of the correlations are presented in Table II. Sets labeled A were correlated with eq 4; sets labeled B were correlated with eq 8.

The confidence levels of r_{12}, r_{13}, and r_{23} are all <90.0% unless otherwise noted.

Halobenzenes.—Of the four sets of iodobenzenes (sets 1–4), two gave excellent, one gave good, and one gave poor results for correlations eq 4. With eq 8, one set gave good and three sets gave excellent correlations. The bromobenzenes (set 5) gave an excellent correlation with both eq 4 and 8.

Phenyl Tosylates.—Best results were obtained for correlations excluding the amino and dimethylamino groups (sets 6–$11A_2$ and 6–$11B_2$). Four sets did not give significant correlations with eq 4, one set gave poor results, and one set gave fair results. With eq 8, one set gave very good, one fair, and two produced poor results; two sets did not give significant correlations.

Benzaldehydes.—Of the eight sets of benzaldehydes (sets 12–19), one gave very good, one fair, and three gave poor results. Three sets did not give significant correlations with eq 4. Correlation with eq 8 gave poor results for four sets, excellent for one set, fair for one set. Two sets did not give significant results.

Nitrobenzenes.—The four sets of nitrobenzenes in neutral or acid media (sets 20–23) were correlated both with (A_1 and B_1 sets) and without (A_2 and B_2 sets) the values for the amino and hydroxy groups. The results are not greatly affected by the exclusion of these values.

(14) Footnote *e*, Table I.
(15) Reference 2, p 78.

With eq 4, three sets gave good and one set gave very good results. With eq 8, three sets gave excellent and one set gave very good results. Of the three sets of nitrobenzenes in alkaline media, one gave fair correlation with eq 4, whereas two did not give significant correlations. With eq 8, two sets gave poor results and one set did not give significant correlation.

Phenylferrocenes.—The phenylferrocenes (set 27) gave excellent correlations with both eq 4 and eq 8.

Overall, significant correlations with eq 4 were obtained for 18 of the 27 sets studied, whereas, for correlation with eq 8, 22 sets gave significant results.

Discussion

Steric Effect.—We may now consider the question of the presence of steric effects in terms of our previous discussion. Only one of the 27 sets correlated with eq 4 gave a significant value of ψ, and even in this case ψ was barely significant. We conclude that we may reject the existence of a steric effect related to the van der Waals radii of the group. As successful correlations were obtained with eq 8 in 22 of the 27 sets studied, we may exclude the existence of a steric effect represented by some other parameters other than the van der Waals radius in most if not all cases. We may also exclude the existence of a steric effect which does not obey a linear free-energy relationship (case 2) at least in those sets which are correlated by eq 8. As for those five sets which are not correlated by eq 8, no conclusions can be reached as the lack of correlation may be due to causes other than the presence of a steric effect. Since in those sets which are correlated by eq 8, the value for X = H lies on the correlation line, $h_{obsd} = h_{calcd}$ and we may reject the possibility of the existence of a constant steric effect (case 3). We are forced to the conclusion that, in general, the polarographic data studied in this work exemplify the absence of any steric effect (case 4). This result is in agreement with our findings for other ortho substituted benzene data.[4,6-8,16] It again *refutes* the often quoted concept that the so-called proximity effect of ortho substituents is largely steric in nature.

Magnitude of the Electrical Effect.—The magnitude of the electrical effect is measured by the value of α. The bromobenzenes give the largest value of α. Somewhat smaller values are found for the iodobenzenes. The benzaldehydes and nitrobenzenes give about the same average value of α of 0.3. Thus, for bromobenzenes α is about 2.7 times the value of α observed for benzaldehydes and nitrobenzenes. The tosylates gave an average value of α of 0.2.

Composition of the Ortho Electrical Effect.—We may conveniently describe the composition of the electrical effect of a substituent in terms of ϵ where[17]

$$\epsilon = \beta/\alpha \qquad (10)$$

(16) M. Charton and B. I. Charton, *J. Org. Chem.*, **33**, 3872 (1968).

For the purpose of calculating values of ϵ, α, and β, values taken from the correlations with eq 8 were used as, in general, best results were obtained for correlation with eq 8. Values of ϵ are in Table III. The values

TABLE III
VALUES OF ϵ

Set	ϵ	Set	ϵ	Set	ϵ
1	0[a]	11	0.71	20	0.77
2	0[a]	12	0.55	21	0[a]
3	0[a]	13	0.70	22	0[a]
4	0.22	14	0.71	23	0[a]
5	0.17	15	0.70	25	0[a]
7	0.87	17	...[b]	26	0.81
8	0.72	18	0.73	27	0.99
10	0.69				

[a] β was not significant. [b] α was not significant.

of ϵ obtained for the iodobenzenes lie in the range 0–0.2. The value for the bromobenzenes lies in the same range. There does not seem to be any effect of solvent on ϵ values, although the data are too scanty to make this conclusion certain. An average value of ϵ of 0.7 is obtained for the benzaldehyde (excluding set 17). There seems to be no dependence of ϵ on pH or on medium. With the exception of sets 20 and 26 for which ϵ equals 0.8, the nitrobenzenes generally have low values of ϵ. Again, there seems to be no dependence on pH. It is interesting that, although the magnitude of the electrical effect is about the same for benzaldehydes as for nitrobenzenes, the composition of the electrical effect is very different. We are unable at the present time to explain this observation.

The phenylferrocenes give a value of ϵ of 0.99. It is difficult to compare this result with the other values obtained, however, as this represents the results of the correlation of chronopotentiometric quarter-wave potentials, whereas the other ϵ values have generally been obtained for polarographic half-wave potentials.

The results obtained show clearly the impossibility of defining a single generally useful set of ortho-substituent constants to be used for all ortho-substituted sets.[18] The values of ϵ obtained range from 0 to 0.99.

The Inclusion of the Unsubstituted Member of the Set.—It has been noted that the value of hydrogen (the unsubstituted compound) frequently does not lie on the correlation line for ortho-substituted compounds. This does not seem to be the case for polarographic half-wave potentials. Inclusion of the value for hydrogen in all sets seems, if anything, to have improved the correlations. We conclude that in the case of polarographic data, the value for the unsubstituted compound does in fact lie on the correlation line.

(17) M. Charton, *J. Amer. Chem. Soc.*, **86**, 2033 (1964).
(18) M. Charton, *ibid.*, **91**, 6649 (1969).

The Nature of the Ortho Effect. VII. Nuclear Magnetic Resonance Spectra

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Twenty-seven sets of nmr chemical shifts and related data for ortho-substituted benzenes and naphthalenes were correlated with the equation $Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + \psi r_V + h$ and the extended Hammett equation $Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + h$. Significant correlations were obtained for 22 of 26 sets correlated with the former equation and 24 of 27 sets correlated with the latter equation. The results obtained show that ψ is not significant in most of the sets studied and that better correlation is generally obtained with the latter equation than with the former. There is no steric effect exerted by the ortho substituents in most of the sets studied. The substituent effect, thus, is purely electrical. The composition of the electrical effect depends upon structure and solvent. For the chemical shifts of aromatic ring protons, the resonance effect predominates. In the majority of the sets studied, the value for the unsubstituted compound does lie on the correlation line.

In continuation of our studies[1-6] on the nature of the ortho effect, it seemed of interest to investigate nmr spectra. A number of authors have attempted the correlation of nmr data with the simple Hammett equation

$$Q_X = \rho\sigma_X + h \quad (1)$$

Thus, Bray and Barnes[7] found a linear correlation between the Cl^{35} pure quadrupole resonance frequencies in substituted dichlorobenzenes, including ortho-substituted compounds, and Hammett substituent constants. For the ortho-substituted compounds, substituent constants were defined from the ionization constants of 2-substituted benzoic acids. A correlation between the chemical shifts of ortho protons in substituted benzenes and the σ_p constants was reported by Diehl[8] and Kondo, *et al.*,[9] report the correlation of the infinite dilution chemical shifts of 2-substituted benzoic acids with σ_p and with the Taft σ_o^* constants The definition of σ_o constants from the OH chemical shifts of 2-substituted phenols has been proposed by Traynham and his coworkers.[10,11] The correlation of OH chemical shifts for 2-substituted phenols with σ_o^* has been reported by Dietrich, Nash, and Keller.[12] The NH chemical shifts of 2-substituted anilines have been correlated with both σ_p and σ_o by Lynch, MacDonald, and Webb.[13] The chemical shifts of the S ring protons of 2-substituted N^4-acetyl-N^1-phenylsulfanilamides are said to be correlated by the σ_o^* constants according to Cammarata and Allen.[14] The proton and ^{13}C chemical shifts in 2-substituted pyridines are correlated with σ_p by Retcofsky and McDonald.[15] Infinite dilution chemical shifts of substituted benzenes were correlated with the extended Hammett equation

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + h \quad (2)$$

by Hayamizu and Yamamoto.[16]

In all of this work, there has been no systematic attempt to determine whether or not steric effects are present or with the exception of the work of Hayamizu and Yamomoto to ascertain the composition of the electrical effect.

It will be useful at this point to review our method[6] for determining the presence or absence of steric effects. There are four cases of interest to us. They are the following. (1) The steric effect obeys a linear free energy relationship. Then using a suitable steric parameter, we may write an equation including both electrical and steric effects such as

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + \psi\zeta_X + h \quad (3)$$

where σ_I is a measure of the localized electrical effect, σ_R is a measure of the delocalized electrical effect, and ζ_X is a measure of the steric effect. As a steric effect parameter, we have chosen the van der Waals radius of that atom or group of atoms which is bonded to the benzene ring. Thus, we have the expression

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + \psi r_{V,X} + h \quad (4)$$

(2) The steric effect does not obey a linear free energy relationship. We may then write for any particular datum in the set

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + S_X + h \quad (5)$$

where S_X is the steric effect of the X substituent and is independent of any linear free energy relationship.

(3) The steric effect is constant. In this event

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + h' \quad (6)$$

where

$$h' = h + S_X \quad (7)$$

(4) The steric effect is negligible or nonexistent. Then

$$Q_X = \alpha\sigma_{I,X} + \beta\sigma_{R,X} + h \quad (2)$$

Equations 2 and 6 are equivalent.

In order to detect the presence or absence of a steric effect the data are correlated with eq 2 and 4.

Successful correlations with eq 4 are not in themselves sufficient to imply the existence of case 1. Conclusive

(1) M. Charton, *J. Org. Chem.*, **34**, 278 (1969).
(2) M. Charton, *J. Amer. Chem. Soc.*, **91**, 615 (1969).
(3) M. Charton, *ibid.*, **91**, 619 (1969).
(4) M. Charton, *ibid.*, **91**, 624 (1969).
(5) M. Charton, *ibid.*, **91**, 6649 (1969).
(6) M. Charton and B. I. Charton, Abstracts, 4th Mid-Atlantic Regional Meeting of the American Chemical Society, Washington, D. C., Feb 1969.
(7) P. J. Bray and R. G. Barnes, *J. Chem. Phys.*, **27**, 551 (1957).
(8) P. Diehl, *Helv. Chim. Acta*, **44**, 829 (1961).
(9) Y. Kondo, K. Kondo, T. Takemoto, and T. Ikenoue, *Chem. Pharm. Bull.*, **14**, 332 (1966).
(10) J. G. Traynham and G. A. Knesel, *J. Org. Chem.*, **31**, 3350 (1966).
(11) M. T. Tribble and J. G. Traynham, *J. Amer. Chem. Soc.*, **91**, 379 (1969).
(12) M. W. Dietrich, J. S. Nash, and R. E. Keller, *Anal. Chem.*, **38**, 1474 (1966).
(13) B. M. Lynch, B. C. MacDonald, and J. G. K. Webb, *Tetrahedron*, **24**, 3595 (1968).
(14) A. Cammarata and R. C. Allen, *J. Med. Chem.*, **11**, 204 (1968).
(15) H. L. Retcofsky and F. R. McDonald, *Tetrahedron Lett.*, 2575 (1968).
(16) K. Hayamizu and O. Yamamoto, *J. Mol. Spectrosc.*, **29**, 183 (1969).

TABLE I

DATA USED IN CORRELATIONS

1. δ_0. Disubstituted benzenes (Pr_2):[a] NH_2, 68; OH 56; OMe, 42; F, 25; Me, 17; Cl, −5; Br, −22; CN, −35; I, −41; CO_2Me, −74; NO_2, −98.
2. δ_0. Disubstituted benzenes (CCl_4, 35°):[b] MeNH, 0.80; NH_2, 0.75; OH, 0.52; OMe, 0.47; Me, 0.21; Et, 0.18; *i*-Pr, 0.16; *tert*-Bu, −0.02; Cl, −0.03; CH_2Cl, −0.05; CH_2Br, −0.18; Br, −0.18; I, −0.35; CN, −0.35; Ac, −0.60; CO_2Me, −0.67; NO_2, −0.93.
3. $\Delta\delta_0$. Substituted benzenes (c-C_6H_{12}):[c] F, 18.5; Cl, −1.2; Br, −13.4; I, −24.0; OMe, 26.0; NH_2, 45.3; NMe_2, 36.0; CHO, −34.8; NO_2, −56.9.
4. δ_0. Substituted benzenes (CCl_4):[d] NO_2, −95.2; COCl, −84.0; COBr, −80.1; SO_2Cl,[e] −76.5; CO_2Me, −71.3; CO_2-*i*-Pr, −70.2; CO_2-*i*-Bu, −71.5; Ac, −61.9; COEt, −62.5; CHO, −56.1; SO_2Me, −60.4; CCl_3, −63.8; CN, −36.1; I, −38.8; Br, −18.3; Cl, −2.6; OAc, 25.2; OMe, 48.4; OH, 55.8; NH_2, 74.6; NHMe, 79.5; NMe_2, 65.9; Me, 20.1; *tert*-Bu, −1.9.
5. δ_{H^2}. 1-Substituted 3,4-dimethoxybenzenes (c-C_6H_{12}):[f] NH_2, 1.09; OMe, 0.80; Me, 0.62; H, 0.47; Br, 0.35; CHO, −0.11; CO_2Me, −0.28; NO_2, −0.37.
6. δ_{H^5}. 1-Substituted 3,4-dimethoxybenzenes (c-C_6H_{12}):[f] NH_2, 1.17; OMe, 0.96; Me, 0.62; H, 0.47; Br, 0.31; CHO, −0.05; CO_2Me, −0.35; NO_2, −0.52.
7. δ_{H^1}. 2-Substituted naphthalenes (c-C_6H_{12}):[g] NH_2, 0.43; OMe, 0.25; Me, −0.13; H, −0.50; Cl, −0.53; Br, −0.66; CN, −0.83; Ac, −1.12; CHO, −0.96; CO_2Me, −1.23.
8. δ_{H^3}. 2-Substituted naphthalenes (c-C_6H_{12}):[g] NH_2, 0.50; OMe, 0.16; Me, −0.09; H, −0.16; Cl, −0.18, Br, −0.26; CN, −0.32; Ac, −0.78; CHO, −0.66; CO_2Me, −0.70.
9. δ_{H^1}. 2-Substituted 6-methoxynaphthalenes (CCl_4):[g] NH_2, 0.44; OMe, 0.32; Et, −0.17; H, −0.44; Br, −0.56; Ac, −0.98; CO_2Me, −1.17.
10. δ_{H^3}. 2-Substituted 6-methoxynaphthalenes (CCl_4):[g] NH_2, 0.45; OMe, 0.36; Et, 0.08; H, −0.03; Br, −0.11; Ac, −0.64; CO_2Me, −0.68.
11. δ_{H^4}. 5-Substituted benzo[*b*]thiophenes ($CDCl_3$):[h] NH_2, 0.75; OH, 0.61; OMe, 0.54; Me, 0.35; OAc, 0.34; D, 0; OSO_2Me,[e] 0.07; Cl, 0.07; CH_2OH, 0.09; CH_2Cl, 0.01; Br, −0.10; CN, −0.28; NHAc, −0.29; I, −0.34; CHO, −0.46; CO_2Me, −0.72; CO_2H, −0.80; NO_2, −0.89.
12. δ_{H^6}. 5-Substituted benzo[*b*]thiophenes ($CDCl_3$):[h] NH_2, 0.60; OH, 0.43; OMe, 0.35; Me, 0.31; OAc, 0.31; D, 0; OSO_2Me,[e] 0.08; Cl, 0.07; CH_2OH, 0.08; CH_2Cl, −0.01; Br, −0.06; CN, −0.18; NHAc, 0.02; I, −0.25; CHO, −0.51; CO_2Me, −0.66; CO_2H, −0.73; NO_2, −0.84.
13. δ sulfanilyl ring protons. 2′-Substituted N^4-acetyl-N^1-phenylsulfanilamides (THF):[i] MeO, 6.0; Cl, 4.0; Br, 3.7; I, 3.5; NO_2, −1.0.
14. $\tau_{o\text{-Me}}$. Substituted mesitylenes (Pr_2):[j] F, 7.85; Cl, 7.74; Br, 7.68; I, 7.62; OH, 7.90; NH_2, 7.98; NO_2, 7.81; H, 7.81.
15. $\tau_{o\text{-Me}}$. Substituted durenes (Pr_2):[j] F, 7.91; Cl, 7.76; Br, 7.71; I, 7.62; OH, 7.92; NH_2, 8.07; NO_2, 7.95; H, 7.88.
16. δ_{Me}. 2-Substituted toluenes (neat, 11–12°):[k] NO_2, 1.09; CN, 0.99; Cl, 0.78; Me, 0.61; OH, 0.76; NH_2, 0.37; H, 0.75.
17. δ_{Me}. 2-Substituted toluenes (Ph, 11–12°):[k] NO_2, 0.80; CN, 0.73; Cl, 0.71; Me, 0.61; OH, 0.69; NH_2, 0.39; H, 0.71.
18. δ_{Me}. 2-Substituted toluenes (pyridine, 11–12°):[k] NO_2, 1.14; CN, 1.02; Cl, 0.85; Me, 0.74; OH, 1.11; NH_2, 0.88; H, 0.81.
19. δ_{Me}. 2-Substituted toluenes (dioxane, 11–12°):[k] NO_2, 1.18; CN, 1.12; Cl, 0.91; Me, 0.77; OH, 0.74; NH_2, 0.61; H, 0.89.
20. δ_{Me}. 2-Substituted toluenes (CCl_4, 11–12°):[k] NO_2, 1.16; CN, 1.11; Cl, 0.93; Me, 0.81; OH, 0.77; NH_2, 0.58; H, 0.90.
21. δ_{OH}. 2-Substituted phenols (Me_2SO, 28°):[l] Me, −9.14; Ph, −9.38; Cl, −9.96; Br, −10.14.
22. δ_{OH}. 2-Substituted phenols (Me_2SO, 40°):[m] F, 9.70; Cl, 10.00; Br, 10.07; I, 10.20; NO_2, 10.8; Cn, 10.97; CF_3, 10.44; Me, 9.10; Et, 9.07; Pr, 9.06; *i*-Pr, 9.07; *sec*-Bu, 9.03; *tert*-Bu, 9.17; $ViCH_2$, 9.19; $PhCH_2$, 9.29; CH_2OH, 9.18; Ph, 9.46; CHO, 10.75; Ac, 11.97; Bz, 10.61; CO_2Me, 10.55; OH, 8.70; OMe, 8.76; OEt, 8.66; NHAc, 9.29; NMe_2, 8.78; MeS, 9.59; MeSO, 10.50.
23. δ_{OH}. 2-Substituted phenols (hexamethylphosphoramide, 40°):[n] H, 10.30; Me, 10.22; Et, 10.20; Pr, 10.18; *i*-Pr, 10.22; *sec*-Bu, 10.17; *tert*-Bu, 10.33; c-C_6H_{11}, 10.15; Ac, 11.88; Br, 11.27; CHO, 11.67; I, 11.35; MeO, 9.92; NO_2, 12.1; Ph, 10 57.
24. δ_{NH}. 2-Substituted anilines (Me_2SO, 37°):[o] Me, 278.0; OMe, 276.0; OEt, 274.0; Cl, 312.0; Br, 312.0; NO_2, 440.0.
25. τ_{OMe}. 2-Substituted anisoles (CCl_4, 30°):[p] Me, 6.35; NH_2, 6.34; NO_2, 6.16; Br, 6.18; I, 6.22; CO_2H, 6.22; AcNH, 6.24; Ph, 6.37; H, 6.34.
26. $J^{13}_{C\text{-}F}$. 2-Substituted fluorobenzenes (neat or CCl_4, 25°):[q] NH_2, 236.7; OH, 241.6; OMe, 246.2; F, 254.5; CHO, 256.4.
27. $f_{^{35}Cl}$. 2-Substituted chlorobenzenes (77°K):[r] NO_2, 37.260; Cl, 35.755; CO_2H, 36.305; NHAc, 35.150; CN, 35.500.

[a] Reference 8. [b] N. Van Meurs, *Recl. Trav. Chim. Pays-Bas.*, 87, 145 (1968). [c] H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, 35, 731 (1961). [d] Reference 16 and K. Hayamizu and O. Yamamoto, *J. Mol. Spectrosc.*, 28, 89 (1968). [e] This value was not included in the correlation as constants for it are unknown. [f] M. Suzuki, *Chem. Pharm. Bull.*, 16, 1193 (1968). [g] Y. Sasaki, M. Suzuki, T. Hibino, K. Karai, M. Hatanaka, and I. Shiraishi, *ibid.*, 16, 1367 (1968). [h] B. Caddy, M. Martin-Smith, R. K. Norris, S. T. Reid, and S. Sternhell, *Aust. J. Chem.*, 21, 1853 (1968). [i] Reference 14. [j] P. Diehl and G. Svegliado, *Helv. Chim. Acta*, 46, 461 (1963). [k] N. Nakagawa and S. Fujiwara, *Bull. Chem. Soc. Jap.*, 34, 143 (1961). [l] Reference 10. [m] Reference 11. [n] Reference 12. [o] Reference 13. [p] C. Heathcock, *Can. J. Chem.*, 40, 1865 (1962). [q] S. Mohanty and P. Venkateswarlu, *Mol. Phys.*, 12, 277 (1967). [r] Reference 7.

evidence may be obtained from the confidence level of ψ, the coefficient of the van der Waals radius term in eq 4. This confidence level is obtained by means of a "Student's t test" for the significance of ψ. When the confidence level of ψ is $\geqq 90.0$, the steric effect term is considered significant. A lack of correlation with eq 4 coupled with a lack of correlation by eq 2 does not imply case 2. It may also be the result of case 1 due to faulty choice of the steric parameter. Correlation by eq 2 implies the existence of either case 3 or case 4, as, if steric effects are present and unaccounted for, no correlation with eq 2 is to be expected. Case 3 may be distinguished from case 4 by a comparison of h_{obsd} (the value for the unsubstituted compound) with h_{calcd} from the correlation. When

$$h_{obsd} \neq h_{calcd} \tag{8}$$

case 3 occurs, whereas when

$$h_{obsd} = h_{calcd}$$

case 4 results. The data have been correlated with eq 2 and 4 by means of multiple linear regression analysis.[17] The data used in the correlation are set forth in Table I.

(17) K. A. Brownlee, "Statistical Theory and Methodology in Science and Engineering," 2nd ed, Wiley, New York, N. Y., 1965; E. L. Crow, F. A. Davis, and M. W. Maxfield, "Statistics Manual," Dover Publications, New York, N. Y., 1960.

TABLE II
SUBSTITUENT CONSTANTS

Subst	σ_I	Ref	σ_R	Ref	Subst	σ_I	Ref	σ_R	Ref
COCl	0.44	*a*	0.19	*b*	COBr	0.45	*c*	0.19	*b*
CO_2-*i*-Pr	0.34	*d*	0.11	*e*	CO_2-*i*-Bu	0.34	*d*	0.11	*e*
COEt	0.29	*f*	0.09	*b*	NH_2	0.10	*a*		
NHMe	0.10	*a*			NMe_2	0.10	*a*		
$ViCH_2$			−0.13	*g*	$PhCH_2$			−0.14	*h*
MeS			−0.35	*i*	*c*-C_6H_{11}			−0.12	*j*
OAc	0.42	*a*	−0.12	*k*					

[a] M. Charton and B. I. Charton, *J. Chem. Soc. B*, 43 (1967). [b] σ_p was calculated from $\sigma_{p,COX} = 0.546\ \sigma_{m,X} + 0.422$; σ_R was then calculated from eq 4. [c] This value is an average of values of 0.25 and 0.21 calculated from the equation $\sigma_{I,COX} = 0.308\ \sigma_{m,X} + 0.31$ (determined from pK_a values) and $\sigma_{I,COX} = 0.648\ \sigma_{m,X} + 0.21$ (determined from ^{19}F shielding in nmr spectra, respectively: M. Charton, Abstracts, 148th National Meeting of the American Chemical Society, Chicago, Ill., 1964, p 56V. [d] Assumed equal to σ_I for CO_2Me. [e] Assumed equal to σ_R for CO_2Me. [f] Calculated from $\sigma_{I,X,COX} = 0.308\sigma_{m,X} + 0.31$. [g] σ_p was calculated from $\sigma_{p,XCH_2} = 0.522\sigma_{I,X} - 0.131$. σ_R was then calculated from eq 4. [h] Calculated from eq 4 using the σ_p value given by O. Exner and J. Jonas, *Collect. Czech. Chem. Commun.*, **27**, 2296 (1962). [i] M. Charton, Abstracts, 154th National Meeting of the American Chemical Society, Chicago, Ill., 1967, p 137S. [j] Assumed equal to $\sigma_{R,i\text{-}Pr}$. [k] Calculated from eq 4 using value of σ_p given by C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, **2**, 323 (1964).

The σ_I constants are from our compilation[18] when available. The σ_R constants were obtained from the equation

$$\sigma_R = \sigma_p - \sigma_I \qquad (9)$$

using where possible the σ_p constants of McDaniel and Brown.[19] Substituent constants from other sources are given in Table II. Values of r_V used were from the collection of Bondi[20] or are group values calculated by us ($r_{V,min}$).[2]

It would be well at this point to consider our choice of electrical effect parameters in the light of the recent work of Swain and Lupton[21] who have proposed a new separation of electrical effects into localized and delocalized contributions. These authors agree with most other workers that the σ_I constants are a true measure of the localized effect. They have proposed a new definition of resonance effect constants however, and believe that the σ_R values are not pure resonance effect parameters. We believe that the Swain–Lupton treatment is invalid for the following reasons. (1) The results are based on σ_m and σ_p values for Me_3N^+ which are reported by McDaniel and Brown. These authors report probable errors of ±0.2 for these substituent constants. A scale based on values subject to so much error seems to us of dubious value.

(2) The results depend on the assumption that the trimethylammonio substituent is free of resonance interaction; that is, it has no resonance effect. As this substituent is isoelectronic with the *tert*-butyl group which is well known to be an electron donor by resonance, we find this hard to believe. We have continued to use σ_R values, therefore, because we do not believe that a better resonance parameter is as yet available.

Results

Results of the correlations are presented in Table III. Sets labeled A were correlated with eq 4; sets labeled B were correlated with eq 2.

Aromatic Ring Proton Sets.—Of the 13 sets of data involving chemical shifts of aromatic ring protons (sets 1–13) which were correlated with eq 4, ten gave excellent correlations, two gave fair results, and one gave poor results. Correlations of these sets with eq 2 gave excellent results for 11 sets, very good results for one set, and poor results for one set.

Methylbenzene Proton Sets.—The substituted mesitylene and substituted durene sets gave fair and not significant correlations, respectively, with eq 4 (sets $14A_1$, $15A_1$), and no significant correlation with eq 2 (sets $14B_1$ and $15B_1$). Exclusion of the value for the nitro group from these sets gave excellent and good correlations, respectively, with eq 4 (sets $14A_2$, $15A_2$) but fair correlations, respectively, with eq 2 (sets $14B_2$ and $15B_2$).

The substituted toluene sets in various solvents gave two excellent correlations (sets 19A, 20A), one poor correlation (set 16A), and two correlations which were not significant (sets $17A_1$, $18A_1$) with eq 4. Exclusion of the value for the hydroxy group gave improved correlations with eq 4 for the substituted toluenes in the liquid state (set $16A_2$), and was without effect on the significance of the correlation of the substituted toluenes in benzene (set $17A_2$) and in pyridine (set $18A_2$). Correlation of the substituted toluenes with eq 2 gave excellent results for two sets (sets 19B, 20B), good results for one set (set $16B_1$), and results which were not significant for two sets (set $17B_1$, $18B_1$). Exclusion of the value for the hydroxy group gave improved results for two sets ($16B_2$ and $17B_2$) and was without effect in one set ($18B_2$).

OH and NH Chemical Shift Sets.—Of the three sets correlated with eq 4 (sets $22A_1$, 23A, 24A), two gave excellent and one gave very good results. Exclusion of the value for the acetyl group gave improved results for the 2-substituted phenols in DMSO (set $22A_2$). Of the four sets correlated with eq 2 (sets 21B, $22B_1$, 23B, 24B), two gave excellent results, one gave fair results, and one did not give significant correlation. Again, exclusion of the value for the acetyl group gave improved results for the 2-substituted phenols in DMSO (set $22B_2$).

Miscellaneous Sets.—The chemical shifts of the methoxy protons in 2-substituted anisoles gave very good correlation with eq 4 and excellent correlation with eq 2 (sets $25A_1$, $25B_1$). Exclusion of the value for the phenyl group improved the correlation with both eq 4 and eq 2 (sets $25A_2$, $25B_2$). The coupling constants of 2-substituted fluorobenzenes did not give significant

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TABLE III

RESULTS OF CORRELATIONS

Set	α	β	ψ	h	R^a	F^b	$r_{12}{}^c$	$r_{13}{}^c$	$r_{23}{}^c$
1A	−71.0	−132.0	−27.0	30.5	0.951	21.97[g]	0.469	0.024	0.411
1B	−65.4	−139.0		−18.2	0.948	35.54[g]	0.469		
2A	−0.937	−1.10	−0.193	0.325	0.963	54.59[g]	0.283	0.391	0.293
2B	−0.826	−1.17		−0.0524	0.959	80.14[g]	0.283		
3A	−34.3	−72.6	−20.2	21.2	0.950	18.40[h]	0.468	0.462	0.128
3B	−44.8	−71.1		−7.48	0.942	27.68[g]	0.468		
4A	−64.0	−123.0	−17.8	12.8	0.941	51.52[g]	0.484[l]	0.124	0.241
4B	−64.2	−127.0		−18.6	0.936	74.66[g]	0.484[l]		
5A	−0.954	−1.21	−0.0840	0.506	0.977	27.77[h]	0.345	0.359	0.047
5B	−0.980	−1.20		0.379	0.976	51.09[g]	0.345		
6A	−1.08	−1.38	−0.0911	0.526	0.977	28.42[h]	0.345	0.359	0.047
6B	−1.11	−1.38		0.388	0.977	52.37[g]	0.345		
7A	−0.669	−1.54	−0.292	−0.0814	0.958	22.18[h]	0.256	0.509	0.107
7B	−0.799	−1.53		−0.519	0.954	35.75[g]	0.256		
8A	−0.142	−1.15	−0.461	0.381	0.954	20.27[h]	0.256	0.509	0.107
8B	−0.348	−1.14		−0.312	0.937	25.23[g]	0.256		
9A	−1.05	−1.52	−0.0400	−0.374	0.969	14.58[l]	0.128	0.585	0.116
9B	−1.08	−1.52		−0.434	0.967	29.11[h]	0.128		
10A	−0.760	−1.08	−0.103	0.0348	0.954	10.14[l]	0.128	0.585	0.116
10B	−0.828	−1.08		−0.117	0.953	19.91[i]	0.128		
11A	−0.775	−1.32	−0.189	0.370	0.872	13.70[g]	0.289	0.243	0.160
11B	−0.809	−1.33		−0.0315	0.869	21.66[g]	0.289		
12A	−0.677	−1.12	−0.132	−0.182	0.861	12.36[g]	0.289	0.243	0.160
12B	−0.701	−1.12		−0.0283	0.859	19.70[g]	0.289		
13A	−0.669	−11.0	4.16	−5.87	0.997	64.96[m]	0.913	0.115	0.171
13B	−9.24	−4.96		6.39	0.970	16.12[m]	0.913[m]		
$14A_1$	0.0970	−0.267	−0.349	8.25	0.934	9.089[l]	0.355	0.464	0.051
$14A_2$	−0.0837	−0.331	−0.243	8.10	0.994	86.72[h]	0.075	0.640	0.120
$14B_1$	−0.0956	−0.230		7.77	0.679	2.144[n]	0.355		
$14B_2$	−0.286	−0.348		7.77	0.916	10.40[l]	0.075		
$15A_1$	0.189	−0.256	−0.491	8.50	0.867	4.044[n]	0.355	0.464	0.051
$15A_2$	−0.116	−0.364	−0.311	8.25	0.981	26.25[k]	0.075	0.040	0.120
$15B_1$	−0.0811	−0.204		7.82	0.480	0.749[n]	0.355		
$15B_2$	−0.375	−0.386		7.82	0.890	7.653[l]	0.075		
$16A_1$	0.539	0.335	−0.235	1.05	0.945	8.425[m]	0.384	0.304	0.100
$16A_2$	0.459	0.507	−0.118	0.892	0.999	299.8[h]	0.412	0.300	0.169
$16B_1$	0.480	0.367		0.707	0.931	13.01[k]	0.384		
$16B_2$	0.426	0.532		0.722	0.996	172.0[g]	0.412		
$17A_1$	0.192	0.222	−0.122	0.846	0.833	2.264[n]	0.384	0.304	0.100
$17A_2$	0.125	0.366	−0.0237	0.715	0.961	8.137[n]	0.412	0.300	0.169
$17B_1$	0.162	0.238		0.669	0.819	4.069[n]	0.384		
$17B_2$	0.119	0.371		0.681	0.961	18.09[k]	0.412		
$18A_1$	0.532	−0.183	−0.334	1.26	0.856	2.737[n]	0.384	0.304	0.100
$18A_2$	0.469	−0.0489	−0.242	1.14	0.918	3.554[n]	0.412	0.300	0.169
$18B_1$	0.449	−0.138		0.775	0.777	3.051[n]	0.384		
$18B_2$	0.402	0.00310		0.788	0.871	4.693[n]	0.412		
19A	0.419	0.369	−0.137	1.06	0.998	330.9[g]	0.384	0.304	0.100
19B	0.385	0.388		0.863	0.992	128.4[g]	0.384		
20A	0.358	0.394	−0.0736	0.993	0.993	70.93[h]	0.384	0.304	0.100
20B	0.340	0.403		0.886	0.991	111.3[g]	0.384		
21B	−1.96	−0.680		−9.30	0.982	13.90[h]	0.951		
$22A_1$	2.14	2.04	−0.112	9.73	0.897	33.02[g]	0.145	0.369	0.330
$22A_2$	2.25	1.63	0.140	9.14	0.943	61.08[g]	0.137	0.367	0.357
$22B_1$	2.19	2.00		9.52	0.897	51.36[g]	0.145		
$22B_2$	2.18	1.68		9.41	0.942	94.19[g]	0.137		
23A	2.46	2.23	0.230	10.11	0.984	109.3[g]	0.193	0.337	0.114
23B	2.36	2.20		10.55	0.979	137.2[g]	0.193		
24A	130.0	186.0	−0.143	554.0	0.997	118.1[i]	0.392	0.032	0.300
24B	145.0	154.0		304.0	0.952	14.40[l]	0.392		
$25A_1$	−0.314	−0.0156	−0.00530	6.36	0.943	13.49[i]	0.314	0.312	0.005
$25A_2$	−0.272	−0.0338	−0.408	6.39	0.978	29.29[h]	0.341	0.379	0.018
$25B_1$	−0.316	−0.0150		6.35	0.943	24.23[h]	0.314		
$25B_2$	−0.289	−0.0281		6.33	0.971	41.59[g]	0.341		
26A	26.5	25.8	9.23	239.0	0.994	25.41[n]	0.522	0.306	0.955
26B	32.3	14.2		244.0	0.991	52.41[k]	0.522		
27A	1.93	1.87	0.551	34.3	0.718	0.356[n]	0.530	0.273	0.128
27B	1.86	1.86		35.2	0.716	10.52[n]	0.530		

TABLE III (*Continued*)

Set	s_{est}[d]	s_α[d]	s_β[d]	s_ψ[d]	s_h[d]	t_α[e]	t_β[e]	t_ψ[e]	t_h[e]	n[f]
1A	19.5	33.9	26.5	44.1	81.2	20.93[m]	4.966[i]	0.612[q]	0.375[q]	11
1B	18.8	31.4	22.3		15.9	2.085[m]	6.237[q]		1.144[p]	11
2A	0.145	0.195	0.133	0.176	0.351	4.805[q]	8.269[q]	1.095[p]	0.928[p]	17
2B	0.147	0.168	0.119		0.0633	4.918[q]	9.795[q]		8.29[p]	17
3A	12.5	24.6	13.5	21.7	32.5	1.391[p]	5.371[i]	0.933[p]	0.651[q]	10
3B	12.4	21.7	13.3		10.6	2.068[m]	5.349[i]		0.708[q]	10
4A	20.2	24.1	14.0	14.5	27.2	2.650[j]	8.823[q]	1.234[p]	0.470[q]	24
4B	20.5	24.4	13.8		9.72	2.627[j]	9.170[q]		1.914[m]	24
5A	0.150	0.265	0.190	0.311	0.479	3.598[l]	6.339[i]	0.270[r]	1.057[p]	8
5B	0.135	0.223	0.171		0.0884	4.400[i]	7.024[q]		4.291[i]	8
6A	0.169	0.298	0.214	0.350	0.539	3.609[l]	6.443[i]	0.260[r]	0.976[p]	8
6B	0.152	0.251	0.192		0.0994	4.411[i]	7.146[q]		3.906[j]	8
7A	0.197	0.379	0.223	0.426	0.651	1.764[o]	6.892[q]	0.685[q]	0.125[r]	10
7B	0.190	0.316	0.214		0.117	2.532[l]	7.152[q]		4.454[i]	10
8A	0.146	0.281	0.165	0.315	0.482	0.504[q]	6.948[q]	1.463[o]	0.719[p]	10
8B	0.158	0.262	0.178		0.0969	1.325[p]	6.408[q]		3.216[j]	10
9A	0.218	0.596	0.259	0.523	0.786	1.771[o]	5.881[i]	0.077[r]	0.476[q]	7
9B	0.189	0.421	0.224		0.121	2.568[m]	6.798[i]		3.590[l]	7
10A	0.188	0.512	0.223	0.450	0.676	1.484[p]	4.829[j]	0.228[r]	0.051[r]	7
10B	0.164	0.365	0.194		0.105	2.269[m]	5.550[i]		1.118[p]	7
11A	0.267	0.355	0.267	0.406	0.661	2.186[l]	4.956[q]	0.466[q]	0.409[q]	17
11B	0.259	0.337	0.258		0.134	2.402[l]	5.171[q]		0.235[r]	17
12A	0.238	0.316	0.238	0.362	0.589	2.141[m]	4.687[q]	0.365[q]	0.309[q]	17
12B	0.230	0.299	0.229		0.119	2.340[l]	4.899[q]		0.237[r]	17
13A	0.367	3.93	2.75	1.29	4.15	0.170[r]	4.005[o]	3.231[o]	1.414[p]	5
13B	0.879	6.94	4.82		4.03	1.332[p]	1.030[p]		1.586[p]	5
$14A_1$	0.0553	0.112	0.0751	0.0976	0.144	0.863[p]	3.555[l]	3.582[l]	57.22[q]	8
$14A_2$	0.0190	0.0506	0.0284	0.0387	0.0563	1.653[o]	11.69[i]	6.279[i]	143.9[q]	7
$14B_1$	0.101	0.181	0.136		0.0941	0.528[q]	1.685[o]		82.49[q]	8
$14B_2$	0.0620	0.127	0.0919		0.0576	2.252[m]	3.787[j]		134.9[q]	7
$15A_1$	0.0959	0.195	0.130	0.169	0.250	0.971[p]	1.964[o]	2.901[l]	33.98[q]	8
$15A_2$	0.0410	0.109	0.0611	0.0834	0.121	1.060[p]	5.968[i]	3.734[l]	68.02[q]	7
$15B_1$	0.151	0.270	0.203		0.140	0.300[q]	1.003[p]		55.76[q]	8
$15B_2$	0.0844	0.173	0.125		0.0784	2.168[m]	3.085[l]		99.83[q]	7
$16A_1$	0.109	0.179	0.145	0.268	0.397	3.009[m]	2.305[o]	0.877[p]	2.638[m]	7
$16A_2$	0.0193	0.0328	0.0313	0.0490	0.0722	13.99[i]	16.21[i]	2.406[o]	12.36[i]	6
$16B_1$	0.106	0.161	0.137		0.0763	2.978[l]	2.679[m]		9.266[q]	7
$16B_2$	0.0311	0.0481	0.0474		0.0225	8.852[i]	11.21[i]		32.02[q]	6
$17A_1$	0.104	0.170	0.139	0.255	0.378	1.127[p]	1.605[p]	0.476[q]	2.235[o]	7
$17A_2$	0.0630	0.107	0.102	0.160	0.235	1.170[p]	3.586[m]	0.148[r]	3.040[m]	6
$17B_1$	0.0933	0.142	0.121		0.0672	1.139[p]	1.977[o]		9.957[q]	7
$17B_2$	0.0517	0.0799	0.0788		0.0374	1.482[p]	4.703[j]		18.19[q]	6
$18A_1$	0.113	0.186	0.151	0.278	0.412	2.861[m]	1.211[p]	1.199[p]	3.055[m]	7
$18A_2$	0.0925	0.157	0.150	0.234	0.345	2.990[m]	0.327[q]	1.033[p]	3.294[m]	6
$18B_1$	0.119	0.182	0.154		0.0859	2.470[m]	0.897[p]		9.021[q]	7
$18B_2$	0.0935	0.145	0.412		0.0677	2.783[m]	0.022[r]		11.64[i]	6
19A	0.0159	0.0261	0.0212	0.0391	0.580	16.02[q]	17.40[q]	3.503[l]	18.32[q]	7
19B	0.0311	0.0474	0.0402		0.0223	8.115[i]	9.642[q]		38.53[q]	7
20A	0.0333	0.0547	0.0444	0.0818	0.121	6.548[i]	8.857[i]	0.899[p]	8.178[i]	7
20B	0.0325	0.0495	0.420		0.0234	6.861[i]	9.600[q]		37.82[q]	7
21B	0.152	1.11	4.26		0.494	1.774[p]	0.159[r]		18.83[l]	4
$22A_1$	0.396	0.392	0.326	0.380	0.744	5.464[q]	6.263[q]	0.294[q]	13.09[q]	28
$22A_2$	0.261	0.259	0.227	0.254	0.501	8.688[q]	7.177[q]	0.552[q]	18.25[q]	27
$22B_1$	0.389	0.344	0.291		0.124	6.368[q]	6.881[q]		76.62[q]	28
$22B_2$	0.257	0.227	0.200		0.0840	9.593[q]	8.409[q]		112.0[q]	27
23A	0.149	0.182	0.251	0.129	0.250	13.57[q]	8.873[q]	1.790[o]	40.51[q]	15
23B	0.162	0.187	0.273		0.0585	12.62[q]	8.081[q]		180.4[q]	15
24A	7.53	14.9	16.4	25.5	45.1	8.733[j]	11.30[i]	5.623[l]	12.27[q]	6
24B	25.2	49.2	51.7		27.1	2.737[m]	2.983[m]		11.21[i]	6
$25A_1$	0.0339	0.0564	0.0485	0.0566	0.0903	5.568[i]	0.321[r]	0.094[r]	70.36[q]	9
$25A_2$	0.0211	0.0377	0.0307	0.0371	0.0575	7.203[i]	1.100[p]	1.100[p]	111.3[q]	8
$25B_1$	0.0310	0.0486	0.0440		0.0190	6.493[q]	0.342[q]		334.6[q]	9
$25B_2$	0.0215	0.0351	0.0309		0.0144	8.221[q]	0.908[p]		439.0[q]	8
26A	1.91	11.2	17.8	13.8	8.80	2.364[p]	1.449[p]	0.668[q]	27.12[l]	5
26B	1.62	6.10	3.00		2.88	5.292[l]	4.711[l]		84.81[q]	5
27A	1.15	4.17	3.44	6.49	11.2	0.463[q]	0.542[q]	0.085[r]	3.074[p]	5
27B	0.813	2.90	2.44		1.47	0.642[q]	0.763[q]		23.92[i]	5

[a] Multiple correlation coefficient. [b] F test for significance of regression. [c] Partial correlation coefficients of σ_I on σ_R, σ_I on r_V, and σ_R on r_V, respectively. All values of r_{12}, r_{13}, and r_{23} have confidence level < 90.0% unless otherwise noted. [d] Standard errors of the estimate, α, β, ψ, and h. [e] "Student t tests" for significance of α, β, ψ, and h. [f] Number of points in set. [g] 99.9% confidence level (cl). [h] 99.5% cl. [i] 99.0% cl. [j] 98% cl. [k] 97.5% cl. [l] 95% cl. [m] 90.0% cl. [n] <90.0% cl. [o] 80.0% cl. [p] 50% cl. [q] 20.0% cl. [r] <20% cl.

correlation with eq 4, but gave good results with eq 2 (sets 26A, 26B). The nuclear quadrupole frequencies of 2-substituted chlorobenzenes did not give significant correlation with either eq 4 or eq 2 (sets 27A, 27B).

Overall, of 26 sets correlated with eq 4, 17 gave excellent, one very good, one good, and two fair, and one gave poor results while four did not give significant correlation. Of 27 sets correlated with eq 2, 17 gave excellent, one very good, two good, and three fair, and one gave poor results while three did not give significant correlation. The results obtained with eq 4 are not quite so good as those obtained with eq 2.

Discussion

Steric Effect.—Of the 13 aromatic ring proton sets (1A–13A) correlated with eq 4, none gave a significant value of ψ as is shown by the "t" tests and confidence levels reported in Table III. Three of the seven sets of methylbenzenes (14A–20A) gave significant values of ψ on correlation with eq 4. Thus, there may be some steric effect in ortho-substituted methylbenzenes. Of the remaining sets studied only the NH chemical shifts of 2-substituted anilines showed a significant value of ψ. Overall, of 26 sets correlated with eq 4, four show significant values of ψ (sets $14A_2$, $15A_2$, 19A, and 24A). Furthermore, it has already been noted that correlation with eq 2 is generally better than correlation with eq 4. These results force us to the inescapable conclusion that *in general* steric effects are not important. In support of this conclusion we may further cite the wide range of substituent types in sets 2, 4, 11, and 12. It would seem therefore that the effect of ortho substituents on the nmr spectrum is solely an electrical effect. This is in agreement with what has been previously found with regard to the nature of the ortho electrical effect.[1-6] In all of the systems studied so far, electrical effects are *generally* predominant.

Composition of the Ortho Electrical Effect.—It will be convenient to describe the composition of the electrical effect of a substituent by means of ϵ where[22]

$$\epsilon = \beta/\alpha \qquad (10)$$

Values of ϵ were calculated using α and β values obtained from correlation with eq 2 as in most cases results of correlation with eq 2 are better than those obtained with eq 4. Values of ϵ are reported in Table IV. The aromatic ring proton sets (sets 1–13) all show $\epsilon > 1$ indicating the predominance of resonance effects. This is in sharp contrast to the ionization of 2-substituted pyridines and quinolines in which the localized effect is predominant.[20] Thus the substituent effects which govern the ionization of ring protons are radically different from those which determine the chemical shifts of ring protons. The chemical shifts of the methyl protons in 2-substituted methylbenzenes (sets 14–20) show ϵ values ranging from 1.0 to 1.2. There may be some solvent dependence of ϵ in the case of the 2-substituted toluenes which gave ϵ values of 1.0 and 1.2 in dioxane and CCl_4, respectively. The OH chemical shifts of 2-substituted phenols (sets 22, 23) also seem to show a solvent dependence. The values are 0.77 for dimethyl sulfoxide and 0.93 for hexamethylphosphoramide. The values of ϵ for the 2-substituted phenols show a much smaller dependence on σ_R than do the values of ϵ for aromatic ring protons. The value of ϵ for the NH chemical shift of 2-substituted anilines is comparable to the values previously observed for 2-substituted phenols. The chemical shifts of the methoxy protons in 2-substituted anisoles have $\epsilon \cong 0$, corresponding to a dependence solely on the localized effect. The coupling constants of 2-substituted fluorobenzenes show an ϵ value of 0.44 indicating slight predominance of the localized effect.

Overall, the values of ϵ vary from 0.0 to 2.1. These results clearly preclude the definition of a single set of ortho-substituent constants to be applied to the nmr spectra of ortho-substituted compounds.

The Deviation of the Unsubstituted Compound.—The unsubstituted compound has often been found to deviate from the correlation line obtained for an ortho-substituted set. We have previously shown that it is indeed the case for the ionization constants of 2-substituted benzoic acids. We have also observed, however, that in the case of polarographic half-wave potentials all of the 22 sets which gave significant results with eq 2 included the value for the unsubstituted compound.[6] In the sets of nmr data studied in this paper, the value for the unsubstituted compound was included in all the sets for which it was available. Of these 19 sets, 18

TABLE IV
VALUES OF ϵ

Set	ϵ	Set	ϵ	Set	ϵ
1	2.1	10	1.3	19	1.0
2	1.4	11	1.6	20	1.2
3	1.6	12	1.6	21	...[d]
4	...[a]	13	...[c]	22	0.77
5	1.2	14	1.2	23	0.93
6	1.2	15	1.0	24	1.1
7	1.9	16	1.2	25	...[e]
8	...[b]	17	...[b]	26	0.44
9	1.3	18	...[d]	27	...[d]

[a] r_{12} was significant; therefore σ_I is a function of σ_R. [b] α was not significant. [c] α and β were not significant. [d] Correlation with eq 2 was not significant. [e] β was not significant.

(22) M. Charton, *J. Amer. Chem. Soc.*, **86**, 2033 (1964).

TABLE V
"t" TESTS OF h_{obsd}

Set	h_{obsd}	h^a	Δ^b	$s_h{}^a$	t	n^c
3	0	−7.48	7.48	10.6	0.706[d]	10
4	0	−18 6	18.6	9.72	1.914[e]	24
5	0.47	0 379	0.091	0.0884	1.029[f]	8
6	0.47	0 388	0.082	0.0994	0.825[f]	8
7	−0.50	−0 519	0.019	0.117	0.162[g]	10
8	−0.16	−0 312	0.152	0.0969	1.569[h]	10
9	−0.44	−0 434	0.006	0.121	0.005[g]	7
10	−0.03	−0 117	0.087	0.105	0.829[f]	7
11	0	−0 0315	0.0315	0.134	0.235[g]	17
12	0	−0 0283	0.0283	0.119	0.238[g]	17
14	7.81	7 77	0.04	0.0576	0.694[d]	7
15	7.88	7 82	0.06	0.0784	0.765[f]	7
16	0.75	0 722	0.028	0.0225	1.244[f]	6
17	0.71	0 681	0.029	0.0374	0.775[f]	6
19	0.89	0 863	0.027	0.0224	1.205[f]	7
20	0.90	0 886	0.014	0.0234	0.598[d]	7
23	10.30	10 55	0.25	0.0585	4.273[i]	15
25	6.34	6 33	0.01	0.0144	0.694[d]	8

[a] From Table III. [b] $\Delta = |h_{obsd} - h|$. [c] Number of points in set. [d] 20% cl. [e] 90% cl. [f] 50% cl. [g] < 20% cl. [h] 80.0% cl. [i] 99.0% cl.

gave significant correlations with eq 2. There is generally good agreement observed between the experimentally observed values of the unsubstituted compound, h_{obsd}, and the calculated value, h of eq 2. To determine quantitatively whether h_{obsd} is significantly different from h, "Student t tests"[17] were carried out for all of the h_{obsd} values available for sets which gave significant correlations with eq 2. The results are set forth in Table V. In 16 of the 18 sets studied, h_{obsd} does not differ significantly from h. We conclude therefore that the value for the unsubstituted compound generally lies on the correlation line for ortho-substituted nmr data. We further conclude from the previous discussion of our method of detecting steric effects that no constant steric effect is generally extant in these sets.

Mobile Keto Allyl Systems. IX.[1] Kinetics and Mechanism of Amine Exchange Reactions with β-Ketoallylamines

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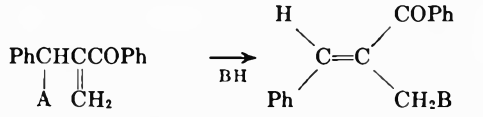
Rate data for the reaction of 2-[(α-substituted amino)benzyl]acrylophenones (1) with morpholine and with *tert*-butylamine in acetonitrile and in isooctane were obtained. Overall second-order kinetics were observed. From rate and thermodynamic constants, the mechanism of the proposed "SN2′-type" reaction is discussed.

In a preceding paper of this series,[3] kinetic data concerning the aminotropic allylic rearrangements of 2-[(α-substituted amino)benzyl]-1-indenones to 3-substituted amino-2-benzal-1-indanones were interpreted by a variant of an SN2′ mechanism.

The reactions of 2-[(α-substituted amino)benzyl]-acrylophenones (1) with amines to give the corresponding α-(aminomethyl)chalcones (2) have been reported previously.[4] The need for quantitative information concerning the amine exchange reactions of **1** prompted this investigation.



1a, A = *tert*-BuNH
b, A = $(Et)_2CNH$

2a, B = morpholino
b, B = *tert*-BuNH

In a preliminary experiment, it was shown that the rates of rearrangement of 2-[(α-substituted amino)benzyl]acrylophenones (1) to the corresponding α-(aminomethyl)chalcones (2) without added amine (BH) were at least 100 times as slow as the rates of the amine exchange reactions we have studied.

Similarly, the rates of reaction of compounds **2a** and of **2b** with *tert*-butylamine and with morpholine were negligible compared with rates of the amine exchange reactions of compounds **1a** and **1b**.

The kinetic results reported below in Tables I, II, IV, and V show that the reaction of **1a** with the *tert*-butylamine produced in the reaction of morpholine with **1a** may be discounted, since in acetonitrile the ratio k(morpholine)/k(*tert*-butylamine) is *ca.* 80 and in isooctane the same ratio is *ca.* 17.

Hence the rate data for the rearrangements of compounds **1** with amines would not contain any appreciable contribution from other multistep routes.

The reaction of **1a** with morpholine in acetonitrile exhibited second-order kinetics and was first order in **1a** and in the amine; the rate coefficients are given in Table I.

TABLE I
VALUES OF SECOND-ORDER RATE COEFFICIENTS k_2 FOR THE REACTION OF 2-[α-(*tert*-BUTYLAMINO)BENZYL]ACRYLOPHENONE (1a) WITH MORPHOLINE IN ACETONITRILE

Temp, °C	[Aminoacryl-ophenone], mol/l.	[Morpholine], mol/l.	$10k_2$,[a] l. mol^{-1} min^{-1}
10.0	0.00738	0.00649	4.9
10.0	0.00742	0.0148	4.8
10.0	0.00614	0.0221	5.1
20.0	0.00904	0.0127	9.5
20.0	0.00817	0.0221	9.4
20.0	0.00395	0.0150	9.4
30.0	0.00501	0.00252	19
30.0	0.00527	0.00988	17
30.0	0.00324	0.0137	18

[a] E = 12 kcal/mol [$k_2 = Ae(-E/RT)$], $\Delta S^{\ddagger}_{20} = -27$ eu [$k_2 = (ekT/h)\exp(-E/RT)\exp(\Delta S^{\ddagger}/R)$].

The reaction of **1a** with *tert*-butylamine in acetonitrile was pseudo first order in **1a**, as required by the kinetic equation[3] (Table II).

TABLE II
VALUES FOR THE SECOND-ORDER RATE COEFFICIENTS k_2 IN THE REACTION OF 2-[α-(*tert*-BUTYLAMINO)BENZYL]ACRYLOPHENONE (1a) WITH *tert*-BUTYLAMINE, IN ACETONITRILE

Temp, °C	[Aminoacryl-ophenone], mol/l.	[*tert*-Butylamine], mol/l.	10^2k_2[a] l. mol^{-1} min^{-1}
20.0	0.00727	0.0942	1.2
20.0	0.00648	0.145	1.2
20.0	0.00628	0.221	1.1
30.0	0.00655	0.137	2.2
30.0	0.00797	0.177	2.2
30.0	0.0115	0.139	2.2
40.0	0.00828	0.062	4.5
40.0	0.00821	0.093	4.3
40.0	0.00882	0.124	4.3

[a] E = 12 kcal/mol, $\Delta S^{\ddagger}_{20} = -36$ eu.

(1) For paper VIII in this series, see G. Maury and N. H. Cromwell, *J. Org. Chem.*, **34**, 596 (1969).

(2) To whom inquiries concerning this article should be addressed.

(3) G. Maury, E.-M. Wu, and N. H. Cromwell, *J. Org. Chem.*, **33**, 1907 (1968).

(4) (a) R. P. Rehman and N. H. Cromwell, *Tetrahedron Lett.*, No. 52, 4833 (1965); (b) N. H. Cromwell and R. P. Rehman, *J. Org. Chem.*, **32**, 3830 (1967).

The reaction of 2-[α-(triethylcarbinylamino)benzyl]-acrylophenone (**1b**) with morpholine was followed kinetically in order to investigate the steric effect of the leaving amino group. The results are presented in Table III.

TABLE III
VALUES FOR THE SECOND-ORDER RATE COEFFICIENTS k_2 IN THE REACTION OF 2-[α-(TRIETHYLCARBINYLAMINO)BENZYL]ACRYLOPHENONE WITH MORPHOLINE, IN ACETONITRILE

Temp, °C	[Aminoacrylophenone], mol/l.	[Morpholine], mol/l.	$10k_2$ l. mol^{-1} min^{-1}
20.0	0.00596	0.00710	5.50
20.0	0.00695	0.0142	5.47
20.0	0.00596	0.0213	5.47

In the nonpolar solvent isooctane, the rate data for the reaction of **1a** with morpholine and with *tert*-butylamine were obtained, and are shown in Tables IV and V.

TABLE IV
VALUES FOR THE SECOND-ORDER RATE COEFFICIENTS k_2 IN THE REACTION OF 2-[α-(*tert*-BUTYLAMINO)BENZYL]ACRYLOPHENONE WITH MORPHOLINE, IN ISOOCTANE

Temp, °C	[Aminoacrylophenone], mol/l.	[Morpholine], mol/l.	10^3k_2[a] l. mol^{-1} min^{-1}
20.0	0.00612	0.193	1.5
20.0	0.00834	0.116	1.5
20.0	0.00766	0.0774	1.4
30.0	0.00181	0.0132	3.0
30.0	0.00115	0.0129	3.2
30.0	0.00383	0.0110	3.1
40.0	0.00947	0.0986	6.1
40.0	0.0101	0.0407	5.8
40.0	0.00789	0.163	6.0

[a] E = 13 kcal/mol, $\Delta S^{\pm}_{20}$ = −32 eu.

TABLE V
VALUES FOR THE SECOND-ORDER RATE COEFFICIENTS k_2 IN THE REACTION OF 2-[α-(*tert*-BUTYLAMINO)BENZYL]ACRYLOPHENONE (**1a**) WITH *tert*-BUTYLAMINE, IN ISOOCTANE

Temp, °C	[Aminoacrylophenone], mol/l.	[*tert*-Butylamine], mol/l.	10^3k_2 l. mol^{-1} min^{-1}
30.0	0.00851	0.166	2.0
30.0	0.00937	0.154	1.9
30.0	0.0108	0.295	1.9

Discussion

Nucleophilic substitution reactions in which the strength of the new CN bond is of major kinetic importance frequently exhibit an order of reactivity which parallels the order of basicity of the nucleophile toward a proton.[5a] For example, the order of reactivity, di-*n*-butylamine > cyclohexylamine, for the direct substitution reactions of arylsulphonylhalogenoethylenes[5b] is in agreement with the relative basicities of the amines.[6] However, the observed order of reactivity of morpholine and of *tert*-butylamine toward 2-[α-(*tert*-butylamino)benzyl]acrylophenone, k(morpholine)/k(*tert*-butylamine) ~ 80, opposes the relative basicities of these amines in aqueous solution[6] and is indicative of a considerable sensitivity of the reaction toward the steric requirements of the nucleophile. A similar but smaller sensitivity for the size of the leaving group is apparent in the reactions of **1a** and of **1b** with morpholine, where the rate ratio k(**1a**)/k(**1b**) ~ 2.

Stork and White established a cis orientation of the incoming and leaving groups in a SN2′ reaction.[7] The steric effects observed in the reactions of **1a** and of **1b** with amines may result from a similar cis orientation of the nucleophile and the departing amine in a rate limiting transition state.

Solvent effects on the rates of the reactions of 2-[α-(*tert*-butylamino)benzyl]acrylophenone with morpholine and with *tert*-butylamine were k(acetonitrile)/k(isooctane) ~ 60 and ~ 12, respectively. The observed rate enhancement by a factor of 60 for the reaction of morpholine in acetonitrile and the less negative value for the entropy of activation in acetonitrile (−27 eu) compared with the entropy of activation in isooctane (−32 eu) are of an order of magnitude which may be accommodated by a dipolar transition state.[8] A dipolar transition state may result if the carbonyl group were to act as a sink for a considerable amount of the developing negative charge. The smaller solvent effect on the rate of the reaction with *tert*-butylamine may be attributed to steric hindrance of solvation.

Two main reaction pathways may be envisaged as rationale of the present observations. The reaction may be synchronous, with a small amount of bond cleavage as represented by path a, in Scheme I. Alternatively, the mechanism may involve the addition of the amine to the α,β-unsaturated ketone to give an intermediate, followed by the elimination of a molecule of amine in a second step. Initial addition of the amine may give structure **8**. If the collapse of **8**, resulting in the departure of the leaving group, were to occur more rapidly than proton transfer to the carbonyl group, then **8** would represent a metastable intermediate. If proton transfer were the more rapid process or if the amine added in a concerted manner to the starting substituted aminobenzylacrylophenone, the 1,4 adduct **5** or **6** would result as the intermediate. Although the adduct **5** or **6** was not detected in any of the reactions, such negative evidence does not preclude its existence.

In summary, all of the data obtained are consistent with a variant of an SN2′ mechanism in which the β-carbonyl function supports a major portion of the developing negative charge in a dipolar transition state.

Experimental Section[9]

2-[α-(*N*-Triethylcarbinylamino)benzyl]acrylophenone (1b).—From 6.02 g (0.02 mol) of α-(bromomethyl)chalcone[4] was obtained 5.0 g of **1b**: yield, 78%; mp 71° (recrystallized from *n*-hexane); $\nu_{C=O}$ (CCl_4) 1681 cm^{-1}; nmr peaks *ca.* 445 (m, 10 H, aromatic), 380 (t, 1 H, J = 1.5 Hz, vinyl), 334 (t, 1 H, J = 1.5, vinyl), 301

(5) (a) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Organic Chemistry monographs, Vol. 6, A. T. Blomquist, Ed., Academic Press, London, 1965, Chapter 4. (b) S. Ghersetti, *et al.*, *J. Chem. Soc.*, 2227 (1965).

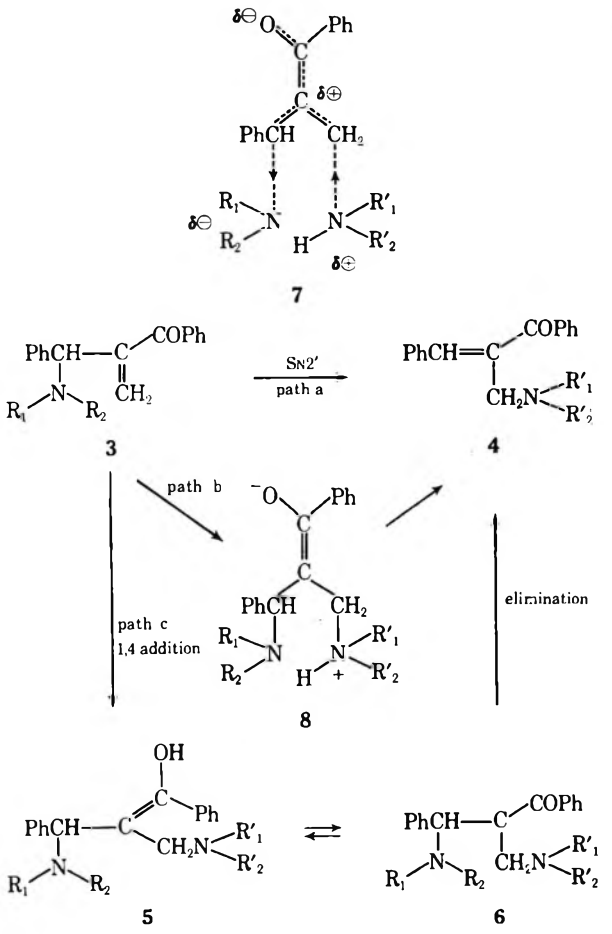
(6) J. J. Christenson, *et al.*, *J. Chem. Soc. A*, 1212 (1969).

(7) G. Stork and W. N. White, *J. Amer. Chem. Soc.*, **78**, 4609 (1956).

(8) K. B. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1964, p 379.

(9) Melting points were read with a calibrated thermometer. Infrared spectra were measured with a Perkin-Elmer Model 21 instrument. Nmr spectra were determined with a Varian A-60 spectrometer. Ultraviolet absorption spectra were obtained with a Cary Model 14 spectrophotometer. Elemental analyses were performed by Micro-Tech Laboratories, Inc.

SCHEME I



(s, 1 H, benzyl), 82 (q, 6 H, J = 7 Hz, methylene), 41.5 Hz (t, 9 H, J = 7 Hz, methyl).

Anal. Calcd for $C_{23}H_{29}NO$: C, 82.33; H, 8.71; N, 4.11. Found: C, 82.22; H, 8.75; N, 4.12.

Synthetic and Kinetic Procedures.—The reactants were prepared by methods previously reported[4,10] and recrystallized from Spectrograde *n*-hexane or isooctane.

The morpholine and *tert*-butylamine were distilled over BaO and then redistilled twice. Spectro grade acetonitrile and isooctane were used as solvents.

A constant temperature water bath was employed with a contact thermometer, which had an accuracy of ±0.03°. Optical densities were determined on a Cary Model 14 ultraviolet spectrophotometer.

The stabilities of the starting aminoacrylophenones and resulting aminochalcones were checked under the conditions used during the kinetic studies and found to be satisfactory.

The reaction rate was followed by measuring the rate of appearance of the band at 282 mμ due to the cinnamoyl chromophore of the aminochalcone. A correction was made in each case for the interference by slight absorption in this region due to the reactant. The concentrations of the reactant and product were deduced from the corrected optical density at λ_{max} (282 mμ).

(10) E. Doomes and N. H. Cromwell, *J. Org. Chem.*, **34**, 310 (1969).

The rate constants were calculated using the following expression, $k_2 = 1/(b-a)\ln[a(b-x)/b(a-x)]$, where a and b are the initial concentrations of the starting ketone and amine, respectively; x is the concentration of the product. Rate constants were obtained by the least-squares method.

Reaction of 2b with Morpholine in Methanol, Benzene, and Acetonitrile.—A 0.30-g sample of **2b** was dissolved in 20 ml of methanol and 1.01 g (10 equiv) of morpholine added and the mixture stirred for 8 days. After evaporation of solvent under vacuum, a sample of the oily residue was dissolved in carbon tetrachloride containing TMS. Nmr analysis showed the presence of only **2a**. The pale yellow crystals were obtained from *n*-hexane, 0.29 g (90%). The experiment described above was repeated in benzene and in acetonitrile. A 100% conversion to **2a** was observed in acetonitrile and a 75% conversion in benzene using nmr analyses. Periodic analysis during the course of the reaction in benzene-d_6 and in acetonitrile-d_3 showed the presence of only **2a** and **2b**.

Attempts to Prepare Other 2-[(α-Substituted amino)benzyl]-acrylophenones. Reaction of α-(Bromomethyl)chalcone with Diisopropylamine.—The mixture of 1.50 g (0.005 mol) of α-(bromomethyl)chalcone and 10.0 g (0.01 mol) of diisopropylamine in 120 ml of benzene was stirred for 24 hr and allowed to stand at room temperature for 15 days. Periodic nmr analysis showed the presence of α-(*N*-diisopropylamino)methylchalcone (main) and of only a small amount of the corresponding acrylophenone. The precipitated amine hydrobromide was removed by filtration. Evaporation of solvent gave an oil. Attempts at crystallization failed.

This oily material turned in color from yellow to purple on standing for a day: nmr peaks 420–490 (m, 11 H, vinyl and aromatic), 224 (d, 2 H, J = 1.2 Hz, methylene), 108.5 (quintuplet, 2 H, J = 6.5 Hz, methine), 48 and 65 Hz (two d, 12 H, J = 6.5 Hz, methyl). In this case only weak signals due to the aminoacrylophenone were detected, *i.e.*, 322 (t, J = 15 Hz, vinyl), 351 (s, vinyl), 328 Hz (s, methine). These signals did not disappear after 24 hr in chloroform-*d* at room temperature. The same reaction was carried out in acetonitrile. Only the aminomethylchalcone was obtained.

Reaction of α-(Bromomethyl)chalcone with Methyl Isopropylamine.—A 6.02-g sample (0.02 mol) of α-(bromomethyl)chalcone was dissolved in 500 ml of *n*-pentane. To this solution 2.93 g (0.04 mol) of methyl isopropylamine was added with stirring. After 1 hr almost all of the α-(bromomethyl)chalcone had disappeared (tlc). The precipitated amine hydrobromide was removed and evaporation of solvent gave oily products. Nmr showed the presence of 2-[α-(methylisopropylamino)benzyl]-acrylophenone and 2-(α-methylisopropylaminobenzyl)chalcone in *ca.* 1:1 proportion. In this case, the signals due to the aminoacrylophenone disappeared in chloroform-*d* after 24 hr at room temperature: nmr peaks for the aminochalcone 430–480 (m, 11 H, aromatic and vinyl), 219.5 (s, 2 H, methylene), 172 (quintuplet, 1 H, J = 6.5 Hz, methine), 131 (s, 3 H, *N*-methyl), 58 Hz (d, 6 H, J = 6.5 Hz, methyl). The same reaction was carried out in acetonitrile and only the aminomethylchalcone was obtained.

Registry No.—**1a**, 7204-42-4; **1b**, 26885-66-5; morpholine, 110-91-8; *tert*-butylamine, 75-64-9.

Acknowledgments.—This investigation was supported in part by the National Cancer Institute of the U. S. Public Health Service, Grant No. CA-02931, and in part by the Research Council of the University of Nebraska.

The Stereochemistry of Addition Reactions of Allenes. IV. Stereospecificity of Iodination of 2,3-Pentadiene[1-3]

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Iodine, iodine bromide, and iodine chloride react with (*R*)-(−)-2,3-pentadiene in methanol to give (−)-*trans*-3-iodo-(4*S*)-methoxy-2-pentene as the major product. The optical purity of the product was found to vary with the nature of the iodinating agent in the order ICl > IBr > I_2. The origin of the apparent low stereospecificity of addition with I_2 in methanol has been traced to the presence of iodide ion produced in the reaction. Optically active 2,3-pentadiene was observed to racemize extensively in the presence of I_2–I^- in diglyme–carbon tetrachloride mixtures. Racemization is attributed to a reaction sequence involving addition of molecular iodine to give *trans*-3,4-diiodo-2-pentene followed by competitive E2 and SN2 reactions of the adduct with I^-. The racemization accompanying SN2 displacement manifests itself in the recovery of partially racemized 2,3-pentadiene and isolation of *trans*-3-iodo-4-methoxy-2-pentene of low optical purity.

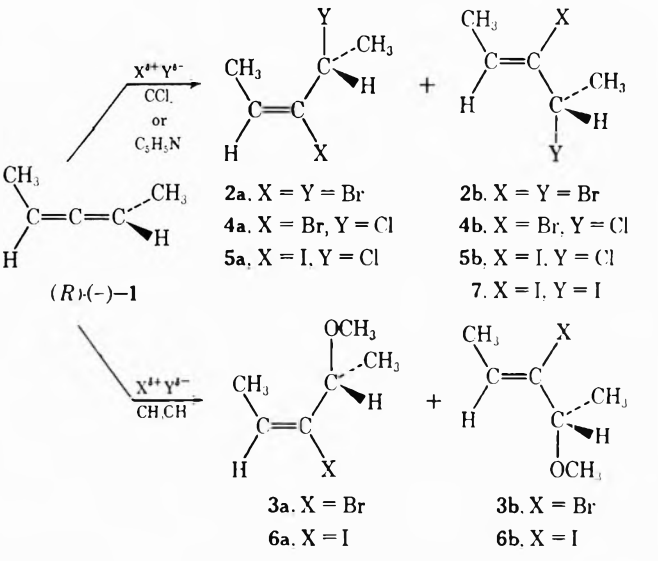
There are several aspects of interest concerning electrophilic addition reactions of allenes. The orientation of addition of unsymmetrical reagents indicates the selectivity of the attacking electrophile for attachment to the central or terminal allenic carbon. The monoadducts formed may be cis and trans isomers, depending on the structure of the allene and the electrophile; the isomer distribution reflects the control of the substituents at one double bond on the direction of approach of the electrophile to the other double bond. Also, the stereochemistry of addition to the reacting double bond is important in a study of the reaction mechanism since it provides information as to the possible types of intermediates involved.

We have recently investigated the orientation and stereochemistry of bromine addition to 2,3-pentadiene **1** and have found that a mixture of *cis*- and *trans*-3,4-dibromo-2-pentene, **2a** and **2b**, is formed in carbon tetrachloride. In methanol a mixture of *cis*- and *trans*-3-bromo-4-methoxy-2-pentene, **3a** and **3b**, is formed.[4] The orientation of bromine addition to **1** is therefore similar to that observed with allene[5] and amounts to the attachment of the electrophile to the central carbon and the nucleophile (Br^- or hydroxylic solvent) to the terminal carbon. The major adduct is the trans isomer (Scheme I).

We have also observed that reaction of bromine with optically active **1** gives optically active adducts **2** in carbon tetrachloride and **3** in methanol.[4] From the configurational relationships between the dissymmetric allene and the asymmetric adducts, the stereochemistry of addition was determined as trans. Similar results were obtained for the reaction of iodine with (−)-**1** in methanol and imply that the adducts in both bromine and iodine addition reactions are formed from dissymmetric reaction intermediates such as bridged bromonium and iodonium ions **8**.

The objectives of the present work were to extend our investigation of electrophilic halogen addition to include other halogens. We report at this time further results on the addition of bromine, bromine chloride, iodine, iodine bromide, and iodine chloride to optically active and inactive 2,3-pentadiene. The work is pertinent to the overall stereospecificity of addition and indicates that, in iodination, the optical purity of the adducts obtained depends significantly on the nature of the iodinating agent.

SCHEME I



Results and Discussion

Bromination.—Bromine chloride in carbon tetrachloride reacted rapidly with 1 equiv of **1** at 5° to give 3-bromo-4-chloro-2-pentene **4** as a 28:72 cis–trans mixture. Small amounts (<16%) of the dibromo adduct **2** were also obtained. Under similar conditions, molecular bromine gave a 20:80 cis–trans mixture of **2a** and **2b**. In methanol, both bromine and bromine chloride reacted with **1** to give 3-bromo-4-methoxy-2-pentene **3** as the major product (85%) formed as a 20:80 cis–trans mixture. The minor products (15%) were the corresponding dihalo adducts **2** or **4**. Optically active (*R*)-(−)-**1** gave optically active adducts with bromine and bromine chloride in both carbon tetrachloride and methanol. The observed rotation of the bromo ether **3** was found to be the same, within experimental error, whether prepared from bromine in methanol or bromine chloride in methanol (Table I). We therefore conclude that the stereospecificity of reaction to give **3** is the same for the two electrophiles, Br_2 and BrCl.

* To whom correspondence should be addressed.

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work (PRF-2357-A1, 4).

(2) Presented in part at the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969.

(3) Part III: L. R. Byrd and M. C. Caserio, *J. Amer. Chem. Soc.*, **92**, 5422 (1970).

(4) W. L. Waters, W. S. Linn, and M. C. Caserio, *ibid.*, **90**, 6741 (1968).

(5) H. G. Peer, *Recl. Trav. Chim. Pays-Bas*, **81**, 113 (1962).

TABLE I

OPTICAL ROTATION DATA FOR HALOGENATION OF 2,3-PENTADIENE IN METHANOL

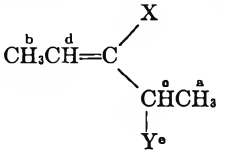
		Halo ether adducts[a]		
1, $[\alpha]_D$	Halogen	cis, %	trans, %	$[\alpha]_D$[b]
−19.8	Br_2	20	80	−11.8
−19.8	BrCl	28	72	−11.1
−15.9	I_2	6	94	−4.1
−19.8	I_2	6	94	−5.5
−19.8	IBr	6	94	−7.8
−19.8	ICl	6	94	−13.4
−19.8	ICl	6	94	−12.5

[a] 3 or 6. [b] Optical rotation data are corrected for the rotations due to any dihalides 2, 4, or 5 present.

Iodination.—Iodine and iodine bromide reacted over a period of several hours with active and inactive **1** in methanol solution to give 6% *cis*- and 94% *trans*-3-iodo-4-methoxy-2-pentene, **6a** and **6b**, respectively. No dihalo adducts were detected in the product mixtures. In contrast, iodine monochloride gave a 6:94 cis–trans mixture of **6** together with 20% *trans*-3-iodo-4-chloro-2-pentene, **5b**. Addition of ICl to **1** in carbon tetrachloride did not proceed cleanly but gave a complex mixture of products that could not be identified satisfactorily. In pyridine, however, ICl reacted smoothly to give the monoadducts, **5a** and **5b**, as the sole products in the ratio of 15:85. The nmr spectral parameters of the adducts prepared in this work are summarized in Table II.

TABLE II

PROTON MAGNETIC RESONANCE DATA FOR ADDUCTS OF 2,3-PENTADIENE

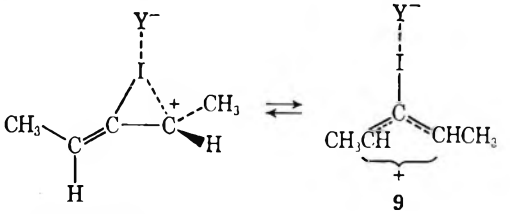


Compd[f]	X	Y	δ_a[a]	δ_b[b]	δ_c[c]	δ_d[d]	δ_e[e]
2a	Br	Br	1.77	1.79	5.12	6.00	
2b	Br	Br	1.80	1.84	4.79	6.22	
3a	Br	OCH_3	1.19	1.72	4.05	6.05	3.14
3b	Br	OCH_3	1.21	1.75	3.62	5.95	3.13
4a	Br	Cl	1.60	1.75	5.00	6.00	
4b	Br	Cl	1.65	1.76	4.65	6.17	
5a	I	Cl	1.49	1.71	4.3	6.0	
5b	I	Cl	1.57	1.74	4.33	6.01	
6a	I	OCH_3	1.17	1.75	3.52	6.43	3.20
6b	I	OCH_3	1.22	1.79	3.31	5.95	3.18
7	I	I	1.73	2.00	5.05	6.18	

[a] (d, 3, J = 6.5 Hz). [b] (d, 3, J = 6 Hz). [c] (m, 1). [d] (m, 1). [e] Y = OCH_3 (s, 3). [f] In CCl_4; chemical shifts in parts per million downfield from internal TMS.

Optically active adducts were obtained from (*R*)-(−)-**1** and I_2, IBr, and ICl in both methanol and carbon tetrachloride or pyridine. However, the observed rotations of the iodo ether obtained in methanol solution varied significantly with the nature of the iodinating agent (Table I). The data show that the optical rotation and hence optical purity of **6** was greatest when prepared from ICl and least when prepared from I_2. This observation prompted us to investigate the reaction of molecular iodine with **1** in more detail in order to determine the possible cause for the apparent low stereospecificity of addition in methanol.

Racemization Mechanisms.—The iodo ether **6** was found to be optically stable in the presence of excess iodine in methanol, which rules out the possibility of racemization of the product under the reaction conditions. Loss in optical purity must therefore occur prior to the product-forming step. One possible explanation for the variation in the observed rotations of **6** with the iodinating agent is that the stability of the dissymmetric iodonium ion intermediate **8**, which is presumably formed during the reaction, depends on the nature of the associated anion, I^-, Br^-, or Cl^-. Assuming that the anion is not completely dissociated from the cation in **8**, then the nature of this anion might well affect the ease of interconversion of **8** with its symmetrical allylic counterpart **9**. Any product derived from the reaction of **9** with solvent would be expected to be racemic. Precedent for this may be found in the oxymercuration of dissymmetric allenes where the stereospecificity of reaction has been found to vary widely with the nature of the ligand on the mercury electrophile.[6,7] An argument against this, however, is the observation that bromine and bromine chloride show no sensible difference in stereospecificity of their respective reactions with **1** in methanol (Table I). It seems unlikely that the stability of iodonium ions would be dependent on the counter anion, whereas the structurally related bromonium ion would be insensitive to these same anions.



(Y = Cl, Br, or I)

8 **9**

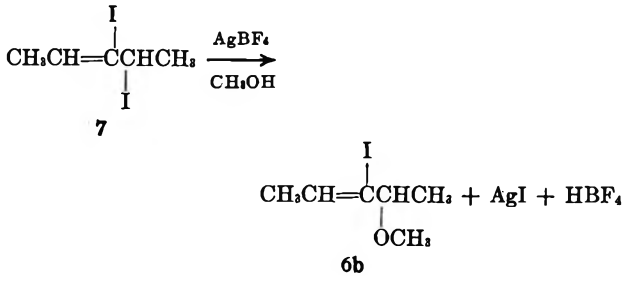
An alternate explanation of the data of Table I is that racemization of the starting allene occurs during reaction to an extent that depends in part on the nature of the electrophile. Unfortunately, attempts to recover unreacted (*R*)-(−)-**1** from reactions with iodine in methanol were unsuccessful, but reaction of excess (*R*)-(−)-**1**, $[\alpha]_D$ −13.7 ± 0.3°, with iodine in carbon tetrachloride led to the recovery of **1** having $[\alpha]_D$ −12.1 ± 0.7°. This represents 12 ± 7% loss in specific rotation over a reaction period of 1.33 hr. In a related experiment, (*R*)-(−)-**1**, $[\alpha]_D$ −10.7 ± 0.1°, was reacted with iodine in a 3:4 mixture of diglyme and carbon tetrachloride and, when 50% of the allene had been consumed, the remainder was recovered by distillation and found to have $[\alpha]_D$ −10.9 ± 1.0°. We therefore conclude that **1** is not significantly racemized by molecular iodine under the reaction conditions employed.

The product of addition of iodine to **1** in CCl_4 was a moderately stable light brown oil that was identified from its nmr spectrum (Table II) and from its conversion to **6b** on treatment with silver tetrafluoroborate in

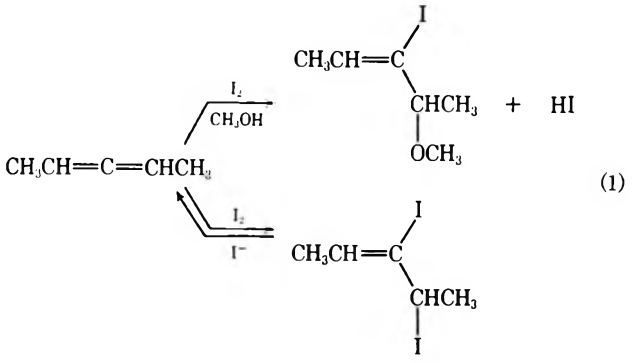
(6) R. D. Bach, *J. Amer. Chem. Soc.*, **91**, 1771 (1969); *Tetrahedron Lett.*, 5841 (1968).

(7) W. S. Linn, W. L. Waters, and M. C. Caserio, *J. Amer. Chem. Soc.*, **92**, 4018 (1970).

methanol as *trans*-3,4-diiodo-2-pentene (**7**). No diiodide formation was detected in the reaction of **1** with iodine in methanol, which is not surprising since the adduct may be expected to be formed reversibly owing



to the presence of iodide ions in the reaction mixture (eq 1). Accordingly, treatment of **7** with sodium iodide in a 1:1 mixture of carbon tetrachloride and diglyme led to immediate formation of iodine and 2,3-pentadiene. On standing for long periods of time (3–50 hr), this reaction mixture generated small amounts (2–3%) of 1,3-pentadiene. Since 1,3-pentadiene was not observed until long after the reaction of **7** with iodide was complete, we conclude that its formation is unrelated to the elimination reaction of interest.

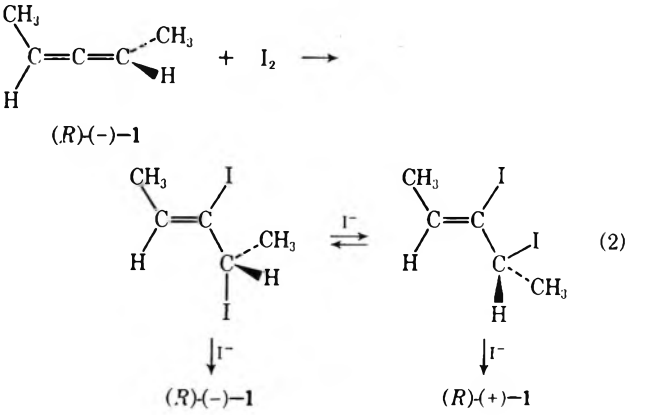


(1)

To test the possibility that racemization of **1** might occur by the reversible addition of iodine in the presence of iodide ions, (*R*)-(−)-**1** having $[\alpha]_D$ −10.7 ± 0.1° was allowed to react with iodine in a 1:1 mixture of diglyme and carbon tetrachloride which was saturated with sodium iodide. The diglyme was necessary to solubilize the sodium iodide. The allene was recovered after 50% conversion to **7** and found to have $[\alpha]_D$ −6.54 ± 0.5° showing that the presence of iodide ion produced some 39% racemization of **1** within 1.33 hr. Although this result might be interpreted to mean that the iodide-induced elimination of **7** is not completely stereospecific, evidence in support of stereospecific elimination of vicinal dihalides with halide ions is very strong.[8,9] For this reason it seems doubtful that the iodine–iodide induced racemization of **1** stems from nonstereospecific elimination of **7**. A likely explanation for the observed racemization of **1** is shown in the reaction sequence of eq 2. The initial addition of iodine to give **7** and its subsequent E2 elimination to **1** are visualized as stereospecific processes which appear to be nonstereospecific because of a competing SN2 reaction of **7** with iodide ion that leads to the racemization of **7**.

(8) D. V. Banthorpe, "Elimination Reactions," E. D. Hughes, Ed., Elsevier, New York, N. Y., 1963.

(9) E. Baciocchi and A. Schiroli, *J. Chem. Soc., B*, 554 (1969).

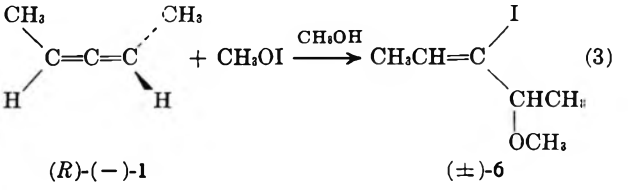


(2)

Conclusions

The observation that the optical purity of the iodo ether **6** varies with the nature of the iodinating agent used in its preparation from **1** can be understood in terms of the relative nucleophilicities of the product ions I^-, Br^-, and Cl^-. In the case of reaction with ICl in methanol, both the iodo ether **6** and the iodochloro adduct **5** are formed *irreversibly* since chloride ion is ineffective in promoting elimination of **5**. Racemization of **1** directly or indirectly by reversible halogen addition is therefore precluded and the optical purity of the iodoether obtained is relatively high. With molecular iodine the iodo ether adduct **6** is formed irreversibly, but the diiodide **7** is formed rapidly and reversibly and is probably racemized to a significant extent by iodide ions in a straightforward displacement reaction. The net result of this is the formation of **6** of low optical purity. Iodine bromide, as expected, represents an intermediate situation since the nucleophilicity of Br^- toward halogen and carbon is less than that of I^- but greater than that of Cl^-.

In order to eliminate the attendant racemization by iodide ions in the reaction of **1** with iodine in methanol, addition of methyl hypoiodite to (*R*)-(−)-**1** was attempted (eq 3). The electrophile was prepared as a



(3)

solution in methanol by the reaction of iodine with silver tetrafluoroborate in methanol. However, the adduct obtained from the reaction of methyl hypoiodite with **1** was found to be a mixture of **6a** (41%) and **6b** (59%) with no observable optical rotation. This contrasts markedly with the product composition obtained from the reaction of iodine with **1** in methanol and suggests that a different type of reaction may be involved. Since a similar reaction of methyl hypoiodite with cyclohexene gave methoxycyclohexane as the major reaction product (60%), the incursion of a free-radical process is strongly implicated even though the reactions were carried out at low temperatures in the dark. In view of this, the results obtained with methyl hypoiodite and **1** cannot be related with any reliability to the comparable reactions of either methanolic iodine, iodine bromide, or iodine chloride with 2,3-pentadiene.

Since we were unable to show that the optical purity of 6 could be increased if it were prepared from 1 and methanolic iodine in the *absence* of iodide ions, the effect of *added* sodium iodide was studied. Starting with equimolar amounts of iodine and (+)-1 of rotation $[\alpha]_D$ +23.6° (*c* 75, ether), the iodo ethers **6a** and **6b** obtained in pure methanol had $[\alpha]_D$ +6.3° (*c* 10, ether); in contrast, the iodo ethers obtained in methanol containing a fourfold excess of sodium iodide had *no observable rotation*. This result adds further support to the plausibility of eq 1 and 2 as routes for the racemization of **1**, **6**, and **7**.

Experimental Section

Iodine monochloride (Eastman Kodak) was distilled before use and had bp 97°. Iodine bromide was prepared from molecular iodine and bromine and was obtained as dark brown crystals having mp 40°. Solutions of bromine chloride were prepared by passing chlorine gas into cooled methanol or carbon tetrachloride; 1 equiv of bromine was then added to the solution.[5] The addition of halogens to 2,3-pentadiene in methanol or carbon tetrachloride were carried out as described previously,[4] and the products were analyzed by nmr and glpc. In pyridine (25 ml) equimolar amounts of iodine monochloride and 1 (10 mmol) were stirred at room temperature in the dark for 14 hr, ether (30 ml) was added, and the solution was then washed repeatedly with water followed by extraction with dilute hydrochloric acid. The ether extract was dried, filtered, and evaporated, and the residue analyzed by nmr and glpc.

3,4-Diiodo-2-pentene was prepared by the addition of 1.12 g (16.4 mmol) of 1 as a 40% solution in ether to a solution of 4.17 g (16.4 mmol) of iodine in 100 ml of carbon tetrachloride. The mixture was stirred and maintained at −40° in the dark for 5.5 hr. Unreacted iodine was destroyed with aqueous sodium thiosulfate; the solvents were removed at reduced pressure from the dried organic extract. The nmr spectrum of the crude product was consistent with the structure assigned as *trans*-3,4-diiodo-2-pentene, **7** (Table II). Addition of a slight excess of silver tetrafluoroborate in methanol to **7** gave an immediate precipitate of silver iodide. After neutralization with sodium carbonate the mixture was filtered and the filtrate evaporated. The nmr spectrum of the residue in carbon tetrachloride was identical with that of a known sample of *trans*-3-iodo-4-methoxy-2-pentene, **6b** (Table II).

Optical rotations of the halo ethers **3** and **6** obtained from the addition of halogens to (*R*)-(−)-1 in methanol solution were corrected for the rotations due to dihalo adducts present in the reaction mixtures. Corrections were necessary only in the case of bromine, bromine chloride, and iodine chloride addition. The assumption was made that the specific rotations of the dihalo adducts were the same when obtained in methanol as in carbon tetrachloride or pyridine.

Racemization of (−)-2,3-Pentadiene.—Reaction of iodine with 1, $[\alpha]^{25}_D$ −13.7° ± 0.3 (ether), was carried out as described above except that aqueous sodium thiosulfate was added when half of 1 had been consumed. The unreacted allene was recovered from the organic extract by fractional distillation and had $[\alpha]^{25}_D$ −12.1 ± 0.7° (ether). A similar reaction of 1, $[\alpha]^{25}_D$ −10.7 ± 0.1° (ether), in a mixture of diglyme (3 ml) and carbon tetrachloride (4 ml) led to the recovery of unreacted 1 having $[\alpha]_D$ −10.9 ± 1.0° (ether, CCl_4). Iodine (16.6 mmol) and sodium iodide (1.86 mmol) in 4 ml of diglyme and 4 ml of carbon tetrachloride were added to 1.13 g (16.6 mmol) of 1, $[\alpha]_D$ −10.7 ± 0.10° (ether), as a 40% solution in ether and the mixture stirred at −42° for 1.33 hr in the dark. Excess iodine was destroyed as before and the unreacted allene recovered by distillation. The specific rotation of recovered 1 was $[\alpha]^{25}_D$ −6.54 ± 0.5° (ether). No 1,3-pentadiene was detected.

2,3-Pentadiene from 3,4-Diiodo-2-pentene.—To 2.5 g (8.3 mmol) of **7** in 1.4 ml of carbon tetrachloride was added 0.11 g (0.7 mmol) of sodium iodide in 1.5 ml of diglyme. The reaction mixture was protected from light throughout the experiment. After 3 hr the iodine was removed by extraction with aqueous sodium thiosulfate, and the organic layer was analyzed by glpc. The major product was 2,3-pentadiene contaminated with up to 3% of 1,3-pentadiene. Analysis of the reaction mixture by glpc immediately following addition of sodium iodide showed 2,3-pentadiene as the only volatile product. On standing for 3 hr or longer, small amounts of 1,3-pentadiene were detected.

Addition of Methyl Hypoiodite to 2,3-Pentadiene.—To 3.26 g (4.8 mmol) of (*R*)-(−)-1 as a 50% solution in ether, $[\alpha]^{25}_D$ −8.43 ± 0.20°, was added 9.35 g (4.8 mmol) of silver tetrafluoroborate, 4.5 g (4.8 mmol) of sodium carbonate, and 12.19 g (4.8 mmol) of iodine in 50 ml of methanol. After stirring for 18 hr in the dark the reaction was quenched with aqueous sodium thiosulfate and the organic layer repeatedly washed with water, dried, and evaporated. The product had $[\alpha]_D$ 0 ± 1° (CCl_4), and was identified by nmr as a 41:59 mixture of 6a and 6b.

Addition of Methyl Hypoiodite to Cyclohexene.[10]—To 3.52 g (9.1 mmol) of silver tetrafluoroborate and 2.3 g (9.1 mmol) of iodine in 75 ml of methanol were added 1.5 g (9.1 mmol) of cyclohexene. The mixture was stirred for 0.5 hr in the dark in the presence of 2.5 g (25 mmol) of calcium carbonate. The product mixture was extracted with ether and water. The ether extract was dried and evaporated and the residue analyzed by glpc and nmr. The products were identified as 60% methoxycyclohexane [(singlet 3.34 ppm, complex 3.0 ppm, complex region 0.8–2.2 ppm downfield from TMS) (CCl_4)] and 35% *trans*-2-iodo-1-methoxycyclohexane [(quartet 4.1 ppm, singlet 3.34 ppm, quartet 3.18 ppm, and complex region 0.8–2.4 ppm, all downfield from TMS) (CCl_4)].

Registry No.—(*R*)-(−)-1, 20431-56-5; **2a**, 26889-28-1; **2b**, 26889-29-2; **3a**, 26889-30-5; **3b**, 26889-31-6; **4a**, 26889-32-7; **4b**, 26889-33-8; **5a**, 26889-34-9; **5b**, 26889-35-0; **6a**, 26889-36-1; **6b**, 26889-37-2; **7**, 26889-38-3.

(10) L. Birckenbach and J. Goubeau, *Ber.*, **65**, 395 (1932).

The Reduction of Nitrogen Heterocycles by Lithium in Liquid Ammonia. III. Indoles and Quinolines[1]

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Received April 15, 1970

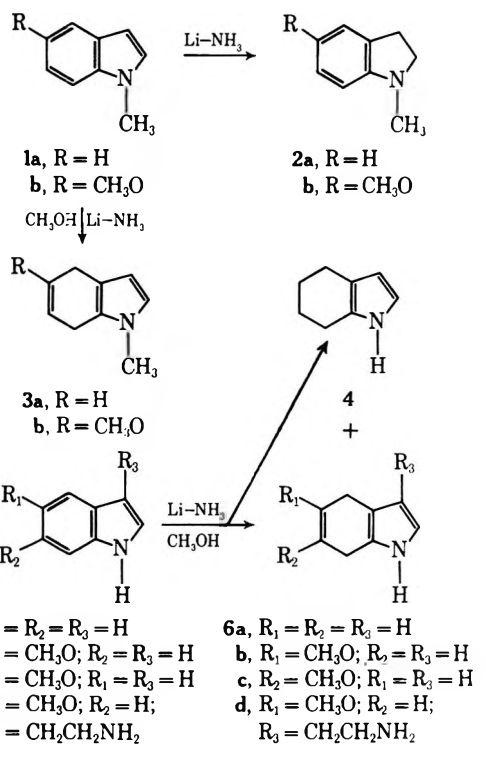
Either the benzene rings or heterocyclic rings of certain quinolines and N-alkylindoles may be preferentially reduced by lithium in ammonia, depending upon the proton source. When excess methanol is present the benzene rings are preferentially reduced, possibly by protonation of intermediate radical anions. If methanol is omitted or added later the heterocyclic rings are preferentially reduced, presumably by protonation of intermediate dianions. Indoles unsubstituted on nitrogen afford salts which are not reduced in the absence of a proton source such as methanol. In the presence of methanol they give only benzene ring reduction.

Although the metal-in-ammonia reduction of aromatic carbocycles has been extensively investigated, comparatively little is known about the corresponding reductions of aromatic heterocycles.[3] Since the nitrogen heterocycles are of great importance in chemistry and biology, we have undertaken an investigation of the reduction of certain of these compounds, attempting both to elucidate the reduction processes and to utilize this knowledge in controlling which products are formed. This paper is concerned with the reduction of indoles and quinolines by lithium and methanol in liquid ammonia.

The most significant result of our study was that ring selectivity could be controlled in the reductions of certain of these heterocycles. In the example with highest selectivity, 5-methoxy-1-methylindole (**1b**) was reduced by lithium in ammonia containing excess methanol to the corresponding 4,7-dihydroindole **3b** in 60% yield. Only 5% of 5-methoxy-1-methylindoline (**2b**) was obtained. Reduction of **1b** in the absence of methanol contrasted the previous reaction both in rate and in product distribution. Whereas reaction in the presence of methanol was almost instantaneous, reaction in its absence required excess lithium and much longer times (4 hr) for appreciable reduction. The latter reaction gave only indoline **2b** in 70% yield. (Scheme I).[4,5]

1-Methylindole (**1a**) was also reduced with a high degree of specificity to the corresponding indoline **2a** by excess lithium. However, reduction in the presence of methanol was less selective. It afforded a mixture which contained both **2a** (32%) and the 4,7-dihydro derivative (**3a**, 37%), plus four minor components (total 5%). Similar ratios of **2a** and **3a** were reported previously for the reduction of **1a** in the presence of methanol.[6]

SCHEME I



When indoles are unsubstituted on nitrogen, the NH proton is sufficiently acidic ($pK_a \approx 17$) to give indolyl salt formation with metals in ammonia. These salts are not reduced in the absence of a proton source such as methanol. An earlier publication revealed that addition of methanol to a mixture of indole **5a** and a large excess of sodium in ammonia gave a mixture composed of equal parts of 4,7-dihydroindole (**6a**) and 4,5,-6,7-tetrahydroindole (**4**).[6] The authors suggested that methanol is the optimum proton source for this reduction because it is acidic enough ($pK_a = 16$) to maintain a portion of the indole in the NH form, but not so acidic that it competes with this form for reduction by the metal.

We have reinvestigated the reduction of indole and confirmed these findings. However, we have also found that the large excess of alkali metal is unnecessary. Reduction with only 2 equiv of lithium afforded (glc analysis of the crude product) 44% of dihydroindole **6a**, 15% of tetrahydroindole **4**, and 39% of starting mate-

(1) (a) Part of the investigation was described in a preliminary communication: W. A. Remers, G. J. Gibs, C. Pidacks, and M. J. Weiss, *J. Amer. Chem. Soc.*, **89**, 5513 (1967). A brief account also appears in "Topics in Heterocyclic Chemistry," R. N. Castle, Ed., Wiley, New York, N. Y., 1969, p 178. (b) For the second paper in this series, see W. A. Remers and M. J. Weiss, *Tetrahedron Lett.*, 81 (1968).

(2) To whom inquiries should be addressed at the Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, Lafayette, Ind. 47907.

(3) H. Smith in "Chemistry in Nonaqueous Ionizing Solvents," Vol. I, part 2, G. Jander, H. Spandau, and C. C. Addison, Ed., Wiley-Interscience, New York, N. Y., 1963.

(4) If methanol was added to an ongoing reduction of **1b**, the faster reduction to **3b** superseded that which gave **2b**. The relative proportions of **3b** and **2b** then reflected the time which had elapsed before the methanol was added (see Table I).

(5) Both indoline **2b** and 4,7-dihydroindole **3b** were stable in the presence of lithium amide. Excess lithium further reduced **2b** when methanol was present, but not in its absence. Neither set of conditions lead to further reduction of **3b**, which agrees with a previous report[6] on the resistance of the pyrrole ring to such reductions.

(6) S. O'Brien and D. C. C. Smith, *J. Chem. Soc.*, 4609 (1960).

rial. When a third equiv of lithium was used, the recovery of starting material fell to 11% and yields of the two products were increased correspondingly (Table I). If methanol was not present prior to the addition

TABLE I

PRODUCTS FROM THE REDUCTION OF INDOLE 5a WITH LITHIUM IN AMMONIA[a]

Experimental conditions	Product, % 4	Product, % 6a	Recovered 5a, %
Excess CH_3OH, 2 Li added	14	43	38
Excess CH_3OH, 3 Li added	26	56	11
Excess CH_3OH, 4 Li added	31	57	6
4 Li, CH_3OH added	20	59	12

[a] A CH_2Cl_2 solution of the product mixture (totally distillable at reduced pressure) was passed through a 6-ft column of 20% SE-30 at 200°. Compounds are listed in the order in which they came off the glc column.

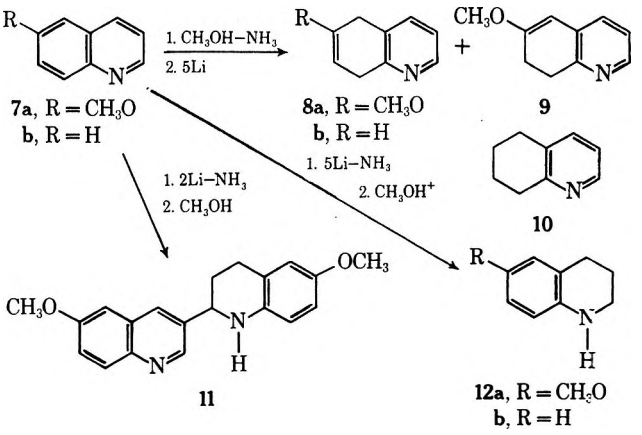
of lithium, 1 equiv of this metal was immediately consumed in forming the indolyl salt. However, a relatively small additional amount of lithium sufficed for reduction of this salt when methanol was added. Thus, 4 equiv of lithium followed by methanol (until discharge of the blue color) gave 63% of **6a**, 21% of **4**,[7] and only 6% of starting material. It should be noted that the ratio of **6a**:**4** is essentially the same whether the methanol was present in excess before addition of lithium or if it was added after the lithium.

The previously reported[6] mixture of **6a** and **4** had not been resolved into its pure components; hence some doubt remained about the proof of their structures. We resolved this mixture by preparative glc and confirmed the assigned structures. The identity of **4** with a known sample prepared by an independent route was established (Experimental Section), whereas the structure of **6a** was clearly delineated by its nmr spectrum (Table II) which showed two protons on a pyrrole ring, two protons on a double bond, and four aliphatic protons strongly deshielded. Reduction of 5-methoxyindole (**5b**) under similar conditions was highly specific. The 4,7-dihydro derivative **6b** was obtained in 83% yield (after recrystallization). As in the example of **1b** the methoxy group appears to enhance selectivity in the reduction of an indole. It also helps accelerate the reduction, which is in agreement with a rate-enhancing effect of the methoxy group in other Birch reductions.[8,9] Thus, in a competitive experiment **5b** was reduced more rapidly than indole.

6-Methoxyindole (**5c**) was also reduced to a crystalline 4,7-dihydro derivative (**6c**, 65% yield) but an appreciable amount of tetrahydrofuran was required as cosolvent. Attempted reduction of 7-methoxyindole was unsuccessful. More complex indoles, such as 5-methoxytryptamine (**5d**) were also reduced to their 4,7-dihydro derivatives (*e.g.*, **6d**). These reductions were less efficient than those of the simpler indoles and generally required a large excess of lithium. The conversion of tryptophan into its 4,7-dihydro derivative was reported previously.[10] Tryptamine quaternary salts afforded either cleavage at the quaternary center or reduction of the indole nucleus, depending upon whether or not methanol was present during the reduction (cleavage occurred in the absence of methanol).[11]

In contrast to the indoles, quinoline derivatives immediately decolorized 2 equiv of lithium even in the absence of methanol. This probably resulted in dianion formation as discussed below. Addition of methanol and work-ups gave mixtures of products which were separated by liquid–liquid partition chromatography. From 6-methoxyquinoline **7a** the main product isolated was an interesting unsymmetrical dimer, **11** (Scheme II). The structure of this dimer was revealed by its

SCHEME II



nmr spectrum (Table II), which showed two methoxy groups, six protons on benzene rings, two protons meta on a pyridine ring, and five protons on aliphatic carbons. The last five protons appeared as two two-proton multiplets and a one-proton doubled doublet. Addition of HCl to a dimethyl sulfoxide solution of **11** broadened the one-proton pattern, but did not broaden the other aliphatic protons. This result showed that the single proton was on a carbon next to nitrogen and uniquely determined the structure of the dimer. Other products isolated from this reduction of 6-methoxyquinoline were 5,8-dihydro derivative **8a** (15%) and starting material (14%). An appreciable quantity of amorphous solid (polymer ?) was also present, but it could not be further resolved.

When the previous experiment was repeated with 5 equiv of lithium, no dimer **11** was found in the product mixture. The only products isolated were 6-methoxy-1,2,3,4-tetrahydroquinoline (**12a**, 32%) and 5,8-dihydro derivative **8a** (5%). Some starting material (9%) was recovered.

Reduction of 6-methoxyquinoline (**7a**) in the presence of excess methanol (5 equiv of lithium) resulted in a significant change in the ring selectivity, at least in the isolated products. Products of benzene ring reduction, 5,8-dihydro derivative **8a** (32%) and the isomeric 7,8-dihydro derivative **9** (16%), were obtained,[12] but the only isolated product of pyridine ring reduction was **12a** (5%).

(7) Since 4,7-dihydroindole **6a** is stable in the presence of excess lithium and methanol in ammonia, it is apparent that tetrahydroindole **4** is not formed from **6a**. Probably **4** is formed by way of an isomer of **6a** in which the double bond is conjugated with the pyrrole ring.

(8) A. J. Birch and D. Nasipuri, *Tetrahedron*, **6**, 148 (1959).

(9) A. P. Krapcho and A. A. Bothner-By, *J. Amer. Chem. Soc.*, **81**, 3658 (1959).

(10) O. Yonemitsu, P. Cerutti, and B. Witkop, *ibid.*, **88**, 3941 (1966).

(11) The important role of the proton source in determining preferential reduction was especially evident in these quaternary salts.[1b]

(12) The 7,8-dihydro derivative **9** could arise either from isomerization of 5,8-dihydro derivative **8a** or from protonation of the intermediate (radical anion) at a different site. Thermal isomerization of **8a** to **9** was evident when the crude reaction mixture was distilled. More **9** was present in the distillate than had been in the crude according to tlc.

TABLE II

SPECTROSCOPIC DATA FOR NEW COMPOUNDS[a]

Compd	Bp (mm) or mp, °C	Uv, mμ (ε), in CH_3OH	δ, ppm, in $CDCl_3$ (J in Hz)[b]
3b[c,d]	94 (4)		6.55 (d, J = 3, C_2), 5.91 (d, J = 3, C_3), 4.75 (m, C_6), 3.23 [4, s (broadened), C_4, C_7]
6a	37–39		6.85 (dd, J = 3, J = 3, C_2), 6.04 (dd, J = 3, J = 3, C_3), 5.95 [2, s, (broadened), C_5, C_6], 3.14 [4, s (broadened), C_4, C_7]
6b	65–68		6.67 (dd, J = 3, J = 3, C_2), 6.00 (dd, J = 3, J = 3, C_3), 4.79 (m, C_6), 3.27 [4, s (broadened), C_4, C_7]
6c	70–71		6.15 (dd, J = 3, J = 3, C_2), 6.02 (dd, J = 3, J = 3, C_3), 4.88 (m, C_5), 3.28 [4, s (broadened), C_4, C_7]
6d	151–153[e]		6.50 (broadened, C_2), 4.78 (m, C_6), 3.25 [4, s (broadened), C_4, C_7], 2.9–2.5 (4, m, side chain CH_2CH_2)
8a[f]	138–140 (8)	269 (4100)	8.41 (J = 5, J = 2), 7.45 (J = 5, J = 2), 7.08 [J = 5, J = 5, pyridine ring], 4.77 (m, vinyl), 3.60 (m, 4, aliphatic)
9[g]	164–168	275 (5900)	8.35 (J = 5, J = 2), 8.02 (J = 5, J = 2), 7.08 (J = 5, J = 5, pyridine ring), 5.90 (broad s, vinyl), 3.25 (m), 2.63 (m, aliphatic)[g]
11	159–160	225 (23,400), 329 and 322 (3680)	8.71 (J = 2), 8.00 (J = 2, meta on pyridine ring), 7.30, 6.95, 6.60 (3 protons, aromatic), 4.50 [m, NCH–aromatic (broadens when HCl is added)], 2.75 (2), 2.05 (2, aliphatic)
8b[h,i]	157–169	240 (13,500), 270 (6300) sh, 350 (15,300), 390 (9900) sh	8.75 (J = 5, J = 2), 8.40 (J = 5, J = 2), 7.90 (J = 5, J = 5, pyridine ring), 5.97 (2, vinyl), 3.67 (4, aliphatic)

[a] Satisfactory analytical values (±0.35%) in C, H, and N were reported for all compounds in the table: Ed. [b] Methyl group and NH absorptions omitted. [c] $n^{25}D$ 1.5465. [d] Calcd for N: 8.58. Found: 9.02. [e] Melting point of acetate salt. [f] Calcd for N: 8.69. Found: 9.08 [g] Melting point and nmr of picrate. [h] Melting point and analysis of picrate. [i] Calcd for C: 50.39. Found: 50.00.

When quinoline **7b** was reduced under the same sets of conditions just described for 6-methoxyquinoline, the results were qualitatively similar, although the yields of isolated products were lower and more amorphous solid was obtained. Thus, when excess methanol was present, the isolated products resulted mainly from benzene ring reduction. They were 5,8-dihydroquinoline (**8b**, 24%), 5,6,7,8-tetrahydroquinoline (**10**, 7%), and 1,2,3,4-tetrahydroquinoline (**12b**, 5%), plus 9% of starting material. In contrast, addition of 5 equiv of lithium followed by methanol afforded 36% of **12b**, but only 8% of **8b** and 1% of **10**. Appreciable starting material (26%) also was recovered.[13] The low material balances obtained from some of these quinoline reductions make evaluations of the ring selectivity less certain than in the corresponding indole reductions. However, at least in the reduction of 6-methoxyquinoline with methanol initially present, the material balance allowed ring selectivity to be conclusively established.

At the present time the mechanisms for the metal-in-ammonia reductions of aromatic carbocycles are fairly well understood. They are based upon product distributions,[8] kinetic studies,[9] and molecular orbital calculations.[14] The following application of the salient features of these mechanisms to related nitrogen heterocycles gives a reasonably coherent explanation for the products and ring selectivity observed in their reduction. The most important assumption inherent in this application is that π-electron densities are more important than solvation and counterion effects in determining the site of protonation on intermediate radical anions and dianions. This assumption appears to be true for the carbocycles[15] but remains unproven for nitrogen heterocycles.

The ease of adding electrons to the π-electron system of a molecule is related directly to the energy of the lowest unoccupied molecular orbital (LUMO) of that system.[14] In liquid ammonia, which is especially effective in stabilizing dianions,[16] molecules such as naphthalene (LUMO at -0.60β)[14] readily form dianions when treated with an alkali metal. Both of these electrons go into the LUMO. Our observations on quinoline (-0.43β) and 6-methoxyquinoline (-0.45β)[17] are consistent with this view. Both of these compounds immediately decolorized 2 equiv of lithium in ammonia, forming colored (greenish) intermediates. Benzene does not readily give a dianion because its LUMO is too high (-1.00β). It does not decolorize a solution of lithium in ammonia, nor does it undergo reduction. However, if methanol is added the benzene is readily reduced. This reduction is thought to occur by rapid protonation of the radical anion formed to a small extent in an equilibrium with benzene and solvated electrons.[9] *N*-Alkylindoles (**1a** and **1b**) lie between naphthalene and benzene in LUMO energy (-0.87β).[19] They were reduced in the absence of methanol but only very slowly. In the presence of methanol their reduction was rapid. We suggest that in the presence of methanol (pK_a = 16) the radical anion is protonated as it forms in equilibrium with the *N*-alkylindole. In the absence of methanol, the only proton source is ammonia (pK_a = 34), which is not acidic enough to protonate this

(13) W. Huckel and L. Hagedorn reported [*Chem. Ber.*, **90**, 752 (1957)] the preparation in 85% yield of 1,2-dihydroquinoline by treatment of quinoline with 2 equiv of sodium followed by ammonium chloride (−65° under N_2).

(14) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1962.

(15) H. E. Zimmerman, *Tetrahedron*, **16**, 169 (1961).

(16) W. Huckel, *Fortschr. Chem. Forsch.*, **6**, 197 (1966).

(17) LCAO–MO calculations based upon parameters ($\alpha_N = \alpha_C + 0.5\beta$, $\beta_{CN} = \beta_{CC}$) which afforded a reasonable correlation between calculated and observed hyperfine splitting constants in the esr spectrum of quinoline radical anion.[18] For oxygen, $\alpha_O = \alpha_C + 2.0\beta$, $\beta_{CO} = 0.8\beta_{CC}$ were used.

(18) J. Chaudhuri, S. Kume, J. Jagur-Grodzinski, and M. Szwarc, *J. Amer. Chem. Soc.*, **90**, 6421 (1968).

(19) LCAO–MO calculations based upon the parameters suggested by Streitwieser (ref 14).

radical anion. However, ammonia will protonate the dianion which exists to a small extent in equilibrium with the radical anion. Benzene apparently does not give a sufficient concentration of dianion to allow significant reduction when ammonia is the only proton source.

The ring selectivity observed in the reduction on *N*-alkylindoles can be related to this difference in the intermediate protonated in the presence or absence of methanol. Thus, the radical anion might be preferentially protonated in the benzene ring, whereas protonation in the pyrrole ring might be favored with the dianion. Support for this view is afforded by the NH indoles (**5a**, **5b**, and **5c**) which are reduced exclusively in their benzene rings. These compounds could give only the radical anion since methanol must be present to reverse indolyl salt formation.

It is also conceivable that the ring selectivity observed in the quinoline examples reflects preferential protonation of a dianion when methanol is not initially present and protonation of a radical anion when methanol is initially present in excess. This concept would require that the radical anion, formed by reversible addition of one electron to the π system of the quinoline, be protonated by methanol before the second proton adds. The selective benzene ring reduction observed by treatment of 6-methoxyquinoline with lithium in the presence of methanol fits this picture. Unfortunately, the low material balances obtained in most of the other examples do not afford further concrete evidence for this point.

In an important paper by Zimmerman,[15] the site of protonation of radical anions derived from various methoxybenzene derivatives was successfully correlated with the total π-electron density at the several carbon atoms in the aromatic rings of those anions. Although in certain cases the difference in π-electron density between two atoms was very small, it was always considered to be the determining factor. It was further noted that in certain compounds the pattern of π-electron density in the radical anion differed from that in the starting material. Thus, for anisole, the increase in total π-electron density afforded by addition of one electron to the π system was much higher at the ortho and meta positions than at the para position.

An extension of these ideas to the nitrogen heterocycles might help explain the observed ring selectivity in their reductions. For example, in 5-methoxy-1-methylindole (**1b**) the highest total π-electron density on carbon is at C-3, whereas it is at C-4 in the radical anion and at C-2 in the dianion. It should be noted that protonation at these positions in the radical anion and in the dianion would lead to the observed selective products of benzene ring reduction and pyrrole ring reduction, respectively. Similarly, there is correspondence between the sites of protonation and highest total π-electron densities on carbon[20] for the radical anion and dianion derived from 6-methoxyquinoline. However, the calculated total π-electron densities for quinoline do not predict the correct products from protonation of the radical anion (although the material balance was very poor in this case).

(20) The total π-electron densities on pyridyl nitrogens are actually much higher than those on carbon atoms. Product determining protonation on carbon would, therefore, require that protonation on nitrogen be reversible under the experimental conditions.

At the present time the experimental evidence is not strong enough to compel acceptance of the above interpretation of ring selectivity in the reduction of nitrogen heterocycles. For one thing, the assumption that solvent and counterion effects do not determine the site of protonation might not be as valid for nitrogen heterocycles as it appears to be for carbocycles. Furthermore, the position of highest total π-electron density can vary with the choice of parameters used in the LCAO–MO calculations (we used parameters recommended in the literature).[17,19] However, it still seems valid to call attention to this interpretation, since it should serve as the most reasonable starting point for more rigorous calculations and mechanistic studies in this important area of heterocyclic chemistry.

Finally, some further comment will be made on the formation of unsymmetrical dimer **11**. It seemed at first that such a dimer might be produced by the coupling of two molecules of 6-methoxyquinoline radical anion or by the addition of one molecule of radical anion to one molecule of starting material. However, treatment of 6-methoxyquinoline with either 1 or 0.5 equiv of lithium, hypothetical conditions for these modes of formation, gave no dimer. Only starting material was recovered. These results suggest that the dimer is produced instead by intermediates which occur after formation of a dihydroquinoline reduction product.[21]

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are corrected. Ultraviolet spectra were determined in methanol solution with a Cary recording spectrophotometer. Infrared spectra were determined in potassium bromide disks or neat with a Perkin-Elmer Model 21 spectrophotometer. Nuclear magnetic resonance spectra were determined in deuteriochloroform (unless otherwise specified) with a Varian A-60 spectrometer. Solutions were dried over anhydrous magnesium sulfate and concentrated under reduced pressure on a rotary evaporator.

5-Methoxy-1-methylindole (**1b**).—This compound was previously prepared by a less direct method.[23] In the present method, a solution of 0.1 mol of methylsulfinyl carbanion in 50 ml of dimethyl sulfoxide[24] was treated with a solution of 14.7 g (0.1 mol) of 5-methoxyindole in 50 ml of dimethyl sulfoxide. After 1 hr 28.4 g (0.2 mol) of methyl iodide was added. The resulting solution was stirred overnight under N_2 and then carefully diluted with water, whereupon the product crystallized. Recrystallization from ethanol gave 11.8 g (74%) of colorless prisms, mp 97–103°. Another recrystallization gave mp 102–104° (lit.[24] mp 103–104°).

5-Methoxy-1-methylindoline (**2b**).—This compound was previously obtained as a picrate.[23] In the present investigation, an authentic sample was prepared as a standard for glc determinations. A mixture of 500 mg of 5-methoxy-1-methylindole (**1b**), 6 ml of ethanol, 6 ml of concentrated HCl and 2.0 g of granular tin was heated at reflux temperature for 18 hr, cooled, and filtered. The filtrate was brought to pH 10 with NaOH solution and re-

(21) When quinoline is heated with sodium in toluene, a related dimer, 2,3′-diquinoline, is obtained in 30–40% yield [Weidel, *Monatsh. Chem.*, **2**, 491 (1881)]. The mechanism of this dimerization is not known, although it seems likely that a dimeric dianion of the type observed in tetrahydrofuran solvent is initially formed,[22] and then aromatization occurs with loss of hydride ion. Dimer formation in liquid ammonia probably does not occur by this process because a monomeric dianion is the predominant species in equilibrium, even when less than 2 equiv of lithium is involved.[16]

(22) With typical aromatic compounds in tetrahydrofuran, a dimeric dianion is the predominant species, whereas in hexamethylphosphoramide the corresponding radical anion is favored in equilibrium with this dimeric dianion.[18] The special role of amine solvents in stabilizing monomeric dianions has been pointed out by Huckel.[16]

(23) J. W. Cook, J. D. Loudon, and P. McCloskey, *J. Chem. Soc.* 1203 (1951).

(24) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

filtered. The solids were washed with ether and the combined filtrate and washes were diluted with ether, washed with water, dried, and concentrated. Treatment of a portion of the residual oil (435 mg, n^{25}D 1.5865) with picric acid in ethanol afforded a yellow picrate, mp 171–172° dec after recrystallization from methanol (lit.[23] mp 171–173° dec).

1-Methylindoline (2a).—This compound was prepared by the procedure described for **2b**. From 500 mg of 1-methylindole (**1a**) was obtained 428 mg of pale yellow oil which showed only one peak on glc. It gave a picrate with mp 161–164° after two recrystallizations from benzene (lit.[6] mp 160–165°).

Typical Lithium-in-Ammonia Reduction Procedures for Indoles. A. Excess Methanol Present.—A solution of 10 mmol of the indole derivative in 6 ml of methanol was added to 50 ml of distilled liquid ammonia. The resulting solution was treated portionwise with 280 mg (40 mg-atoms) of Li wire, which reacted very rapidly. After evaporation of the ammonia and removal of the methanol under reduced pressure, the residue was treated with ether and water. The ether layer was dried and concentrated and the residue was weighed and assayed by chromatography as described in Tables I and III. Pure products were obtained by crystallization or distillation as described in Table II. Nmr spectra of these products are recorded in Table II.

Several compounds were insoluble in ammonia or methanol–ammonia mixtures and required modified reduction procedures. Thus, on the same scale, 1-methylindole, 6-methoxyindole, and 7-methoxyindole were dissolved in a mixture of 35 ml of ammonia, 25 ml of tetrahydrofuran, and 8 ml of methanol.

B. Methanol Added Later.—A solution of 10 mmol of the indole derivative in 60 ml of distilled ammonia was treated portionwise with 280 mg (40 mg-atoms) of Li wire. After specified times the blue mixture was then treated dropwise with methanol until this color was discharged. After evaporation of the ammonia the residue was worked up as described above.

C. Methanol Not Used.—A solution of 7.5 mmol of the indole derivative in 10 ml of tetrahydrofuran and 125 ml of distilled ammonia was treated portionwise with 420 mg (60 mg-atoms) of lithium. After 4 hr the excess lithium was discharged by the addition of a small amount of ferric chloride hexahydrate. Methanol was added to neutralize the amide ion and the ammonia was evaporated. The residue was worked up as described above.

Typical Lithium-in-Ammonia Reduction Procedures for Quinolines. A. Excess Methanol Present.—A solution of 10 mmol of the quinoline derivative in 6 ml of methanol was added to 50 ml of distilled liquid ammonia. The resulting solution was treated portionwise with 280 mg (40 mg-atoms) of Li wire, which reacted immediately. After evaporation of the ammonia and removal of the methanol under reduced pressure, the residue was treated with ether and water. The ether layer was dried and concentrated, and the residue was resolved by liquid–liquid partition chromatography as described in Tables IV and V. Monomeric products were examined by glc on a 6-ft column of Carbowax 20M at 200° as a check on the liquid–liquid separation. The results were in agreement.

The isolated products were purified by crystallization, distillation, or picrate formation as described in Table II. Their structures were confirmed by spectral data as recorded in Table II.

TABLE III

PRODUCTS FROM THE REDUCTION OF 5-METHOXY-1-METHYLINDOLE (1b) WITH LITHIUM IN AMMONIA[a]

Experimental conditions	Product, % others	2b	3b	Recovered 1b, %
8 Li, $FeCl_3$ after 4 hr	0	70	0	5
2 Li, $FeCl_3$ after 4 hr	0	18	0	72
Excess CH_3OH, 4 Li added	3	5	60	8
4 Li, CH_3OH added immediately	6	9	38	7
4 Li, CH_3OH added after 45 min	4	11	25	2
4 Li, CH_3OH added after 4 hr	5	25	8	4

[a] The neat product mixture (totally volatile) was passed through a 6-ft Carbowax 20M column at 250°. Compounds are listed in the order in which they came off the glc column.

TABLE IV

PRODUCTS FROM THE REDUCTION OF 6-METHOXYQUINOLINE (7a) WITH LITHIUM IN AMMONIA[a]

Experimental conditions	Product, % 10	8a	9	11	12a	Recovered 7a, %
2 Li, CH_3OH added	0	15	0	35	0	14
5 Li, CH_3OH added	0	0	0	0	32	9
Excess CH_3OH, 5 Li added	3	32	16	0	5	8

[a] The crude product mixtures were resolved by liquid–liquid partition chromatography on diatomaceous earth with a heptane–methyl cellosolve system. In a typical experiment 1.94 g of crude product was dissolved in 45 ml of the lower phase, mixed with 60 g of diatomaceous earth, and packed atop a column prepared from 450 ml of the lower phase and 600 g of diatomaceous earth. The resulting column was eluted with the upper phase, and the effluent was passed through a recording uv spectrophotometer set at 260 mμ. Eluate corresponding to the recorded peaks was then concentrated and the residue was weighed and further purified by crystallization or picrate formation. Compounds are listed in the order in which they came off the chromatography column.

TABLE V

PRODUCTS FROM THE REDUCTION OF QUINOLINE 7b WITH LITHIUM IN AMMONIA[a]

Experimental conditions	Product, % 10	8b	12b	Recovered 7b, %
5 Li, CH_3OH added	1	8	36	26
Excess CH_3OH, 5 Li added	7	24	5	9

[a] The chromatography system and procedure were the same as those described in the footnote of Table I. Compounds are listed in the order in which they came off the chromatography column.

The reduction of 6-methoxyquinoline (**7a**) was carried out on a larger scale. Treatment of 50 g of **7a** and 400 ml of methanol in 21 ml of ammonia afforded 33 g of an oil which upon distillation afforded 17 g of a mixture of isomeric dihydro derivatives **8a** and **9**.

B. Methanol Added Later.—A solution of 10 mmol of the quinoline derivative in 60 ml of distilled ammonia was treated portionwise with Li wire (20 or 50 mg-atoms, depending upon the particular experiment). The mixture was stirred for 1 hr and treated dropwise with methanol until the color was discharged. After evaporation of the ammonia, the residue was worked up as described above.

Identification of Certain Reduction Products with Compounds Previously Reported in the Literature. A. 4,7-Dihydro-1-methylindoline (3a) was isolated from a mixture with 1-methylindoline according to the published procedure.[6] It had an n^{20}D 1.5482 that was equivalent to the literature value of n^{18}D 1.5490.

B. 4,5,6,7-Tetrahydroindole (4) was isolated from a mixture with 4,7-dihydroindole by preparative glc on a 10% SE-30 column (8 ft × 0.5 in.) at 158° and He flow rate 75 ml/min. It had, after recrystallization from *n*-hexane, mp 54–55° (lit.[25] mp 55°).

C. 6-Methoxy-1,2,3,4-tetrahydroquinoline (12a), isolated as described in Table IV, had an ir spectrum superimposable with that of a commercial sample. The two samples had identical retention times on glc.

D. 5,6,7,8-Tetrahydroquinoline (10), isolated as described in Table IV, had an ir spectrum identical with the published one.[26] It gave a picrate with mp 158° (lit.[27] mp 158.5°).

Structure Proofs for New Compounds.—The structures of new compounds were verified by their spectral data (Table II) in addition to microanalyses (Table II). In the ir spectra, the vinyl ether groups showed characteristic sharp peaks at 6.0 μ (KBr disks except **8a** which was neat between salt plates). Dimer **11** showed an NH band at 3.1 μ. The uv spectra of the new compounds are recorded in Table II. Also in this table are listed

(25) J. M. Patterson and S. Soedigdo, *J. Org. Chem.* **32**, 2969 (1967).
(26) E. Godar and P. P. Mariella, *J. Amer. Chem. Soc.*, **79**, 1402 (1957).
(27) M. M. Janot, C. Keufer, and J. LeMen, *Bull. Soc. Chim. Fr.*, 230 (1952).

those nmr peaks most essential to the structure proof. Dimer **11** had a molecular ion at m/e 320 in its mass spectrum.

Registry No.—Lithium, 7439-93-2; **1b**, 2521-13-3; **3b**, 17052-38-9; **5a**, 120-72-9; **6a**, 26686-10-2; **6b**, 17052-39-0; **6c**, 26686-12-4; **6d**, 26573-83-1; **6d** acetate, 26686-14-6; **7a**, 5263-87-6; **7b**, 91-22-5; **8a**, 17052-40-3; **8b**, 26686-17-9; **8b** picrate, 17052-42-5; **9** picrate, 17052-41-4; **11**, 18995-96-5.

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Alkylation of Benzohydroxamic Acid[1]

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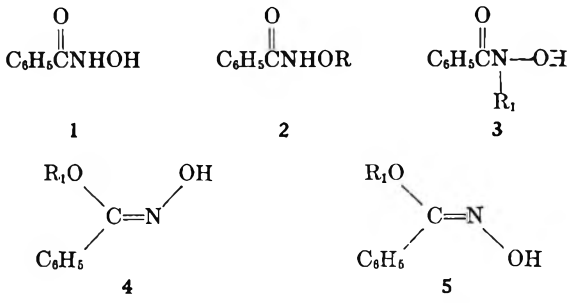
The alkylation behavior of the potassium and silver salts of alkyl benzohydroxamates **2** has been investigated. The structures of the alkylation products were determined by comparison of their nmr spectra and vpc retention times with independently synthesized compounds: ethyl *N*-ethylbenzohydroxamate (**6a**), the *Z* and *E* isomers of ethyl *O*-ethylbenzohydroximate (**7a** and **8a**), *n*-propyl *N*-*n*-propylbenzohydroxamate (**6b**), the *Z* and *E* isomers of ethyl *O*-*n*-propylbenzohydroximate (**7e** and **8e**), the *Z* and *E* isomers of *n*-propyl *O*-isopropylbenzohydroximate (**7f** and **8f**), *n*-propyl *N*-benzylbenzohydroxamate (**6h**), and the *Z* and *E* isomers of benzyl *O*-*n*-propylbenzohydroximate (**7h** and **8h**). Alkylation of the potassium salts of **2** with primary alkyl halides in methanol–water solutions gives mixtures of **6** (major product) and **7** (minor product). Isopropyl halides lead to mixtures of **6** and **7** in which **7** predominates. Oxygen alkylation of the potassium salts is increased considerably in dimethyl sulfoxide or dimethylformamide. Alkylation of potassium benzohydroxamate with 1,2-dibromoethane, 1,3-dibromopropane, and 1,4-dibromobutane gives cyclized products **16**, **17**, and **18**, respectively. Heterogeneous reactions of the silver salts of **2** with alkyl halides in anhydrous ether give mixtures of **7** and **8**. Alkyl iodides give mainly (*Z*)-hydroximates (**7**), whereas alkyl bromides favor hydroximates with the *E* configuration (**8**). The amount of the *Z* isomer increases when dimethylformamide is used as the solvent. The configuration of the products from the reactions of alkylbenzohydroximoyl chlorides (**19**) with sodium alkoxides were determined. In all of the reactions investigated only the *Z* isomers (**7**) of the hydroximates are formed. The alkylbenzohydroximoyl chlorides are prepared by the reaction of **2** with phosphorus pentachloride. Mechanisms for the alkylation reactions are discussed.

In connection with another study currently being carried out in our laboratory we have found it necessary to investigate methods of synthesizing and identifying the geometrical isomers of alkyl *O*-alkylbenzohydroximates[3] (**7** and **8**). The most direct route to these compounds appeared to be alkylation of alkyl benzohydroxamates **2**. Recent reports[4-6] on the alkylation of benzohydroxamates prompts us to describe our observations concerning alkylations of the ambident anions derived from this class of compounds.

Benzohydroxamic acid **1** offers three sites for alkylation: the hydroxylamine oxygen, the nitrogen, and the carbonyl oxygen. The four possible monoalkylation products are an alkyl benzohydroxamate **2**, an *N*-alkylbenzohydroxamic acid **3**, and the *Z* and *E* isomers of an alkyl benzohydroximate (**4** and **5**, respectively).[7]

Extensive study has shown that the monoalkylation of the potassium salt of benzohydroxamic acid results in the exclusive or preferential formation of a hydroxamate **2**.[8,9]



1 **2** **3**

4 **5**

a, R or R_1 = C_2H_5
b, R = *n*-C_3H_7
c, R_1 = *i*-C_3H_7
d, R = *n*-C_4H_9
e, R_1 = $CH_2C_6H_5$

The dialkylation of **1** or the monoalkylation of **2** could give rise to an alkyl *N*-alkylbenzohydroxamate (**6**), an alkyl (*Z*)-*O*-alkylbenzohydroximate (**7**), or an alkyl (*E*)-*O*-alkylbenzohydroximate (**8**). In all of the earlier investigations the alkylation of either **1** or **2** has been reported to give exclusively an alkyl *O*-alkylbenzohy-

(1) A preliminary communication of this work, was presented at the Southwest Regional Meeting of the American Chemical Society, Little Rock, Ark., Dec 7, 1967, Abstracts p 61A.

(2) To whom correspondence should be addressed: Chemistry Department, Texas Woman's University, Denton, Texas 76204.

(3) We have named the compounds described in this paper as derivatives of benzohydroxamic acid, $C_6H_5C(=O)NHOH$, and its tautomer benzohydroximic acid, $C_6H_5C(OH)=N-OH$. Compounds substituted with alkyl or acyl groups on the hydroxylamine oxygen of benzohydroxamic acid are named alkyl or acyl benzohydroxamates. Substitution on the nitrogen is denoted with the prefix *N*-alkyl. A compound with alkyl substitution on the C–OH of benzohydroximic acid is named an alkyl benzohydroximate and substitution on the oxime oxygen is designated with the prefix *O*-alkyl.

(4) M. Chehata, F. Bocabeille, G. Thuillier, and P. Rumpf, *C. R. Acad. Sci., Ser. C*, **268**, 445 (1969).

(5) R. Blaser, P. Imfeld, and O. Schindler, *Helv. Chim. Acta*, **52**, 569 (1969).

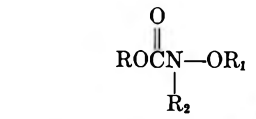
(6) O. Exner and O. Schindler, *ibid.*, **52**, 577 (1969).

(7) In the past the configurational descriptors syn and anti have been used to designate the two geometrical isomers of alkyl benzohydroximates and their derivatives. However, in the older reports[10,21,22] a different convention was used than that proposed more recently by Exner.[19] To avoid confusion we will designate these isomers using the configurational descriptors *Z* and *E*. The rules which permit unambiguous description of double bond stereoisomerism in terms of the descriptors *Z* and *E* have been reported by J. E. Blackwood, G. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, **90**, 509 (1968).

(8) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," Vol. II, W. A. Benjamin, New York, N. Y., 1966, pp 68–98.

(9) J. H. Cooley, W. D. Bills, and J. R. Throckmorton, *J. Org. Chem.*, **25**, 1734 (1960).

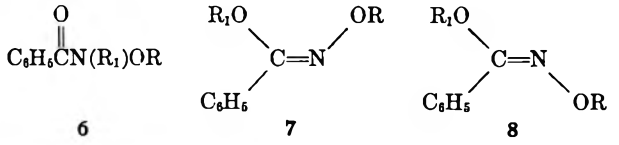
droximate (7 or 8).[8,10-17] No experimental evidence was presented in these reports for the existence of the two geometrical isomers of the alkyl *O*-alkylbenzohydroximates.[18] In contrast, alkyl alkoxyformohydroxamates (9, R_2 = H) have been reported to alkylate primarily on nitrogen.[8]



9a, R = C_2H_5; R_1 = R_2 = H
b, R = R_1 = R_2 = C_2H_5
c, R = C_2H_5; R_1 = R_2 = *n*-C_3H_7

Results

In order to study the alkylation reactions of benzohydroxamic acid, it was desirable to synthesize model compounds so that correlations of nmr spectra and vpc retention times with the structures of the alkylation products could be established. Since a considerable



6 **7** **8**

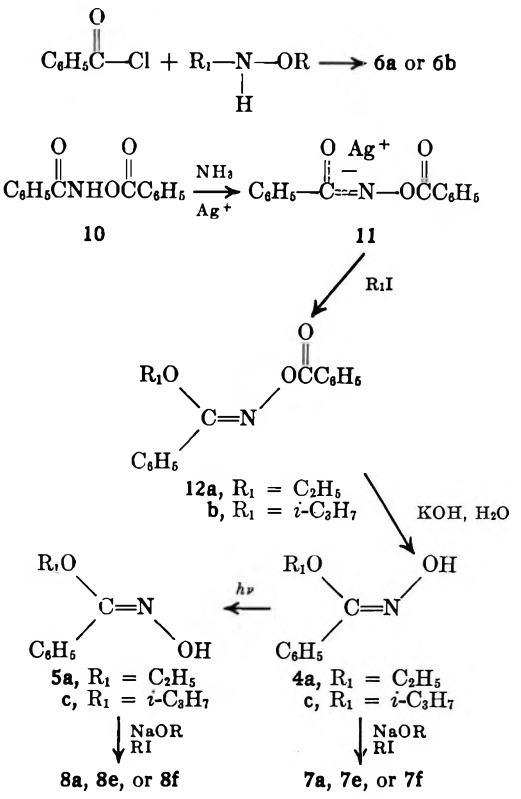
a, R = R_1 = C_2H_5
b, R = R_1 = *n*-C_3H_7
c, R = R_1 = *n*-C_4H_9
d, R = *n*-C_3H_7; R_1 = CH_3
e, R = *n*-C_3H_7; R_1 = C_2H_5
f, R = *n*-C_3H_7; R_1 = *i*-C_3H_7
g, R = *n*-C_3H_7; R_1 = allyl
h, R = *n*-C_3H_7, R_1 = $CH_2C_6H_5$
i, R = R_1 = $CH_2C_6H_5$

amount of work has been published concerning the geometrical isomers of ethyl benzohydroximate (**4a** and **5a**), the first compounds to be independently synthesized in this study were the three diethylated isomers of benzohydroxamic acid (**6a**, **7a**, and **8a**).

The synthesis of ethyl *N*-ethylbenzohydroxamate (**6a**) was accomplished by reacting benzoyl chloride with *O*,*N*-diethylhydroxylamine (Scheme I). The *O*,*N*-diethylhydroxylamine was prepared by diethylation of ethoxyformohydroxamic acid (**9a**) followed by acid hydrolysis.

The *Z* and *E* isomers of ethyl *O*-ethylbenzohydroximate (**7a** and **8a**) were synthesized according to the procedure outlined in Scheme I. Exner, Jehlička, and Reiser[19] have reported the preparation and separation of the ethyl benzohydroximates **4a** and **5a**, but we have found it more convenient to synthesize these isomers by a modification of the older procedure reported by

SCHEME I



Gurke.[20] Benzoyl benzohydroxamate (**10**) was converted into its silver salt **11** and then alkylated with ethyl iodide to produce the *Z* isomer of ethyl benzoylbenzohydroximate (**12a**) along with a small amount of the *E* isomer. Basic hydrolysis of the crude alkylation product gave mainly ethyl (*Z*)-benzohydroximate (**4a**). Alkylation of **4a** with ethyl iodide and sodium ethoxide resulted in the formation of ethyl (*Z*)-*O*-ethylbenzohydroximate (**7a**).

Since **5a** was produced in the hydrolysis of crude **12a** in low yield, isolation of **5a** was not attempted on this sample. Instead the crude hydrolysis product was enriched in the *E* isomer by uv irradiation before attempting the separation. Column chromatography of the irradiated sample afforded pure ethyl (*E*)-benzohydroximate (**5a**) which was alkylated to give ethyl (*E*)-*O*-ethylbenzohydroximate (**8a**).

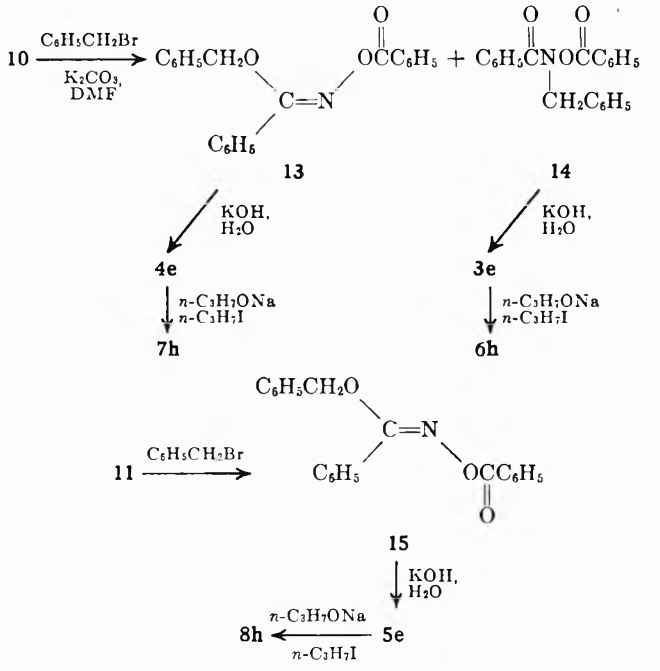
The unambiguity of the syntheses of the authentic samples of the *Z* and *E* isomers of ethyl *O*-ethylbenzohydroximate depends on accurate knowledge of the stereochemistry of their precursors, **4a** and **5a**. Werner[21,22] first reported evidence concerning the stereochemistry of these compounds. He subjected the two isomers to Beckmann rearrangement conditions (phosphorus pentachloride in ether) and found that the isomer with mp 53.5° gave, after hydrolysis, *N*-phenylurethane, whereas the other isomer with mp 67.5–68° did not rearrange and afforded only a phosphate ester after hydrolysis. Werner drew the wrong conclusion concerning the configurations of these compounds since at the time of his work the Beckmann rearrangement was thought to involve migration of the group syn to the

(10) "Beilsteins Handbuch der Organischen Chemie," Vol. IX, Verlag von Julius Springer, Berlin, 1926, pp 309–313.
(11) H. L. Yale, *Chem. Rev.*, **33**, 209 (1944).
(12) A. T. Fuller and H. King, *J. Chem. Soc.*, 963 (1947).
(13) W. Lossen, *Justus Liebigs Ann. Chem.*, **252**, 170 (1889).
(14) W. Lossen, *Ber.*, **24**, 4059 (1891).
(15) M. E. Waldstein, *Justus Liebigs Ann. Chem.*, **181**, 384 (1876).
(16) There have also been several reports of alkylations of the salts of acyl benzohydroxamates to give alkyl *O*-acylbenzohydroximates: (a) W. Lossen, *ibid.*, **281**, 169 (1894); (b) A. Werner and J. Subak, *Ber.*, **29**, 1153 (1896); (c) see also ref 13, 20, and 39.
(17) Cooley, Bill, and Throckmorton[9] have reported a few dialkylated hydroxamic acids but did not assign structures to the compounds.
(18) In the recent literature[6] the synthesis of the *Z* and *E* isomers of methyl *O*-carbethoxymethylbenzohydroximate and some of its derivatives have been reported.
(19) O. Exner, V. Jehlička, and A. Reiser, *Collect. Czech. Chem. Commun.*, **24**, 3207 (1959).
(20) O. Gurke, *Justus Liebigs Ann. Chem.*, **205**, 273 (1880).
(21) A. Werner, *Ber.*, **25**, 27 (1892).
(22) A. Werner, *ibid.*, **26**, 1561 (1893).

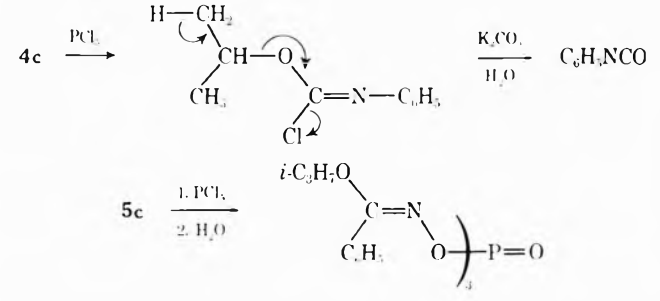
hydroxyl groups. It is now known,[23] of course, that the group anti to the hydroxyl group migrates to nitrogen. One would now conclude that the ethyl benzohydroximate with mp 53.5° has the *Z* configuration (**4a**) and the isomer with mp 67.5–68° has the *E* configuration (**5a**). This conclusion has been substantiated by cyroscopic[24] and dipole moment[19,25] measurements of these two isomers.

Eight additional model compounds were synthesized according to the methods outlined in Scheme I (**6b**, **7e**, **8e**, **7f**, and **8f**) and Scheme II (**6h**, **7h**, and **8h**). The procedures used for the synthesis (Scheme II) of the three isomers **13**, **14**, and **15** depend on the variations of product distribution with changes in the alkylation reaction conditions of benzoyl benzohydroxamate (**10**). Admittedly these procedures were developed in the later stages of this study and were based on the results obtained with alkyl benzohydroxamates.

SCHEME II



The *Z* and *E* isomers of isopropyl benzohydroximate (**4c** and **5c**) have not been previously reported. In order to establish the configurations of these compounds, they were reacted with phosphorus pentachloride in ether. One isomer (**5c**, assigned the *E* configuration) did not undergo a Beckmann rearrangement and was converted into a phosphate ester. The other isomer (**4c**, assigned the *Z* configuration) gave phenyl isocyanate which probably arose by elimination of the isopropyl group from the Beckmann rearrangement product.



The stereochemical assignments[26] for the isomers of benzyl benzohydroximate (**4e** and **5e**) are based on their melting points by comparison to the melting points of the isomeric pairs **4a**–**5a** and **4c**–**5c** and other hydroximates of known configuration.[27] It is assumed that the *Z* isomer **4e** has a lower melting point than the corresponding *E* isomer **5e**. This difference in melting point behavior presumably is due to intramolecular hydrogen bonding in the (*Z*)-hydroximates *vs.* intermolecular hydrogen bonding in the *E* isomers.

The nmr spectra of the isomers **6**, **7**, and **8** differ mainly in the chemical shifts of the methylene hydrogens attached to the nitrogen and oxygen atoms of these molecules. From the nmr spectra of the model compounds the following generalizations have been made. (1) The chemical shift of the $NOCH_2$ hydrogens of the *Z* isomer of an alkyl *O*-alkylbenzohydroximate occurs further downfield than the chemical shift for the $NOCH_2$ hydrogens of the *E* isomer. Similarly, the chemical shift of the $COCH_2$ hydrogens of the *Z* isomer occurs further downfield than the $COCH_2$ hydrogens of the *E* isomer. (2) The chemical shift of the $NOCH_2$ and $COCH_2$ hydrogens of the *E* isomer of an alkyl *O*-alkylbenzohydroximate occurs further downfield than the $NOCH_2$ and NCH_2 hydrogens of an alkyl *N*-alkylbenzohydroxamate.

In addition, on the basis of the results obtained with the model compounds, it has been concluded that the alkylated isomers elute from a vpc column of 20% SE-30 in the following order: alkyl (*E*)-*O*-alkylbenzohydroximate (shortest retention time), alkyl (*Z*)-*O*-alkylbenzohydroximate, and alkyl *N*-alkylbenzohydroxamate (longest retention time).

Chemical shift data for the methylene hydrogens attached to nitrogen or oxygen atoms in the dialkylated hydroxamic acids prepared in this investigation are located in Tables I and II.

Having established methods for determining the product distributions, a systematic study of the alkylation of the salts of alkyl benzohydroxamates was undertaken. The first alkylation reactions investigated were carried out on the potassium salts of alkyl benzohydroxamates. These salts were not isolated but generated *in situ* by adding potassium carbonate to aqueous–methanol solutions of the hydroxamates. The results of this study are summarized in Tables III and IV. The most obvious consequence of this study is that the reaction of the potassium salts of alkyl benzohydroxamates with primary alkyl bromides gives primarily products resulting from alkylation on nitrogen rather than oxygen as previously reported. This is in accord with the recent findings of Chehata, *et al.*[4,28] Furthermore, we have found that the minor product in the reac-

(23) N. V. Sidgwick, I. T. Millar, and H. D. Springall, "The Organic Chemistry of Nitrogen," 3rd ed, Clarendon Press, Oxford, 1966, pp 316–333.

(24) H.-C. Yuan and K.-C. Hua, *J. Chin. Chem. Soc.* (*Taipei*), **7**, 76 (1940).

(25) O. Exner, *Collect. Czech. Chem. Commun.*, **30**, 652 (1965).

(26) Both stereoisomers of benzyl benzohydroximate gave the same major product (by tlc and nmr) when reacted with phosphorus pentachloride. No attempt was made to identify this product.

(27) The configurations of three other pairs of hydroximate isomers have been determined: methyl benzohydroximate[5] (*Z* mp 44°, *E* mp 52–53°), ethyl *p*-nitrobenzohydroximate[19] (*Z* mp 95°, *E* mp 141°), and ethyl *p*-methylbenzohydroximate[24] (*Z* mp 35.5–36°, *E* mp 101.5–102°).

(28) The reaction conditions employed by Chehata, Bocabeille, Thuillier, and Rumpf[4] are somewhat different from ours. They reacted benzyl benzohydroxamate with alkyl iodides in a solution of sodium ethoxide in absolute ethanol.

TABLE I
NMR SPECTRAL DATA FOR BENZOHYDROXIMATES[a]

Compd	Chemical shift, δ, ppm (multiplicity, J in Hz) =NOCH2–	=COCH2
7a[b]	4.11 (q, 7)	4.35 (q, 7)
8a[b]	4.05 (q, 7)	4.18 (q, 7)
7b	4.05 (t, 6.5)	4.24 (t, 6.5)
8b	3.92 (t, 6.5)	4.08 (t, 6.5)
7c	4.08 (t, 6)	4.26 (t, 6)
8c	3.97 (t, 6)	4.13 (t, 6)
7d	4.05 (t, 6.5)	3.96 (CH_3, s)
8d	3.93 (t, 6.5)	3.81 (CH_3, s)
7e	4.05 (t, 6.5)	4.33 (q, 7)
8e	3.93 (t, 6.5)	4.17 (q, 7)
7f	4.05 (t, 6.5)	4.98 (CH, septet, 6)
8f	3.92 (t, 6.5)	5.00 (CH, septet, 6)
8g	3.96 (t, 6.5)	*ca.* 4.69 (m)
7h	4.07 (t, 6.5)	5.31 (s)
8h	3.96 (t, 6.5)	5.17 (s)

[a] Unless otherwise noted all spectra were determined in $CDCl_3$ with tetramethylsilane as an internal standard. [b] Determined on the neat liquid.

TABLE II
NMR SPECTRAL DATA FOR BENZOHYDROXAMATES[a]

Compd	Chemical shift, δ, ppm (multiplicity, J in Hz) NCH2–	OCH2–
6a[b]	3.71 (q, 7)	3.68 (q, 7)
6b	3.72 (t, 7)	3.63 (t, 6.5)
6c	3.75 (t, 6.5)	3.67 (t, 6)
6d	3.34 (CH_3, s)	3.65 (t, 6)
6e	3.76 (q, 7)	3.65 (t, 6.5)
6f	*ca.* 4.52 (CH, m)	3.70 (t, 6)
6g	*ca.* 4.31 (m)	3.63 (t, 6)
6h	4.92 (s)	3.56 (t, 6)
6i	4.67 (s)	4.49 (s)

[a] Unless otherwise noted all spectra were determined in $CDCl_3$ with tetramethylsilane as an internal standard. [b] Determined on the neat liquid.

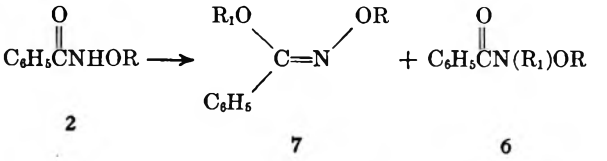
tions with primary alkyl bromides is in all cases studied the *Z* isomer of an alkyl *O*-alkylbenzohydroximate.

We have repeated the two potassium salt reactions described in the older literature. Lossen[13,14] reported that ethyl *O*-ethylbenzohydroximate was the only product from the reaction of ethyl benzohydroxamate with ethyl iodide in an aqueous ethanol solution of potassium hydroxide. We have found that this reaction actually results in the exclusive formation of the *N*-alkylated isomer, **6a**.

Fuller and King[12] have reported that the alkylation of potassium benzohydroxamate with *n*-butyl bromide in a mixture of ethanol and potassium carbonate forms *n*-butyl benzohydroxamate (**2d**) in 33% yield and *n*-butyl *O*-*n*-butylbenzohydroximate (**7c** or **8c**) in 24% yield. In our hands this alkylation gave 43% yield of the monoalkylated product, **2d**, along with an 8% yield of the (*Z*)-hydroximate, **7c**, and a 17% yield of the hydroxamate, **6c**. Fuller and King[29] based their structure assignment for the dialkylated product on a hydrolysis experiment from which they isolated *O*-*n*-butylhydroxylamine hydrochloride. Apparently they isolated only one of the hydrochlorides and overlooked the *O*,*N*-di-*n*-butylhydroxylamine hydrochloride which was probably present in their hydrolysis mixture.

(29) The per cent yields reported in this work are based on vpc analyses of the crude products whereas the yields reported by Fuller and King[12] were of distilled samples.

TABLE III
EFFECT OF THE ALKYLATING AGENT ON THE ALKYLATION PRODUCTS OF THE POTASSIUM SALTS OF ALKYL BENZOHYDROXAMATES[a]



2 7 6

Alkylating agent	R	Crude yield, %	Product distribution, % 7	6
Ethyl bromide	C_2H_5	48	23	77
n-Butyl bromide	*n*-C_4H_9	21	28	72
Methyl iodide	*n*-C_3H_7	91	3	97
Ethyl bromide	*n*-C_3H_7	56	25 (26)	75 (74)
Ethyl iodide	*n*-C_3H_7	78	20 (19)	80 (81)
Diethyl sulfate[b]	*n*-C_3H_7	83	49 (48)	51 (52)
n-Propyl bromide	*n*-C_3H_7	29	26 (28)	74 (72)
n-Propyl iodide	*n*-C_3H_7	31	20 (18)	80 (82)
Isopropyl bromide	*n*-C_3H_7	19	78	22
Isopropyl iodide	*n*-C_3H_7	22	63	37
Allyl chloride	*n*-C_3H_7	47	25	75
Allyl bromide	*n*-C_3H_7	62	19	81
Allyl iodide	*n*-C_3H_7	66	9	91
Benzyl bromide[d]	*n*-C_3H_7	51[c]	15	85

[a] These reactions were carried out using mole ratios of 1:2:1.6 of alkyl benzohydroxamate to alkyl halide to potassium carbonate. The reactions were all run at 38° for 15 hr using methanol–water (1.45:1) as the solvent. The crude yields and product distributions were determined by vpc analyses of the crude products. Numbers in parentheses represent product distributions obtained in duplicate runs. [b] This reaction was carried out in anhydrous ether and was heterogeneous. [c] Per cent yield based on distilled product. [d] Product distribution determined by integration of benzyl hydrogens in nmr spectrum of crude product.

The product distributions for the potassium salt reactions appear to be sensitive to the structure of the alkyl bromide. A small increase in the amount of oxygen alkylation was observed with increase in the length of the straight chain of the primary alkyl bromide, but, more dramatically, isopropyl halides gave more alkylation on oxygen than on nitrogen.

The leaving group may have an effect on the product distribution in the potassium salt reactions as evidenced by the large increase in oxygen alkylation when diethyl sulfate was used as the alkylating agent. However, this reaction cannot be compared to the other potassium salt reactions since it was a heterogeneous reaction carried out in anhydrous ether.

We have considered the possibility that the predominance of nitrogen alkylation in the reactions with primary alkyl halides is due to rearrangement of one or both of the oxygen alkylated isomers. This was of particular concern since rearrangements of this type are known, albeit at elevated temperature.[30] We have subjected mixtures of the oxygen alkylated isomers **7b** and **8b** to the potassium salt reaction conditions and have found no rearrangement to the nitrogen alkylated isomer, **6b**, or for that matter we observed no change in the ratio of the geometrical isomers. We therefore conclude that these isomers are formed irreversibly and that no interconversion between the isomers occurs during the alkylation reactions.

(30) J. W. Schulenberg and S. Archer, *Org. React.*, **14**, 24 (1965).

TABLE IV
EFFECT OF TEMPERATURE, REACTION TIME, SOLVENT, AND CONCENTRATION OF ALKYL BROMIDE ON THE PRODUCT DISTRIBUTIONS IN THE POTASSIUM SALT REACTIONS OF BENZOHYDROXAMIC ACID AND ALKYL BENZOHYDROXAMATES[a]

Hydroxamate	Alkyl bromide	Mole ratio of hydroxamate to alkyl bromide	Reaction time, hr	Temp, °C	Crude yield of dialkylated isomers, %	Product distribution, % 7	6
PhCONHOK	n-C_3H_7	1:3	15	38	29	28	72
PhCONHOK	n-C_3H_7	1:3	15	48	30	23	77
PhCONHOK	n-C_3H_7	1:3	15	58	63	27	73
2b	n-C_3H_7	1:2	15	38	29	28	72
2b	n-C_3H_7	1:2	15	48	58	31	69
2b	n-C_3H_7	1:2	15	58	76	34	66
2b	n-C_3H_7	1:1	15	58	47	34	66
2b	n-C_3H_7	1:3	15	58	77	33	67
2b	n-C_3H_7[b]	1:2	15	58	91	66	34
2b	n-C_3H_7[c]	1:2	15	58	88	63	37
2d	n-C_4H_9	1:2	10	58	62	34	66
2d	n-C_4H_9	1:2	15	58	68	33	67
2d	n-C_4H_9	1:2	20	58	5	33	67
2b	i-C_3H_7	1:2	15	38	19	78	22
2b	i-C_3H_7	1:2	15	58	45	73	27
2b	i-C_3H_7[c]	1:2	15	58	94	92	8

[a] These reactions were carried out using a mole ratio of 1:1.6 of alkyl benzohydroxamate to potassium carbonate or a mole ratio of 1:2 of potassium benzohydroxamate to potassium carbonate. Methanol–water (1.45:1) was used as a solvent except when otherwise noted. [b] In dimethyl sulfoxide solvent. [c] In dimethylformamide solvent.

The effects of temperature, concentration of alkylating agent, and reaction time on the product distributions in the potassium salt reactions (Table IV) have been studied. Although the product distributions changed only slightly with these variables the product yields underwent considerable change. Our data shows that optimum conditions for the potassium salt reactions are a temperature of 58°, a reaction time of 15 hr, and a 2:1 ratio of alkyl bromide to alkyl benzohydroxamate.

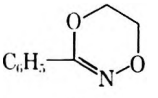
The synthesis of dialkylated hydroxamates, where both alkyl groups are the same, can be carried out starting with potassium benzohydroxamate and adding enough alkyl halide to achieve dialkylation. This method has the obvious advantage of eliminating an isolation step. The product distributions for these reactions are in Table V.

TABLE V
PRODUCTS OF THE REACTION OF POTASSIUM BENZOHYDROXAMATE WITH ALKYL BROMIDES[a]

Alkyl bromide	Crude yield of alkyl benzohydroxamate 2, %	Crude yield of dialkylated products 7 and 6, %	Dialkylation product distribution, % 7	6
C_2H_5	34	33	20	80
n-C_3H_7	62	23	21	79
n-C_4H_9	60	10	32	68
$C_6H_5CH_2$[b]	...[c]	47		100[d]

[a] These reactions were carried out using mole ratios of 1:3:2 of potassium benzohydroxamate to alkyl bromide to potassium carbonate. The reactions were run at 38° for 15 hr and methanol–water (1.45:1) was used as the solvent. The crude yields and distributions of the dialkylated products were determined by vpc analyses of the crude products. [b] This reaction was refluxed for 15 hr. [c] The amount of benzyl benzohydroxamate produced in this reaction was not determined. [d] Tlc analysis of the crude product showed that it contained only one isomer which was assumed to be 6i.

When potassium benzohydroxamate was allowed to react with dibromides cyclized products were obtained. 1,4-Dibromobutane and 1,3-dibromopropane reacted at nitrogen and the hydroxylamine oxygen to give 2-benzoyltetrahydro-1,2-oxazine (18) and 2-benzoyloxazolidine (17), respectively. Cyclization with 1,2-dibromoethane led to the formation of 3-phenyl-5H-1,4,2-dioxazine (16). The structures of these compounds were determined by comparison of their nmr, uv, and ir spectra with the spectra of the model compounds described earlier.



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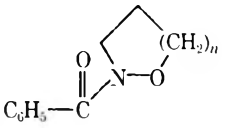


17, $n = 1$
18, $n = 2$

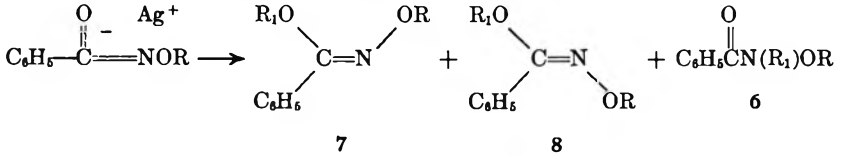
Table VI summarizes data on the product distributions observed for alkylations of the silver salts of alkyl benzohydroxamates. All reactions listed in this table were heterogeneous and conducted in anhydrous solvents under comparable reaction conditions. It is clear that alkylation occurs on oxygen in preference to nitrogen in these reactions. In addition, the halogen of the alkyl halide has a significant effect on the stereochemistry of the product. Whereas alkyl iodides afford mainly (Z)-hydroximates, alkyl bromides favor hydroximates with the E configuration. It should also be noted that there is a substantial difference in the rate of the silver salt alkylations depending on the kind of halogen of the alkyl halide. Alkylations with alkyl iodides are complete in about 3 days, but most of the alkyl bromide reactions require a reaction time of approximately 7 days. Several experiments were carried out to ensure that the observed product distributions did not result from isomerization.

The literature[31] contains another general method for the preparation of alkyl O-alkylbenzohydroximates. This procedure (Scheme III) involves the preparation of

(31) F. Tieman and P. Kruger, *Ber.*, **18**, 727 (1885).

TABLE VI

EFFECT OF THE ALKYLATING AGENT ON THE ALKYLATION PRODUCTS OF THE SILVER SALTS OF ALKYL BENZOHYDROXAMATES[a]



7 8

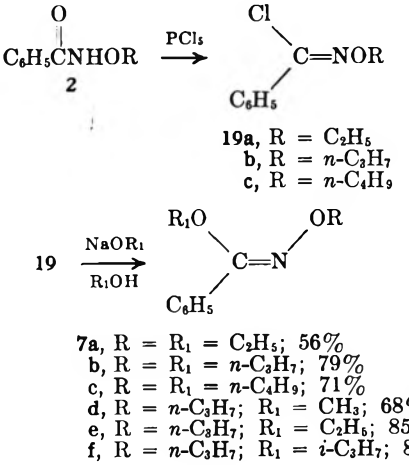
Alkyl halide	R	Crude yield, %	Product distribution, % 7	8	6
Methyl iodide[b]	n-C_3H_7	71	42 (41)	20 (21)	38 (38)
Ethyl bromide	n-C_3H_7	69	23 (23)	74 (74)	3 (3)
Ethyl iodide	n-C_3H_7	81	69 (71)	23 (21)	8 (8)
n-Propyl bromide	n-C_3H_7	22	30 (31)	67 (66)	3 (3)
n-Propyl iodide	n-C_3H_7	67	70	22	8
Isopropyl bromide	n-C_3H_7	72	22	76	2
Isopropyl iodide	n-C_3H_7	66	72	26	2
Allyl bromide	n-C_3H_7	83	9	75	16
Allyl iodide	n-C_3H_7	72	32	38	30
Benzyl bromide[c]	n-C_3H_7	63	20	71	9
Benzyl iodide[c]	n-C_3H_7	100	27	28	45
Ethyl bromide[d]	C_2H_5	49	32	61	7
Ethyl iodide[d]	C_2H_5	54	81	18	1
n-Butyl iodide[d]	n-C_4H_9	50	62	35	3
Ethyl iodide[e]	n-C_3H_7	60	83	8	9
Allyl bromide[e]	n-C_3H_7	68	38	40	22
Benzyl bromide[c,e]	n-C_3H_7	65	42	33	25
Benzyl iodide[c,e]	n-C_3H_7	73	55	13	32

[a] These reactions were carried out using a mole ratio of 1:1.9 of the silver salt of the alkyl benzohydroxamate to the alkyl halide. The reactions were run at room temperature for 7 days. Anhydrous ether was used as the solvent unless otherwise noted and all of the reactions were heterogeneous. The crude yields and product distributions were determined by vpc analyses of the crude products. Numbers in parentheses represent product distributions obtained in duplicate runs. [b] The distribution of isomers as determined from integration of the nmr spectrum of the crude product was 41% **7**, 22% **8**, and 37% **6**. [c] The relative amounts of the isomers were determined from the nmr spectra by integration of the benzyl hydrogens. [d] The silver salts used in these reactions were prepared by reaction of the alkyl benzohydroxamate with silver nitrate and sodium hydroxide rather than ammonium hydroxide. [e] Reaction solvent was dimethylformamide.

an alkylbenzohydroximoyl chloride (**19**)[32] by the reaction of an alkyl benzohydroxamate (**2**) with phosphorus pentachloride followed by the reaction of **19** with a sodium alkoxide.[33] In all of the reactions that we have carried out only the *Z* isomers (**4**)[34] of the hydroximates were formed.

During the course of this investigation it was necessary to isolate pure samples of **6** and **8** from mixtures containing two (**6** and **7**) or three (**6**, **7**, and **8**) of the isomers. Though pure samples of the (*E*)-hydroximates (**8**) had to be obtained from these mixtures by preparative vpc, a more convenient method has been developed for preparing pure samples of **6**. This procedure depends on the greater hydrolysis rate (acid catalyzed) of the hydroximates compared to the hydroxamates. Treatment of the mixtures of **6**, **7**, and **8** with warm concentrated hydrochloric acid for short periods caused hydrolysis of **7** and **8** leaving relatively pure **6** which could be further purified by distillation.

SCHEME III



19a, R = C_2H_5
b, R = n-C_3H_7
c, R = n-C_4H_9

7a, R = R_1 = C_2H_5; 56%
b, R = R_1 = n-C_3H_7; 79%
c, R = R_1 = n-C_4H_9; 71%
d, R = n-C_3H_7; R_1 = CH_3; 68%
e, R = n-C_3H_7; R_1 = C_2H_5; 85%
f, R = n-C_3H_7; R_1 = i-C_3H_7; 89%

Discussion

The most interesting result of our alkylation studies was the observation of changes in the distribution of the stereoisomeric benzohydroximates with changes in cation, solvent, and alkylating agent. We believe that two competing factors are important in determining the stereochemistry of the hydroximates. One factor we have considered is the relative stability of the two geometrical isomers. From examination of the structures of the stereoisomeric benzohydroximates it would appear that in all cases the *Z* isomer is more stable than

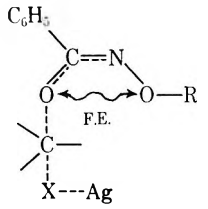
(32) The vapor phase chromatograms and nmr spectra of these compounds show that only one isomer is formed in the reaction of **2** with PCl_5. Work is currently in progress on the determination of the configurations of these compounds.

(33) The reaction to obtain **7d** from **19b** was carried out at 55° with dimethyl sulfoxide as a solvent.

(34) Less than 2% of the *E* isomer was formed in each of these reactions with the exception of the preparation of **7d** in which 4% *E* isomer was obtained.

the *E* isomer. This is based solely on the obvious difference in steric interactions between the *E* and *Z* isomers where the *N*-alkoxy group is interacting with either a phenyl group or the smaller alkoxy group. Clearly, the magnitude of this effect will depend upon the degree of carbon–nitrogen double bond character in the transition state.

A second factor that we have considered is a repulsive field effect (F.E) between the two oxygen atoms in the transition state. The importance of this effect should



change with variations in the magnitude of the negative charge on the carbonyl oxygen in the transition state.

It seems reasonable that bond formation between the silver ion and the halogen of the alkyl halide is further advanced in the case of an alkyl iodide transition state than a corresponding alkyl bromide reaction. This would be expected since silver ion is a soft Lewis acid and should react more readily with iodide which is a softer base than bromide.[35] As a consequence of more advanced silver–halogen bond formation, the incipient carbon–nitrogen double bond may also be further advanced in the alkyl iodide transition states as compared to the alkyl bromides. In addition, the developing bond between the carbonyl oxygen and the carbon atom of the alkylating agent should be formed to a greater extent in the iodide reactions. Accordingly, the carbonyl oxygen should carry a larger negative charge in the alkyl bromide reactions than in reactions with alkyl iodides.

In the alkyl bromide reactions, the repulsive field effect would become negligible if the hydroxylamine oxygen assumed a position opposite to the carbonyl oxygen in the transition state. Obviously, this transition state would lead to the *E* isomer. It is possible that the repulsive field effect in the alkyl bromide reactions outweighs the stability factor causing a predominance of the *E* isomer. In the alkyl iodide reactions the stability factor is more important resulting in the formation of the *Z* isomer.

The hydroximates formed in the potassium salt reactions[36] in all cases studied have the *Z* configuration. It is conceivable that the charge on the carbonyl oxygen in the transition state is dispersed by the solvent molecules thus diminishing the field effect. However, this explanation would lead to the conclusion that dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) are effective in dispersing the charge on the carbonyl oxygen since in these solvents only the *Z* isomers of the hydroximates are obtained. This does not seem to be a plausible conclusion because DMF and DMSO, while being very effective at solvating cations, are relatively ineffective at solvating anions.[37] We propose instead that the lack of a significant field effect in the potassium salt reactions is due to the inherent charge dispersal of a pure or nearly pure SN2 reaction. In other words the potassium salt reactions are typical SN2 reactions with considerable dispersal of the negative charge in the transition state. The field effect, therefore, is important only in those reactions where bond cleavage and bond formation are not completely synchronous. This would be the case in the silver salt reactions where cleavage of the carbon–halogen bond is ahead of carbon–oxygen bond formation.

When DMF was used as the solvent in the silver salt alkylations a significant decrease in the amount of the *E* isomer was observed. It seems likely that in DMF the silver ion is at least partially solvated. This should diminish the effect of the silver ion on the reaction and impart more SN2 character to the transition state. The decrease in the field effect in DMF is thus due to an increase in the SN2 character of the alkylation transition state.

(35) R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, **89**, 1827 (1967).

(36) The mechanisms of alkali metal–ambident anion alkylations have been reviewed: R. Gomper, *Angew. Chem., Int. Ed. Engl.*, **3**, 560 (1964).

(37) (a) N. Kornblum, R. Seltzer, and P. Haberfield, *J. Amer. Chem. Soc.*, **85**, 1148 (1963); (b) E. M. Kosower, "Physical Organic Chemistry," Wiley, New York, N. Y., 1968, pp 334–342.

Experimental Section

Melting points are corrected and were determined on a Thomas–Hoover capillary melting point apparatus. All the boiling points are uncorrected. Magnesium sulfate was employed as a drying agent for ether extracts. The petroleum ether used throughout this work had a boiling point of 30–60°. The thin layer chromatograms were carried out on Mallinckrodt's SilicAR TLC-7GF adsorbent using chloroform–petroleum ether (1:1) as the solvent. The infrared spectra were determined with a Beckman Model IR-20 infrared recording spectrophotometer. The ultraviolet spectra were determined with a Beckman recording spectrophotometer, Model DK-2A. The nmr spectra were determined at 60 Mc with a Varian Model A-60A nmr spectrometer. The chemical shifts are expressed in δ values relative to a tetramethylsilane internal standard. The vapor phase chromatograms were determined with a Beckman Model GC-5 fitted with a Disc Integrator. The chromatograms were obtained with a column (6 ft × 0.25 in.) consisting of 20% silicone gum rubber (SE-30) on 60–70 mesh diatomaceous earth (Anolabs' Anakrom SD) at a column temperature of 200° and a flow rate of 60 ml of He/min. The microanalyses were performed by John R. Springfield of this laboratory using an F & M Scientific Model 185 Carbon, Hydrogen, and Nitrogen Analyzer. The properties for most of the compounds prepared in this work are in Table VII. One example of each type of alkylation procedure is described in this section.

Silver Salt of Benzoyl Benzohydroxamate (11).—A procedure for the preparation of this salt has been reported previously by Lossen.[38] In Lossen's procedure sodium hydroxide was used as the base. A solution of silver nitrate (40.0 g) in distilled water (34 ml) was added to a warm (40°) solution of benzoyl benzohydroxamate (55.5 g) in methanol (860 ml). Concentrated ammonium hydroxide (16 ml) was then added to the vigorously stirred reaction mixture. The precipitate which formed was filtered, washed thoroughly with acetone, and dried in a vacuum desiccator to give 72.4 g (90%) of a white powder.

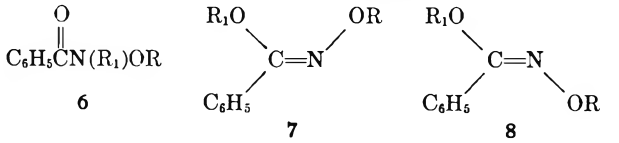
Anal. Calcd for $C_{14}H_{10}NO_3Ag$: C, 48.30; H, 2.90; N, 4.02. Found: C, 47.91; H, 2.80; N, 3.99.

Ethyl (*Z*)-*O*-Benzoylbenzohydroximate (12).—The reaction was carried out according to a procedure described by Eiseler.[39] A mixture of ethyl iodide (39.0 g), the silver salt of benzoyl benzohydroxamate (87.0 g), and anhydrous ether (500 ml) was stirred at room temperature for 3 days. The insoluble salts were removed by filtration and the ether was evaporated from the filtrate. The residual oil solidified upon standing to give 58.4 g (88%) of white crystals, mp 45–48°. The tlc of this crude product showed one major spot (*Z* isomer) along with one small spot (*E* isomer). Several recrystallizations of the crude product from large volumes of petroleum ether gave white needles, mp 58.5–59° (lit.[20,39] mp 58°). The tlc of the recrystallized product showed only one spot due to the *Z* isomer: ir (Nujol) 1750 (m,

(38) W. Lossen, *Justus Liebigs Ann. Chem.*, **161**, 347 (1880).

(39) E. Eisler, *ibid.*, **175**, 326 (1875).

TABLE VII
PROPERTIES OF DIALKYLATED BENZOHYDROXAMIC ACIDS[a]



R	R_1	Compd no.	Bp (mm) or mp, °C	Method of preparation[b]
n-C_3H_7	n-C_3H_7	**8b**		G
n-C_4H_9	n-C_4H_9	**6c**		G
n-C_4H_9	n-C_4H_9	**7c**	129–134 (0.4)	A
n-C_4H_9	n-C_4H_9	**8c**		G
n-C_3H_7	CH_3	**6d**	108–109 (0.4)	E
n-C_3H_7	CH_3	**7d**	85–87 (0.5)	A
n-C_3H_7	CH_3	**8d**		G
n-C_3H_7	C_2H_5	**6e**	126–129 (1.2)	E
n-C_3H_7	C_2H_5	**7e**	86–87 (0.4)	A and B
n-C_3H_7	C_2H_5	**8e**	83–84 (0.5)	C
n-C_3H_7	i-C_3H_7	**7f**	78–79 (0.2)	A and B
n-C_3H_7	i-C_3H_7	**8f**	89–97 (0.5)	C
n-C_3H_7	Allyl	**6g**		G
n-C_3H_7	Allyl	**8g**		G
n-C_3H_7	Benzyl	**6h**	145–147 (0.13)	D
n-C_3H_7	Benzyl	**7h**	151–159 (0.5)	B
n-C_3H_7	Benzyl	**8h**	135–139 (0.15)	C
Benzyl	Benzyl	**6i**	66–67[c]	F

[a] Satisfactory analytical values (±0.30% for C, H, and N) were reported for all compounds in this table: Ed. [b] Pure samples (95% or better by vpc) prepared by distillation (or recrystallization) of samples obtained from reactions of the following types: A, benzohydroximoyl chloride with a sodium alkoxide; B, alkylation of alkyl (*Z*)-benzohydroximate; C, alkylation of alkyl (*E*)-benzohydroximate; D, alkylation of *N*-alkylbenzohydroxamic acid; E, selective hydrolysis of *Z* and *E* hydroximates in a mixture containing **6**, **7**, and **8** or **6** and **7**. Those samples labeled with a G were obtained by preparative vpc of an alkylation reaction mixture. [c] Reported: mp 66° [R. Behrend and K. Leuchs, *Justus Liebigs Ann. Chem.*, **257**, 203 (1890)], 65–66° [R. Kothe, *ibid.*, **266**, 310 (1891)], 65° (ref 4).

C=O), 1615 (m, C=N), 1610 (m, aromatic), 1580 cm^{-1} (w, aromatic).

Ethyl (*Z*)-Benzohydroximate (4a).—The procedure was that of Gurke,[20] with minor modifications. Crude ethyl (*Z*)-*O*-benzoylbenzohydroximate (58.4 g) was dissolved in a solution of potassium hydroxide (28 g) and water (300 ml) and the mixture was stirred and refluxed for 12 hr. Carbon dioxide was then bubbled through the solution until it became cloudy and an oil separated. The mixture was extracted with ether (four 75-ml portions) and the combined ether extracts were dried and evaporated to give an oil that crystallized upon standing at room temperature (27.5 g, 77%), mp 49–50°. The tlc of the crude product showed one major spot (*Z* isomer) along with one small spot (*E* isomer) with a higher R_f value. Three recrystallizations from petroleum ether followed by sublimation yielded white crystals that showed only one spot on tlc: mp 53–53.5° (lit. mp 53.5°,[20] 53°[19]); uv max (95% ethanol) 248 mμ (log ε 4.00); ir (Nujol) 3140 (s, broad, OH), 1630 cm^{-1} (s, C=N); nmr ($CDCl_3$) δ 1.33 (t, 3, J = 7 Hz, OCH_2CH_3), 4.31 (q, 2, J = 7 Hz, OCH_2CH_3), 7.2–8.0 (2 m, 3 and 2, aromatic **H**).

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.45; H, 6.71; N, 8.48. Found: C, 65.86; H, 6.70; N, 8.59.

Ethyl (*E*)-Benzohydroximdate (5a).—A solution of crude ethyl (*Z*)-benzohydroximate (89.5 g) in dry benzene (500 ml) was irradiated for 2 hr at 70° with a Hanovia 450-W high-pressure lamp contained in a quartz water-cooled immersion apparatus (Ace Glass Inc., Vineland, N. J.). Subsequent evaporation of the benzene at aspirator pressure yielded an oily residue that solidified upon cooling. This solid was dissolved in hot petroleum ether and the solution was allowed to cool slowly to room temperature. During the cooling, a dark viscous red oil separated and was removed by decantation. The decantation was repeated several times until the red oil no longer appeared. The solution was then kept at room temperature until crystals (79.2 g, 90%) were obtained, mp 32–36°. The tlc of this material showed two spots with the largest spot corresponding to the *E* isomer.

Column chromatography on silica gel (250 g, 100–200 mesh) of 8.10 g of product using chloroform–petroleum ether (25:75) as the eluting solvent gave **ethyl (*E*)-benzohydroximate** (6.15 g, 68%), mp 61–66°, and ethyl (*Z*)-benzohydroximate (1.75 g, 19%), mp 39–45°. The *E* isomer eluted from the column before the *Z* isomer. Recrystallization of the crude **5a** from petroleum ether gave colorless needles that showed only one spot on tlc: mp 67–67.5° (lit.[19,20] mp 67.5–68°); uv 248 mμ (log ε 3.72); ir (Nujol) 3160 (s, broad, OH), 1650 (s, C=N), 1600 cm^{-1} (w, aromatic); nmr ($CDCl_3$) δ 1.32 (t, 3, J = 7 Hz, OCH_2CH_3), 4.15 (q, 2, J = 7 Hz, OCH_2CH_3), 7.2–8.1 (2 m, 3 and 2, aromatic **H**).

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.45; H, 6.71; N, 8.48. Found: C, 65.73; H, 6.67; N, 8.47.

Ethyl (*E*)-*O*-Ethylbenzohydroximate (8a).—Ethyl (*E*)-benzohydroximate (5.00 g) and ethyl iodide (4.06 g) were added to a solution of sodium ethoxide that had been prepared by adding sodium (0.59 g-atom) to absolute ethanol (50 ml). The resulting solution was heated to 45° and stirred for 72 hr after which time it was found to be acidic to litmus. The ethanol was evaporated at reduced pressure and the residue was triturated with chloroform (100 ml) and filtered. The chloroform filtrate was evaporated at reduced pressure and the residue was distilled to yield a colorless oil, bp 79–80° (0.1 mm). Vpc analysis of the distilled product showed that it was mainly **ethyl (*E*)-*O*-ethylbenzohydroximate** (3.74 g, 75%) contaminated with ethyl benzoate (0.06 g, 2%), ethyl (*Z*)-*O*-ethylbenzohydroximate (0.06 g, 2%), and a mixture of the *E* and *Z* isomers of ethyl benzohydroximate (0.29 g, 7%). A pure sample of **8a** was obtained by preparative vpc:[40] uv max (95% ethanol) 256 mμ (log ε 3.70); ir (neat) 1620 cm^{-1} (m, C=N); nmr (neat) δ 1.22 (t, J = 7 Hz, $COCH_2CH_3$), 1.26 (t, J = 7 Hz, $NOCH_2CH_3$), the signals between 1.0 and 1.5 integrated for a total of 6 H, 4.05 (q, J = 7 Hz, $COCH_2CH_3$), 4.18 (q, J = 7 Hz, $NOCH_2CH_3$), the signals between 3.8 and 4.5 integrate for a total of 4 H, 7.1–8.2 (2 m, 3 and 2, aromatic **H**).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.59; H, 7.83; N, 7.32.

Ethyl (*Z*)-*O*-Ethylbenzohydroximate (7a).—Ethyl (*Z*)-benzohydroximate (5.00 g) and ethyl iodide (5.46 g) were added to a solution of sodium ethoxide prepared from 0.81 g of sodium and 50 ml of ethanol. The solution was heated to 45° and stirred for 48 hr after which time it was found to be acidic to litmus. Compound **7a** (4.27 g, 73%), bp 80–81° (0.1 mm), was isolated as described above: uv max (95% ethanol) 256 mμ (log ε 4.01); ir (neat) 1615 (s, C=N), 1580 cm^{-1} (m, aromatic); nmr (neat) δ 1.25 (t, 6, J = 7 Hz, $NOCH_2CH_3$ and $COCH_2CH_3$), 4.11 (t, J = 7 Hz, $COCH_2CH_3$), 4.35 (t, J = 7 Hz, $NOCH_2CH_3$), the signals between 3.9 and 4.6 integrate for a total of 4 H, 7.1–8.0 (2 m, 3 and 2, aromatic **H**).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.59; H, 7.89; N, 7.38.

Ethyl *N*-Ethylethoxyformohydroxamate (9b).—The procedure was similar to that reported by Major and Fleck.[41] A 20% solution of potassium hydroxide (300 ml) was slowly added to a vigorously stirred solution of ethoxyformohydroxamic acid[12] (50.0 g) and ethyl sulfate (164 g). The mixture was stirred for 3 hr and then acidified with dilute sulfuric acid using congo red paper as an indicator. The mixture was extracted with ether (four 100-ml portions) and the combined ether extracts were washed with 3 *N* sodium hydroxide solution (five 50-ml portions), dried, and evaporated at aspirator pressure. The residue was distilled to yield a colorless oil (48.4 g, 75%), bp 91–98° (34 mm) [lit.[41] 56%, bp 107–112° (70 mm)].

Ethyl *N*-Ethylbenzohydroxamate (6a).—Ethyl *N*-ethylethoxyformohydroxamate (48.4 g) was added to a cold solution (10°) of potassium hydroxide (50.5 g) in 50% ethanol (117 ml). The solution was allowed to warm to room temperature, refluxed for 1 hr, and then distilled at atmospheric pressure. All of the distillate up to 83° was cooled in an ice bath and acidified with cold 12 *N* hydrochloric acid. After the acidified solution had warmed

(40) The preparative vpc was carried out using a Varian Aerograph Autoprep Model 705 with a column (20 ft × 3/8 in.) consisting of 30% silicone gum rubber (SE-30) on 45–60 mesh diatomaceous earth. The column temperature for the chromatography was 200° with nitrogen flow of approximately 300 ml/min.

(41) R. T. Major and E. E. Fleck, *J. Amer. Chem. Soc.*, **50**, 147 (1928).

to room temperature, it was concentrated on a hot plate, cooled in an ice bath, and then made basic to litmus with a concd. solution of potassium hydroxide.

One-half of the above solution (which was assumed to contain 13.4 g of *O,N*-diethylhydroxylamine) was added to benzoyl chloride that had been cooled in an ice bath. During the addition, the reaction was stirred and cooled in an ice bath so that the reaction temperature did not rise above 10°. Potassium carbonate was added during the course of the addition in order to maintain a solution that was basic to litmus. After all the *O,N*-diethylhydroxylamine solution had been added, the reaction mixture was allowed to warm to room temperature and then stirred for 6 hr. After acidification with 12 *N* hydrochloric acid, the material was extracted with ether (six 50-ml portions), the combined extracts were dried, and the solvent was removed at aspirator pressure. Distillation of the residue gave **6a** (12.6 g, 100%) as a colorless oil, bp 75–87° (0.1 mm) (lit.[13] bp 267°); the uv spectrum did not show a maximum but rather an increasing end absorption which had a log ϵ of 3.52 at 256 mμ; ir (neat) δ 0.90 (t, J = 7 Hz, NCH_2CH_3), 1.17 (t, J = 7 Hz, OCH_2CH_3), the signals between 0.70 and 1.40 integrate for a total of 6 H, 3.68 (q, J = 7 Hz, NCH_2CH_3), 3.71 (q, J = 7 Hz, OCH_2CH_3), the signals between 3.3 and 4.0 integrate for a total of 4 H, 7.1–7.9 (2 m, 3 and 2, aromatic **H**).

Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.14; H, 7.65; N, 7.33.

***n*-Propyl *N*-*n*-Propylethoxyformohydroxamate (9c).**—The reaction was carried out by the procedure described for **9b** except that *n*-propyl bromide was used as the alkylating agent. A 37% yield of **6c** was obtained: bp 75–83° (0.2 mm); ir (neat) 1700 cm^{-1} (s, C=O); nmr ($CDCl_3$) δ 0.7–1.9 (m, 13, $OCH_2CH_2CH_3$, $NCH_2CH_2CH_3$ and OCH_2CH_3), 3.40 (t, J = 7 Hz, 2, $NCH_2CH_2CH_3$), 3.78 (t, J = 6 Hz, 2, $OCH_2CH_2CH_3$), 4.11 (q, J = 7 Hz, 2, OCH_2CH_3).

Anal. Calcd for $C_9H_{19}NO_3$: C, 57.12; H, 10.11. Found:[42] C, 56.86; H, 10.15.

***n*-Propyl *N*-*n*-Propylbenzohydroxamate (6b).**—A solution of *O,N*-di-*n*-propylhydroxylamine was prepared by the procedure described above for **3a**. The reaction of the *O,N*-di-*n*-propylhydroxylamine solution with benzoyl chloride gave **6b** in 100% yield: bp 93–97° (0.2 mm); ir (neat) 1645 cm^{-1} (s, C=O); nmr $CDCl_3$ δ 0.5–2.1 (m, 10, $OCH_2CH_2CH_3$ and $NCH_2CH_2CH_3$), 3.63 (t, J = 6.5 Hz, $OCH_2CH_2CH_3$), 3.72 (t, J = 7 Hz, $NCH_2CH_2CH_3$), the signals between 3.4 and 3.9 integrate for a total 4 H, 7.1–7.8 (2 m, 3 and 2, aromatic **H**).

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.62; H, 8.43; N, 6.24.

Benzyl (*E*)-*O*-Benzoylbenzohydroximate (15).—A mixture of benzyl bromide (35.0 g), the silver salt of benzoyl benzohydroxamate (65.0 g), and anhydrous ether (140 ml) was stirred at room temperature for 3 days. When the ether was evaporated from the filtrate of this mixture, an oil (44.7 g) was obtained. The nmr spectrum of this oil indicated that it was a mixture of the isomers **15** (56%), **13** (17%), and **14** (27%). The oil was dissolved in ether–petroleum ether and kept in a freezer for 1 day. This resulted in the formation of an oil along with some crystalline solid. The crystals were collected and recrystallized from ether to yield 19.7 g (32%) of **15**, mp 83–86°. One recrystallization from methanol and two from ether–petroleum ether afforded an analytical sample: mp 86–88°; ir (Nujol) 1730 (s, C=O), 1620 (m, C=N), 1600 (m, aromatic), 1580 cm^{-1} (w, aromatic); nmr ($CDCl_3$) δ 5.48 (s, 2, CH_2), 7.1–8.1 (m, 15, aromatic **H**).

Anal. Calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23. Found: C, 75.87; H, 5.05; N, 4.14.

In several other similar reactions crystallization of the crude oil from ether–petroleum ether did not give pure **15**, but rather a mixture of **15** and **14**. However, it has been found that it is possible to hydrolyze a mixture of **15** and **14** and obtain pure **5e** (see next experiment).

Benzyl (*E*)-Benzohydroximate (5e).—A crystalline mixture (33.4 g) of **15** and **14** in a 73:27 ratio (by nmr) was added to a solution of potassium hydroxide (16.7 g) and water (25 ml) and the mixture was stirred and refluxed for 10 min. Water (40 ml) was added and the solution was extracted with ether (two 100-ml portions). The ether extracts were dried and evaporated to give **4e** (14.3 g, 85% based on the amount of **15** in the starting mixture), mp 127–133°. One recrystallization from methanol and one from benzene yielded a microcrystalline powder: mp 132–134°; ir (Nujol) 3270 (m, broad, OH), 1650 (m, C=N), 1600 cm^{-1} (w, aromatic); nmr ($CDCl_3$) δ 5.19 (s, 2 H, CH_2), 7.1–8.1 (m, 11 H, aromatic **H** and OH).

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.97; H, 5.62; N, 6.28.

Benzyl (*Z*)-*O*-Benzoylbenzohydroximate (13) and Benzoyl *N*-Benzoylbenzohydroxamate (14).—A mixture of benzoyl benzohydroxamate (58.0 g), benzyl bromide (60.0 g), anhydrous potassium carbonate (48 g), and dimethylformamide (250 ml) was stirred at 42° for 1 day (an initial exothermic reaction was controlled by cooling with an ice bath). The mixture was diluted with water (1 l.) and then extracted with chloroform (two 100-ml portions). The chloroform extracts were washed with water (three 500-ml portions), dried, and evaporated. An nmr spectrum of the oil residue (70.1 g) indicated that it consisted of **13** (23%) and **14** (77%). The oil was dissolved in ether (100 ml) and placed in a freezer overnight which resulted in the formation of 55.3 g (69%) of **14**, mp 83–89°. Two recrystallizations from chloroform–petroleum ether gave white prisms: mp 95–96° (lit.[43] mp 96–97°); ir (Nujol) 1745 (s, ester C=O), 1625 (s, amide C=O), 1590 and 1560 cm^{-1} (m, aromatic); nmr ($CDCl_3$) δ 5.11 (s, 2, CH_2), 7.1–8.1 (m, 15, aromatic **H**).

Anal. Calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23. Found: C, 76.23; H, 5.11; N, 4.22.

Petroleum ether was added to the ether filtrate from the above crystallization and after 3 hr in a freezer crystals of **13** (6.40 g, 8%) were obtained, mp 64–66°. Recrystallization from ether–petroleum ether gave white needles: mp 68–70°; ir 1740 (s, C=O), 1610 (s, C=N), 1570 cm^{-1} (w, aromatic); nmr ($CDCl_3$) δ 5.30 (s, 2, CH_2), 7.1–8.2 (m, 15, aromatic **H**).

Anal. Calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23. Found: C, 75.85; H, 5.15; N, 4.23.

Benzyl (*Z*)-Benzohydroximate (4e).—Benzyl (*Z*)-*O*-benzoylbenzohydroximate (6.40 g) was added to a solution of potassium hydroxide (3.3 g) and water (5 ml) and the mixture was heated (steam bath) and stirred until the reaction was homogeneous (*ca.* 5 min). Water (50 ml) was added and carbon dioxide was bubbled through the solution until it became cloudy and an oil separated. The mixture was extracted with ether (two 20-ml portions), the ether extracts were dried and evaporated, and the oil residue was crystallized from benzene–petroleum ether to yield 3.67 g (85%) of **4e**, mp 55–58°. Recrystallization from benzene–petroleum ether provided an analytical sample: mp 58–60°; ir (Nujol) 3120 (m, broad, OH), 1630 (m, C=N), 1580 cm^{-1} (w, aromatic) δ 5.31 (s, 2, CH_2), 7.1–7.8 (m, 10, aromatic **H**).

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.50; H, 5.73; N, 5.95.

***N*-Benzylbenzohydroxamic Acid (3e).**—The hydrolysis of **14** (15.7 g) was carried out by the procedure described in the preceding experiment except that chloroform was used as the extraction solvent. Evaporation of the chloroform extracts gave crystalline **3e** (9.61 g, 89%), mp 100–104°. Two recrystallizations from chloroform–petroleum ether afforded white microcrystals, mp 104–106° (lit.[43] mp 106°) that gave a magenta color with an ethanolic solution of ferric chloride: ir (Nujol) 3250 (m, broad, OH), 1620 (s, C=O), 1600 (m, aromatic), 1570 cm^{-1} (w, aromatic); nmr ($CDCl_3$) δ 4.77 (s, 2, CH_2), 7.0–7.7 (m, 10, aromatic H).

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.13; H, 5.58; N, 6.15.

Isopropyl (*Z*)-*O*-Benzoylbenzohydroximate (12b).—A mixture of isopropyl iodide (30.0 g), the silver salt of benzoyl benzohydroxamate (50.0 g), and anhydrous ether (200 ml) was stirred at room temperature for 3 days. The insoluble salts were removed by filtration and washed with ether. Evaporation of the ether filtrate gave a solid (35.0 g) that was recrystallized from ether–petroleum ether to yield 22.3 g (55%) of **12b**, mp 101–104°. Two more recrystallizations gave white needles: mp 105–106°; ir (Nujol) 1740 (s, C=O), 1620 (s, C=N), 1600 cm^{-1} (m, aromatic).

Anal. Calcd for $C_{17}H_{17}NO_3$: 3, 72.07; H, 6.05; N, 4.94. Found: C, 72.28; H, 6.03; N, 4.99.

Isopropyl (*E*)-Benzohydroximate (5c).—Crude isopropyl (*Z*)-*O*-benzylbenzohydroximate (35.0 g) obtained in an experiment identical with the one described above was added to a solution of

(42) This analysis was carried out by M-H-W Laboratories, Garden City, Mich.

(43) E. Beckmann, *Ber.*, **26**, 2272, 2631 (1893).

potassium hydroxide (17.5 g) and water (25 ml) and the mixture was stirred and refluxed for 10 min. After the reaction mixture had cooled to room temperature, water (100 ml) was added to give a solid which was collected (the aqueous filtrate was kept for further work-up) and triturated with ether. Filtration of the insoluble salts, evaporation of the ether filtrate, and recrystallization of the residue from petroleum ether gave **5c** (3.62 g), mp 95–101°.

Carbon dioxide was bubbled through the aqueous filtrate until it became cloudy. The resulting mixture was extracted with ether (three 100-ml portions) and the ether extracts were dried and evaporated. An nmr spectrum of the oil residue (14.4 g) showed that it was a mixture of **5c** and **4c** in *ca.* 15:85 ratio. The oil was dissolved in benzene (80 ml) and irradiated in quartz tubes for 3 hr in a Rayonet RPR-100 Reactor (The Southern New England Ultraviolet Company, Middletown, Conn.) fitted with 2537-Å lamps. Subsequent evaporation of the benzene at aspirator pressure yielded an oil that was shown by its nmr spectrum to be a mixture of **5c** and **4c** in *ca.* 45:55 ratio. Column chromatography on silica gel (160 g, 100–200 mesh) of this oil using chloroform–petroleum ether (25:75) as the eluting solvent gave in the first fractions **isopropyl (*E*)-benzohydroximate** (3.50 g, mp 97–101° after recrystallization from petroleum ether). Later fractions gave the *Z* isomer (4.62 g, 21%, mp 51–55° after recrystallization from petroleum ether). The combined yield of the *E* isomer was 32%. Two more recrystallizations of the *E* isomer from petroleum ether gave colorless prisms: mp 101–102°; ir (Nujol) 3250 (s, broad, OH), 1555 (s, C=N), 1605 cm^{-1} (w, aromatic); nmr ($CDCl_3$) δ 1.35 (d, J = 6 Hz, 6, CH_3CHCH_3), 4.90 (septet, J = 6 Hz, 1, CH_3CHCH_3), 7.1–8.0 (2 m, 3 and 2, aromatic **H**).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.28; H, 7.21; N, 7.88.

Isopropyl (*Z*)-Benzohydroximate (4c).—Hydrolysis of isopropyl (*Z*)-*O*-benzoylbenzohydroximate (16.0 g, mp 101–104°) was carried out by the procedure described for the preparation of **4e**. The oil left after evaporation of the ether extracts was dissolved in petroleum ether and cooled in a Dry Ice–acetone bath. The crystals (5.46 g, 54%) thus obtained were recrystallized from petroleum ether to afford an analytical sample: mp 53.5–55.5°; ir (Nujol) 3210 (m, broad, OH), 1640 (m, C=N), 1575 cm^{-1} (w, aromatic); nmr ($CDCl_3$) δ 1.34 (d, J = 6 Hz, 6, CH_3CHCH_3), 4.87 (septet, J = 6 Hz, 1, CH_3CHCH_3), 7.2–7.8 (m, 3 and 2, aromatic **H**).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.92; H, 7.01; N, 7.81.

Beckmann Rearrangement of Isopropyl (*Z*)-Benzohydroximate (4c).—Solid phosphorus pentachloride (1.67 g) was added slowly, with stirring, to a solution of **4c** (1.08 g) in ether (10 ml) which was cooled in a water bath. After the addition was complete, the mixture was stirred for an additional 30 min. The reaction mixture was then cooled in an ice bath and water (5 ml) was added slowly with stirring. The ether layer was separated, washed with 10% potassium carbonate (10 ml), dried, and evaporated. An infrared spectrum of the orange colored residual oil (0.62 g) indicated that it contained phenyl isocyanate. To an ether solution of this oil was added a solution of aniline (0.56 g) in ether. The solid (0.40 g, 31%) thus produced was recrystallized from acetone–water to give white crystals, mp 239–241°. A mixture melting point of these crystals with *s*-diphenylurea showed no depression, mp 240–242°.

Attempted Beckmann Rearrangement of Isopropyl (*E*)-Benzohydroximate (5c).—The reaction of **5c** (0.50 g) with phosphorus pentachloride (0.45 g) was carried out by the procedure described in the preceding experiment. Evaporation of the ether gave an oil that partially crystallized upon standing. The crystals were separated and recrystallized from ethanol to give the phosphate ester of **5c** as white needles (0.25 g, 46%), mp 116–117°. One more recrystallization from ethanol gave white needles: mp 117–119°; ir (Nujol) 1620 (m, C=N), 1600 (m, aromatic), 1580 cm^{-1} (w, aromatic); nmr ($CDCl_3$) δ 1.29 (d, J = 6 Hz, 18, CH_3CHCH_3), 5.00 (*ca.* septet, J = 6 Hz, 3, $CH_3CH_3CH_3$), 7.1–7.9 (m, 15, aromatic **H**).

Anal. Calcd for $C_{30}H_{36}N_3O_7P$: C, 61.95; H, 6.24; N, 7.23. Found: C, 62.02; H, 6.19; N, 7.34.

Monalkylation of Potassium Benzohydroxamate with *n*-Propyl Bromide.—A solution of potassium benzohydroxamate (87.4 g), *n*-propyl bromide (69.7 g), and anhydrous potassium carbonate (25.0 g) in methanol (374 ml) and water (250 ml) was stirred at 45° for 3 days. After the methanol was removed by distillation at atmospheric pressure, the residue was cooled to below 10° and acidified with 12 *N* hydrochloric acid. The mixture was extracted with ether (four 100-ml portions) and the combined ether extracts were washed with 10% sodium bicarbonate solution (100 ml). The ether solution was then extracted with 6 *N* sodium hydroxide solution (six 50-ml portions) and the combined basic extracts were acidified with 12 *N* hydrochloric acid and extracted with ether (four 50-ml portions). These ether extracts were dried and the solvent was removed at aspirator pressure. After the residue solidified, it was recrystallized from ether–petroleum ether to yield 63.0 g (71%) of *n*-propyl benzohydroxamate, mp 52–58°. Several more recrystallizations from ether–petroleum ether gave the analytical sample, mp 58–59° (lit.[44] mp 58–59°).

Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.81; H, 7.41; N, 8.04.

The Silver Salt of *n*-Propyl Benzohydroxamate.—A solution of silver nitrate (38.0 g) in distilled water (80 ml) was added slowly to a vigorously stirred solution of *n*-propyl benzohydroxamate (40.5 g) and concentrated ammonium hydroxide (15 ml) in 95% ethanol (160 ml). After approximately half of the silver nitrate solution had been added, a white precipitate began to form. When the addition was complete, the mixture was stirred for an additional 30 min. The precipitate was then filtered, washed thoroughly with acetone, and dried at 60° in a vacuum desiccator for 24 hr to yield 48 g (76%) of a white powder.

Anal. Calcd for $C_{10}H_{12}NO_2Ag$: C, 41.96; H, 4.24; N, 4.90. Found: C, 41.30; H, 4.42; N, 4.99.

Alkylation of the Silver Salt of *n*-Propyl Benzohydroxamate with Methyl Iodide.—A mixture of methyl iodide (8.43 g), the silver salt of *n*-propyl benzohydroxamate (9.00 g), and anhydrous ether (10 ml) was stirred at room temperature (approximately 24°) for 7 days. Addition of more ether, filtration of the insoluble salts, and evaporation of the ether from the filtrate yielded an oil. Vpc analysis of this oil showed that it was a mixture of *n*-propyl benzoate (0.33 g, 6%), methyl (*E*)-*O*-*n*-propylbenzohydroximate (0.87 g, 14%), methyl (*Z*)-*O*-*n*-propylbenzohydroximate (1.87 g, 30%), and *n*-propyl *N*-methylbenzohydroxamate (1.66 g, 27%).

Alkylation of the Potassium Salt of *n*-Propyl Benzohydroxamate with Ethyl Bromide.—A solution of *n*-propyl benzohydroxamate (7.00 g), ethyl bromide (8.72 g), and potassium carbonate (8.45 g) in methanol (22 ml) and water (15 ml) was stirred at 38° in a constant temperature bath for 15 hr. After evaporation of the methanol at aspirator pressure, the residue was cooled to below 10° and acidified with 12 *N* hydrochloric acid. The mixture was then extracted with ether (four 20-ml portions) and the combined ether extracts were washed with 10% sodium bicarbonate solution (40 ml). The acidic material was extracted from the ether with 3 *N* sodium hydroxide solution (three 15-ml portions). The nonacidic material remained in the ether. The combined sodium hydroxide extracts were cooled to below 10°, acidified with 12 *N* hydrochloric acid, and extracted with ether (three 15-ml portions). The ether extracts were dried and the solvent was evaporated at aspirator pressure to yield *n*-propyl benzohydroxamate (2.60 g, 37%).

The ether was evaporated from the nonacidic material at aspirator pressure to yield a light yellow oil. Vpc analysis of this oil showed that it consisted of ethyl (*Z*)-*O*-*n*-propylbenzohydroximate (1.10 g, 14%) and *n*-propyl *N*-ethylbenzohydroxamate (3.40 g, 42%).

Dialkylation of Potassium Benzohydroxamate with *n*-Propyl Bromide.—A solution of potassium benzohydroxamate (10.0 g), *n*-propyl bromide (21.0 g), and anhydrous potassium carbonate (15.8 g) in methanol (42 ml) and water (29 ml) was stirred at 58° in a constant temperature bath for 15 hr. The following products were obtained as described above: *n*-propyl benzohydroxamate (2.07 g, 20%), *n*-propyl (*Z*)-*O*-*n*-propylbenzohydroximate 2.10 g, 17%), and *n*-propyl *N*-*n*-propylbenzohydroxamate (5.82 g, 46%).

***O*-*n*-Propylbenzohydroximoyl Chloride (19b).**—Solid phosphorus pentachloride (58.3 g) was added in small portions to *n*-propyl benzohydroxamate (50.2 g) that was cooled in an ice bath and magnetically stirred. After all the phosphorus pentachloride had been added, the oily reaction mixture was stirred for a few minutes then dissolved in ether and washed with water. The ether was dried and evaporated and the residue was distilled

(44) Cooley, Bills, and Throckmorton[9] prepared this compound by the catalytic hydrogenation of allyl benzohydroxamate.

to yield **19b** (45.1 g, 82%) as a clear liquid: bp 82–83° (0.3 mm); ir (neat) 1590 (w, C=N), 1570 cm^{-1} (w, aromatic); nmr (neat) δ 0.92 (t, 3, J = 7 Hz, $OCH_2CH_2CH_3$, 1.4–2.1 (m, 2, $OCH_2CH_2CH_3$), 4.16 (t, 2, J = 6.5 Hz, $OCH_2CH_2CH_3$), 7.0–8.1 (2 m, 3 and 2, aromatic **H**).

Anal. Calcd for $C_{10}H_{12}NOCl$: C, 60.76; H, 6.12; N, 7.09. Found: C, 60.64; H, 5.90; N, 7.01.

O-**Ethylbenzohydroximoyl Chloride** (**19a**).—By the procedure described above phosphorus pentachloride (8.66 g) and ethyl benzohydroxamate[9] (6.87 g) yielded 6.08 g (80%) of **19a**: bp 85–86° (0.5 mm) [lit. bp 125° (45 mm),[31] bp 239°[13]]; ir (neat) 1585 (w, C=N), 1565 cm^{-1} (w, aromatic); nmr ($CDCl_3$) δ 1.33 (t, 3, J = 7 Hz, OCH_2CH_3), 4.27 (q, 2, J = 7 Hz, OCH_2CH_3) 7.2–7.9 (2 m, 3 and 2, aromatic **H**).

O-*n*-**Butylbenzohydroximoyl Chloride** (**19c**).—Phosphorus pentachloride (5.26 g) and *n*-butyl benzohydroxamate (4.88 g) yielded 3.56 g (62%) of **19c**, bp 104–114° (0.7 mm); ir (neat) 1585 (w, C=N), 1560 cm^{-1} (w, aromatic).

Anal. Calcd for $C_{11}H_{14}NOCl$: C, 62.41; H, 6.66; N, 6.61. Found: C, 61.80; H, 6.47; N, 6.57.

n-**Propyl** (*Z*)-*O*-*n*-**Propylbenzohydroximate** (**7b**).—*O*-*n*-Propylbenzohydroximoyl chloride (25.6 g) was added slowly with stirring to a cold solution of sodium propoxide prepared from sodium (6.0 g) and 1-propanol (250 ml). The mixture was refluxed for 3 hr and the 1-propanol was removed by evaporation at reduced pressure. Water (100 ml) was added to the residue and the mixture extracted with ether (four 50-ml portions). The combined ether extracts were washed with 3 *N* sodium hydroxide solution (three 50-ml portions), dried, and evaporated at aspirator pressure. The residue was distilled to yield **7b** (21 g, 79%): bp 84–86° (0.1 mm); ir (neat) 1610 (s, C=N), 1570 cm^{-1} (m, aromatic); nmr ($CDCl_3$) δ 0.7–2.1 (2 m, 6 and 4, $NOCH_2CH_2CH_3$, and $COCH_2CH_2CH_3$), 4.05 (t, J = 6.5 Hz, $NOCH_2$), 4.24 (t, J = 6.5 Hz, $COCH_2$), the signals between 3.8 and 4.5 integrate for a total of 4 H, 7.1–8.0 (2 m, 3 and 2, aromatic **H**).

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.31; H, 8.65; N, 6.11.

2-**Benzoyltetrahydro-1,2-oxazine** (**18**).—A solution of potassium benzohydroxamate (7.35 g), 1,4-dibromobutane (10.0 g), and anhydrous potassium carbonate (11.6 g) in methanol (31 ml) and water (21 ml) was stirred at 35° in a constant temperature bath for 3 days. The methanol was then removed at reduced pressure, water (50 ml) was added to the residue, and the mixture was extracted with ether (two 50-ml portions). The combined ether extracts were dried and the ether was evaporated at aspirator pressure. The crude product was distilled to give a colorless, viscous liquid (4.33 g, 54%): bp 113–120° (0.1 mm) [lit.[45] bp 152–153° (2 mm)]; rising end absorption in uv with log ε of 3.66 at 256 mμ (95% ethanol); ir (neat) 1640 (s, C=O), 1580 cm^{-1} (w, aromatic); nmr (neat) δ 1.3–1.9 (m, 4, $CH_2CH_2CH_2CH_2$), 3.5–4.1 (m, 4, NCH_2 and OCH_2), 7.2–8.0 (2 m, 3 and 2, aromatic **H**).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.13; H, 6.80; H, 7.52.

2-**Benzoyloxazolidine** (**17**).—By the procedure described above (reaction temperature of 38°), potassium benzohydroxamate (7.35 g), 1,3-dibromopropane (9.35 g), and anhydrous potassium carbonate (11.6 g) in methanol (31 ml) and water (21 ml) yielded 2-**benzoyloxazolidine** (2.13 g, 29%) as a colorless liquid: bp 124–126° (0.16 mm); rising end absorption in uv with log ε of 3.71 at 256 mμ (95% ethanol); ir (neat) 1630 (s, C=O), 1580 cm^{-1} (m, aromatic); nmr ($CDCl_3$) δ 2.17 (quintet, 2, J = 7 Hz, $CH_2CH_2CH_2$), 3.77 (t, J = 7 Hz, OCH_2), 3.82 (t, J = 7 Hz, NCH_2), the signals between 3.6 and 4.0 integrate for a total of 4 H, 7.1–8.0 (2 m, 3 and 2, aromatic **H**).

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 6.90. Found: C, 67.58; H, 6.13; N, 6.92.

3-**Phenyl-5***H*-**1,4,2-dioxazine** (**16**).—By the procedure described above (reaction temperature of 32°), potassium benzohydroxamate (14.7 g), 1,2-dibromoethane (17.5 g), and anhydrous potassium carbonate (23.2 g) in methanol (62 ml) and water (42 ml) yielded 3-**phenyl-5***H*-**1,4,2-dioxazine** (5.72 g, 42%) as a light yellow liquid: bp 103–107° (0.07 mm); uv max (95% ethanol) 252 mμ (log ε 3.95); ir (neat) 1610 (s, C=N), 1580 cm^{-1} (s, aromatic); nmr (neat) δ 3.9–4.5 (2 m, $A_2'X_2'$, 2 and 2, $=COCH_2$ and $=NOCH_2$), 7.1–8.1 (2 m, 3 and 2, aromatic **H**).

Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.10; H, 5.48; N, 8.70.

Alkylation of Potassium Benzohydroxamate with *n*-**Butyl Bromide**.—The reaction was carried out according to a procedure described by Fuller and King[12] except on a smaller scale. A solution of potassium benzohydroxamate (15.0 g), *n*-butyl bromide (13.2 g), and potassium carbonate (12.0 g) in 95% ethanol (72 ml) was stirred and refluxed for 15 hr. The ethanol was evaporated at aspirator pressure and after using the work-up procedure described above the following products were obtained (as determined by vpc analyses of the crude oil): *n*-butyl benzohydroxamate (7.03 g, 43%), *n*-butyl (*Z*)-*O*-*n*-butylbenzohydroximate (1.59 g, 8%), and *n*-butyl *N*-*n*-butylbenzohydroxamate (3.71 g, 17%).

Alkylation of Ethyl Benzohydroxamate with Ethyl Iodide.—The reaction was carried out according to a procedure described by Lossen.[13] A solution of ethyl benzohydroxamate (10.0 g), potassium hydroxide (3.4 g), ethyl iodide (25.8 g), and 70% ethanol (70 ml) was refluxed over a water bath for 2 hr. The reaction was worked up in the usual manner and the nonacidic fraction was distilled *in vacuo* yielding ethyl benzoate (1.27 g) and ethyl *N*-ethylbenzohydroxamate (4.12 g, 36%).

Isolation of *n*-**Propyl** *N*-**Isopropylbenzohydroxamate** (**6f**) **by Selective Hydrolysis of Isopropyl** *Z*-*O*-*n*-**Propylbenzohydroximate** (**7f**) **in a Mixture Containing 6f and 7f**.—An oil (7.26 g) consisting of **6f** and **7f** in a 27:73 ratio (by vpc) was dissolved in concentrated hydrochloric acid (72 ml) and the resulting solution was stirred at 50–54° for 30 min. After the solution had cooled to room temperature, it was neutralized with 6 *N* sodium hydroxide and extracted with ether (two 40-ml portions). The ether extracts were dried and evaporated and the residual oil was distilled to give pure **6f** (1.23 g, 63% based on the amount of **6f** in the starting material): bp 106–110° (0.45 mm); nmr ($CDCl_3$) δ 0.6–1.8 (m, $OCH_2CH_2CH_3$), 1.29 (d, J = 7 Hz, CH_3CHCH_3), the signals between 0.6 and 1.8 integrate for a total of 11 H, 3.7 (t, J = 6 Hz, 2, $OCH_2CH_2CH_3$), *ca.* 4.52 (*ca.* septet, J = 7 Hz, 1, CH_3CHCH_3), 7.2–7.7 (m, 5, aromatic **H**).

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.67; H, 8.68; N, 6.28.

Registry No.—**1**, 495-18-1; **3e**, 7339-99-3; **4a**, 26198-44-7; **4c**, 26889-49-6; **4e**, 26889-50-9; **5a**, 26198-45-8; **5c**, 26889-52-1; **5c** phosphate ester, 26963-86-0; **5e**, 26889-53-2; **6a**, 26893-77-6; **6b**, 26893-52-7; **6c**, 26893-53-8; **6d**, 26893-54-9; **6e**, 26929-64-6; **6f**, 26893-55-0; **6g**, 26893-56-1; **6h**, 26893-57-2; **6i**, 5553-73-1; **7a**, 26889-10-1; **7b**, 26889-11-2; **7c**, 26889-12-3; **7d**, 26889-13-4; **7e**, 26889-14-5; **7f**, 26889-15-6; **7h**, 26893-59-4; **8a**, 26889-16-7; **8b**, 26889-17-8; **8c**, 26889-18-9; **8d**, 26889-19-0; **8e**, 26889-20-3; **8f**, 26889-21-4; **8g**, 26889-22-5; **8h**, 26889-23-6; **9c**, 26893-60-7; **11**, 26893-61-8; **12a**, 26198-46-9; **12b**, 26889-25-8; **13**, 26889-26-9; **14**, 19172-64-6; **15**, 26885-65-4; **16**, 26893-63-0; **17**, 26893-64-1; **18**, 26893-65-2; **19a**, 26893-66-3; **19b**, 26893-67-4; **19c**, 26929-66-8.

Acknowledgments.—The authors gratefully acknowledge support of this project by a grant from the Robert A. Welch Foundation and by a Faculty Research Grant from Sam Houston State University. The authors wish to thank Dr. D. V. Nightingale, University of Missouri, for helpful suggestions concerning the preparation of the manuscript.

(45) This compound has been prepared previously by the reaction of benzoyl chloride with tetrahydro-1,2-oxazine: O. Witchterele and J. Novak, *Collect. Czech. Chem. Commun.*, **15**, 309 (1950).

Nucleophilic Aromatic Substitution during Deoxygenation. Deoxygenation of Nitrosobenzene by Triethyl Phosphite in Alcohols[1a]

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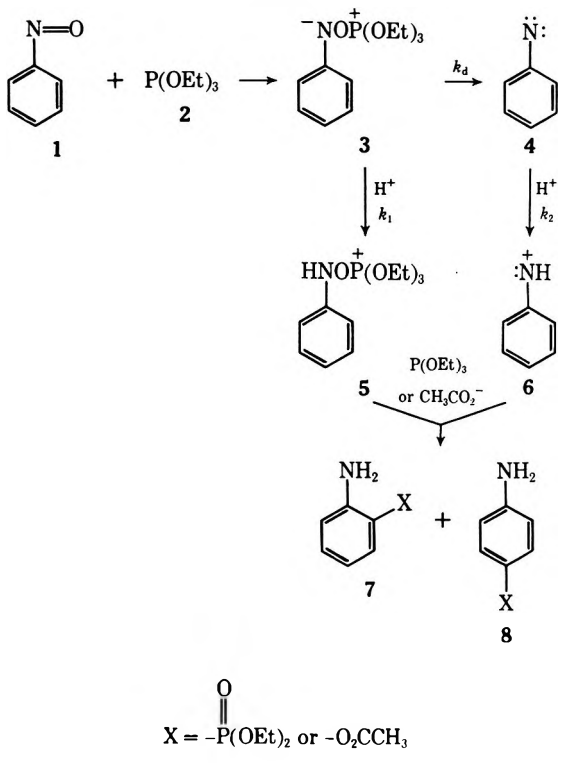
Deoxygenation of nitrosobenzene by triethyl phosphite in methanol has been found to give *o*- and *p*-anisidine in yields up to 70%. Similar deoxygenations in ethanol, 2-methoxyethanol, isopropyl alcohol, and *tert*-butyl alcohol give mixtures of the corresponding *o*- and *p*-alkoxyanilines, but only in the presence of small amounts of acid in the solvent (0.01–1.0 mol % acetic acid). Deoxygenation of *p*-nitrosotoluene in methanol gives 2-methoxy-4-methylaniline and 4-methoxy-4-methyl-2,5-cyclohexadienone. Deoxygenations which lead to aromatic nucleophilic substitution are interpreted in terms of a mechanism which proposes that an intermediate prior to phenylnitrene in the deoxygenation sequence is protonated and undergoes solvolysis leading to the alkoxyanilines.

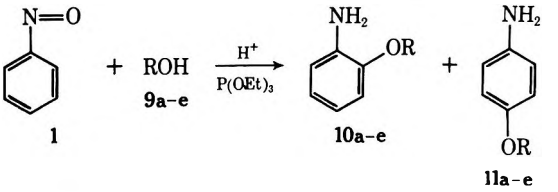
The deoxygenation of nitrosobenzene by trivalent phosphorus compounds has usually been studied in aprotic solvent media. In benzene in the presence of excess nitrosobenzene, a modest yield (21%) of azoxybenzene is formed.[2] In excess triethyl phosphite, deoxygenation occurs, but the products have not proven to be tractable.[2] We have reported that the deoxygenation of nitrosobenzene in triethyl phosphite (TEP) containing 5% by volume acetic acid led to the formation of 2-hydroxyacetanilide and diethyl *o*- and *p*-aminophenylphosphonate.[3] These products, on the basis of their structures, appear to have been formed by a process involving nucleophilic aromatic substitution. We proposed that such products arose as a result of protonation of phenylnitrene or some prior intermediate during the deoxygenation reaction.[3] The addition of a proton to either **3** or **4** would generate an intermediate which would be expected to be attacked by a nucleophile at the ortho and para positions of the ring and thus lead to the observed products.[4] In this paper we present the results of the study of the deoxygenation of nitrosobenzene by TEP in several alcohols. Nucleophilic aromatic substitution has been found to be an important process under these conditions and further evidence has been developed which points to a proton transfer step as being crucial to nucleophilic aromatic substitution under these conditions.

SCHEME I



Results

The deoxygenation of nitrosobenzene was studied using methanol, ethanol, 2-methoxyethanol, isopropyl alcohol, and *tert*-butyl alcohol as solvents. Deoxygenations were also carried out in each alcohol with added amounts of acetic acid in concentrations ranging from 0.01 to 1.0 mol %. The introduction of each of the alcohols as a nucleophile was observed. However, except for methanol, the substitution process was important only in the presence of added acetic acid.



It was possible to isolate samples of the alkoxyanilines **10a–e** and **11a–e** from deoxygenations run on a preparative scale. Each of the anilines was unequivocally identified by preparation of derivatives or by spectral data, as is described fully in the Experimental Section. Quantitative yield data were obtained gas chromatographically using the internal standard method. The data are shown in Table I.

The formation of *o*- and *p*-anisidine in a combined yield of ~60% in the absence of any acid was a reproducible result. Methanol, distilled directly from sodium methoxide under nitrogen and used without exposure to the atmosphere, gave similar yields of anisidines. It, therefore, seems very unlikely that acidic impurities are responsible for the nucleophilic substitu-

(1) (a) Presented in part at the 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 22–27, 1970, Abstract ORGN 65; supported in part by NIH Grant GM 14344; (b) NDEA Fellow, 1966–1969; University of Virginia Du Pont Fellowship, 1969–1970.

(2) P. J. Bunyan and J. I. G. Cadogan, *J. Chem. Soc.*, 42 (1963).

(3) R. J. Sundberg, R. H. Smith, Jr., and J. E. Bloor, *J. Amer. Chem. Soc.*, **91**, 3392 (1969).

(4) For related examples of nucleophilic aromatic substitution, see (a) P. G. Gassman, G. Campbell, and R. Frederick, *ibid.*, **90**, 7377 (1968); (b) P. A. S. Smith, 'Open Chain Nitrogen Compounds," Vol. 2, W. A. Benjamin, New York, N. Y., 1966, pp 225–226; (c) H. J. Shine, "Aromatic Rearrangements," Elsevier, New York, N. Y., 1967, pp 182–190.

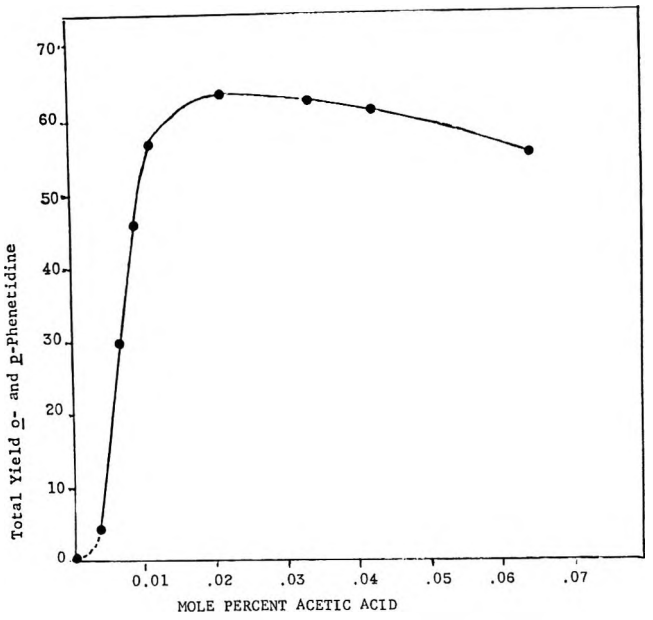


Figure 1.—Yield of phenetidine as a function of acetic acid concentration in ethanol.

TABLE I

ALKOXYANILINES FROM NITROSOBENZENE BY DEOXYGENATION IN ALCOHOLS

Alcohol	R	Mol % acetic acid	% yield[a] 10	% yield[a] 11
9a	CH_3	0.00	11	49
9a	CH_3	0.01	11	61
9b	CH_3CH_2	0.00	<1	<1
9b	CH_3CH_2	0.01	12	42
9b	CH_3CH_2	0.02	14	50
9c	$CH_3OCH_2CH_2$	0.00	0	0
9c	$CH_3OCH_2CH_2$	0.01	8	39
9d	$(CH_3)_2CH$	0.01	2	2
9d	$(CH_3)_2CH$	0.10	15	52
9e	$(CH_3)_3C$	0.10	6	4
9e	$(CH_3)_3C$	1.0	13	24

[a] The yields are averages of at least two runs. The absolute yields are reproducible to ±2% for **10** and ±3% for **11**.

tion which is observed in methanol. Indeed, **10a** and **11a** were formed in a combined yield of 27% when a deoxygenation was carried out in methanol containing 1.0 mol % sodium methoxide. The addition of small amounts of acetic acid resulted in a slight increase in the yield of *o*- and *p*-anisidine (12 and 60%, respectively, in methanol containing 0.2 mol % acetic acid).

The extent of nucleophilic aromatic substitution in ethanol was studied as a function of the concentration of added acetic acid. As shown in Figure 1, the yields of *o*- and *p*-phenetidine rise sharply as the amount of acetic acid is increased from 0.004 to 0.02 mol %, but then remain relatively constant and eventually decrease again at higher acetic acid concentrations.

Both anisidines and phenetidines are formed in methanol–ethanol mixtures. The total yield of alkoxyanilines drops with increasing ethanol concentration, but the proportion of the total mixture which is accounted for by **10b** and **11b** increases as the amount of ethanol in the solvent mixture increases. The data are shown in Table II.

Deoxygenation of nitrosobenzene in methanol-*d* gave reproducibly lower yields (8 ± 1 and 47 ± 1%, respectively) of **10a** and **11a** than identical deoxygenations in

TABLE II

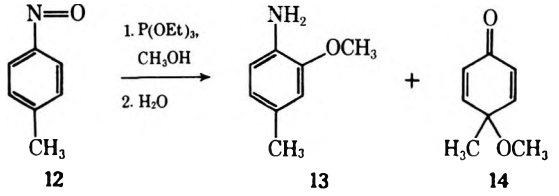
YIELDS OF ALKOXYANILINES IN ETHANOL–METHANOL MIXTURES

Mole % EtOH	% yields[a] 10a	11a	10b	11b	% 10b + 11b of total alkoxyanilines
0	10	49			
10	10	44	1	4	8.5
25	7	32	2	8	20
30	5	21	2	7	26
35	5	22	2	9	29
41	4	14	2	7	33
59	1	5	1	3	40
100			0	0	

[a] Yields were measured gas chromatographically using the internal standard method.

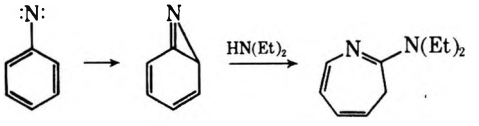
normal methanol (11 ± 1, 60 ± 2, respectively). Because of slightly modified reaction conditions, these data are not directly comparable to those in Table I.

Deoxygenation of *p*-nitrosotoluene (**12**) in methanol also afforded products characteristic of nucleophilic aromatic substitution. 2-Methoxy-4-methylaniline (**13**) and 4-methoxy-4-methyl-2,5-cyclohexadienone (**14**) were isolated and identified as products. The details of product identification are described in the Experimental Section.



12 13 14

Since the major goals of this study included an effort to establish the stage at which the crucial proton transfer occurs, it was of interest to study some alcohol–amine solvent mixtures. Secondary amines are efficient traps for the bicyclic intermediate **15** which is believed to be rapidly formed from phenylnitrene.[5] The nature



15 16

of the products formed in alcohol–amine solvent mixtures should then provide insight into the relative rates of processes leading to **10** and **11** as opposed to those leading to **16** in such solvent mixtures. Figures 2 and 3 record the yields of **11a** and **16** found for deoxygenation in a series of methanol–diethylamine mixtures and for **11b** and **16** in a series of ethanol–diethylamine mixtures. Deoxygenation of nitrosobenzene in methanol–diethylamine also led to the formation of a small amount of 1,1-diethyl-2-phenylhydrazine which was identified by comparison with an authentic sample.[6] The formation of hydrazines from amines and arylnitrenes has

(5) (a) R. Huisgen and M. Appl, *Chem. Ber.*, **91**, 12 (1958); (b) W. von E. Doering and R. A. Odum, *Tetrahedron*, **22**, 81 (1966); (c) R. A. Odum and M. Brenner, *J. Amer. Chem. Soc.*, **88**, 2074 (1966); (d) J. I. G. Cadogan and M. J. Todd, *J. Chem. Soc. C*, 2808 (1969); (e) R. J. Sundberg, B. P. Das, and R. H. Smith, Jr., *J. Amer. Chem. Soc.*, **91**, 658 (1969); (f) R. J. Sundberg, *ibid.*, **88**, 3781 (1966).

(6) K. Kratzl and K. P. Berger, *Monatsh. Chem.*, **89**, 83 (1958).

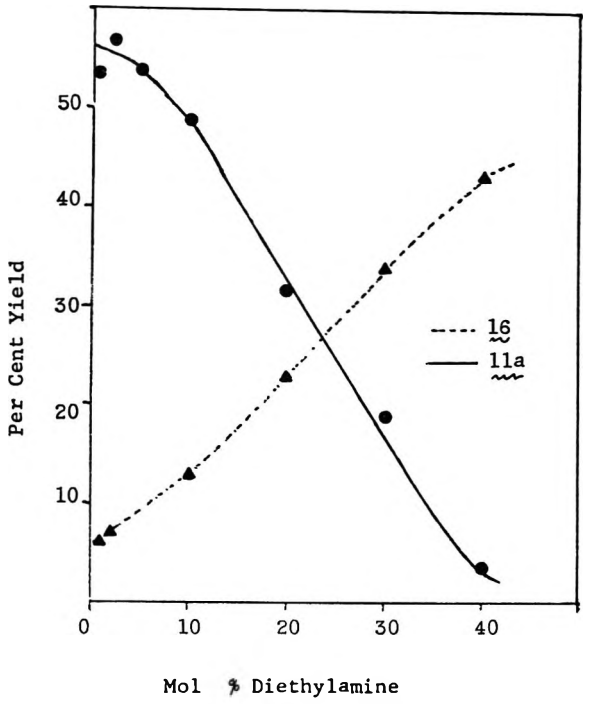


Figure 2.—Product composition in methanol–diethylamine mixtures.

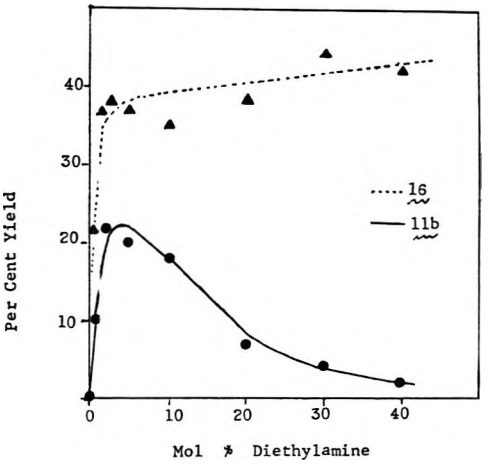


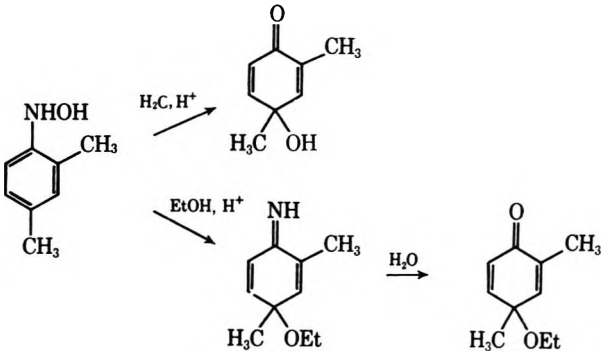
Figure 3.—Product composition in ethanol–diethylamine mixtures.

previously been observed with phenylnitrene,[5c] *p*-cyanophenylnitrene,[7a] and 2-pyrimidylnitrene.[7b]

The photolytic decomposition of phenyl azide in certain protic solvents has been found to give products resulting from apparent nucleophilic aromatic substitution.[5b,8] However, the mechanisms by which net nucleophilic substitution occurs in these systems have not been carefully studied. We have photolyzed phenyl azide in solvent systems similar to those employed in the deoxygenation reactions. Since photolysis of phenyl azide is believed to generate phenylnitrene,[9] these experiments permit a test for the existence of the reaction pathway **4** → **6** → **10** + **11** in alcoholic solutions of acetic acid. Photolysis of phenyl azide in methanol, methanol containing 10% acetic acid, ethanol, and ethanol containing 10% acetic acid gave no significant amounts of alkoxyanilines, indicating that the reaction path **4** → **6** + **10** + **11** is inoperative under these conditions. Interestingly, we observed small yields of 2-alkoxy-3*H*-azepines in these reactions. Their formation can be accounted for by a mechanism similar to that invoked for 2-dialkylamino-3*H*-azepines[5] but the alcohols are evidently much poorer "traps" for the intermediate **15** than are amines.

Discussion

The results of this study have provided a new example of nucleophilic aromatic substitution during deoxygenation reactions. The type of nucleophiles which have been demonstrated to effect substitution of the aromatic ring during deoxygenation processes now include triethyl phosphite,[3] acetic acid or acetate ion,[3] hydrogen fluoride,[10] and primary, secondary, and tertiary alcohols. The isolation of the cyclohexadienone **14** from deoxygenation of *p*-nitrosotoluene in methanol provides further support for the interpretation of the overall reaction as a process involving nucleophilic aromatic substitution. The acid-catalyzed rearrangement of para-substituted phenylhydroxylamines has been shown to provide products related to **14**, as in the case of 2,4-dimethylphenylhydroxylamine.[4c,11]



Several of the qualitative results of our work support the proposal[3] that nucleophilic aromatic substitution occurs when some intermediate in the deoxygenation sequence is protonated. The sharp rise in yields of phenetidines when acetic acid is added to ethanol suggests that protonation is crucial to nucleophilic substitution. The difference in product yield in methanol-*d vs.* methanol can be interpreted on the basis of a decreased rate of protonation in the deuterated solvent. If the yield of **10a** and **11a** depends upon the relative magnitudes of k_1 and k_1 (Scheme I), the magnitude of the solvent isotope effect can be estimated by assuming that the total yield of **10a** and **11a** reflects the fraction of the intermediate **3** which is converted to **5** rather than **4**. In methanol, $k_1 = 71/29\ k_d$. For methanol-*d*, $k_{1'} = 56/44\ k_{d'}$. Assuming k_d is identical in the two solvents, $k_1 = 1.9\ k_{1'}$. This solvent isotope effect could reflect either a kinetic isotope effect on the rate of proton transfer or the diminished extent of autoprotolysis of the deuterated solvent.

The results in the methanol–diethylamine system are

(7) (a) R. A. Odum and A. M. Aaronson, *J. Amer. Chem. Soc.*, **91**, 5681 (1969); (b) R. Huisgen and K. v. Fraunberg, *Tetrahedron Lett.*, 2595 (1969).

(8) T. Shingaki, *Sci. Rep. Coll. Gen. Educ. Osaka Univ.*, **11**, 93 (1963); *Chem. Abstr.*, **60**, 6734 (1964).

(9) G. L'abbé, *Chem. Rev.*, **69**, 345 (1969).

(10) P. H. Scott, C. P. Smith, E. Kober, and J. W. Churchill, *Tetrahedron Lett.*, 1153 (1970).

(11) E. Bamberger and F. Brady, *Chem. Ber.*, **33**, 3642 (1900); E. Bamberger, *ibid.*, **40**, 1906, 1918 (1907); see also the related work of P. G. Gassman and G. A. Campbell, *Chem. Commun.*, 427 (1970).

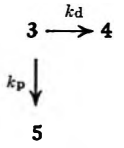
in accord with treating nucleophilic aromatic substitution as a process which competes with formation of phenylnitrene. As shown in Figure 2 the yield of the azepine **16**, which is derived from the nitrene, is greatly diminished in the methanol-rich mixtures which facilitate nucleophilic aromatic substitution. In ethanol, which does not favor nucleophilic aromatic substitution, the yield of azepine is roughly constant over the rage 2–40 mol % diethylamine.

A final qualitative conclusion which can be drawn from the results involves the identity of the species which is protonated. The fact that the nucleophilic aromatic substitution products found from deoxygenations in alcohols are not found when phenyl azide is photolyzed in the same solvents leads to the conclusion that nucleophilic aromatic substitution involves an intermediate which is unique to the deoxygenation reaction. Since currently available evidence[2,5c-f] indicates that phenylnitrene is the earliest intermediate common to both deoxygenation and azide photolysis, we conclude that it is the zwitterion **3** which acts as the proton acceptor and leads to nucleophilic aromatic substitution in deoxygenation reactions. It is entirely reasonable that the conjugate acid **5** would solvolyze in alcohols to give **10** and **11**, since **5** is an aniline derivative with an excellent leaving group, triethyl phosphate, bonded to nitrogen by a relatively weak N–O bond. We, therefore, propose the sequence **1** → **3** → **5** → **10** + **11** as the mechanism by which the formation of alkoxyanilines occurs during deoxygenation.

There are several additional facets of the data which require comment. One of these is the striking contrast in the ability of methanol to promote the formation of aromatic nucleophilic substitution products, as compared to ethanol and the other alcohols studied. Secondly, the data in Figure 2 suggest that the extent of nucleophilic substitution in ethanol rises very sharply over a narrow range of increasing acid concentration. The relative amount of nucleophilic substitution appears to increase by a factor of about five while the acid concentration changes only by a factor of two in the concentration range 0.005–0.010 mol % acetic acid. Finally, as shown in Figure 3, diethylamine in the concentration range 1–30 mol % induces formation of *o*- and *p*-phenetidine.

It is important to consider whether the protonation process **3** → **5** is an equilibrium process under the reaction conditions. A proton transfer to nitrogen from a protic solvent is expected to be rapid. However, decomposition of **3** and **5** by heterolysis of the weak N–O bond may also be fast. Several pieces of data tend to argue against the various solvent effects being reflections of shifts in the position of a **3** ⇌ **5** equilibrium. Extensive nucleophilic aromatic substitution occurs even in the presence of methoxide ion. Under these conditions the equilibrium should be shifted toward **3** unless **3** is a much stronger base than methoxide ion. The induction of nucleophilic aromatic substitution by the base, diethylamine, is also difficult to comprehend in terms of an equilibrium process, since diethylamine could not be expected to shift the equilibrium toward **5**. The present evidence seems more in accord with considering the product-determining protonation step from a kinetic viewpoint and assuming that nucleophilic substitution occurs in solvents in which the protonation step is rapid enough to compete with decomposition of **3** to **4**.

Methanol is a stronger acid than ethanol[12] and the rate of proton transfer to a base is therefore expected to be more rapid for methanol than for ethanol.[13] The rate of dissociation of methanol in autoprotolysis exceeds that of ethanol by a factor of 200.[14] If the rates of protonation of **3** by the two alcohols differed by a comparable magnitude, the observed difference in the extent of nucleophilic substitution in the two alcohols could be readily understood. The magnitude of the rate difference for protonation of **3** by methanol and ethanol would presumably be greatly diminished by a leveling effect if **3** is a very strong base relative to both alcohols. For example, the relative order of protonation of strongly basic aromatic radical anions has been found to fall in the order methanol > ethanol ≈ 1-propanol > 2-propanol, but the protonation rates of methanol and ethanol differ by only a factor of three in this case.[15] The effect of acetic acid in inducing nucleophilic aromatic substitution in ethanol and the other alcohols studied can be interpreted as being the result of an increased rate of proton transfer in the presence of the added acid. We are, however, not able to interpret this effect of the acid concentration in a quantitative way. A simple kinetic scheme which assumes that $k_1 = k_p[HA]$ and that **5** is quantitatively converted to



10b and **11b** predicts that the per cent yield of nucleophilic substitution product will be given by

$$\% \text{ yield} = \frac{100k_p[HA]}{k_p[HA] + k_d}$$

$$\frac{100}{\% \text{ yield}} = 1 + \frac{k_d}{k_p[HA]}$$

The observed increase in yield of **10b** and **11b** over the range 0.005–0.015 mol % acetic acid is much sharper than predicted by the previous equation.

The extent of formation of *o*- and *p*-phenetidine in diethylamine–ethanol mixtures is surprising. This effect does not appear to be a case of base-catalyzed nucleophilic attack on the intermediate **3** since deoxygenation of nitrosobenzene in ethanol containing sodium ethoxide does not lead to detectable amounts of phenetidines. The possibility that solvolysis of the amine furnishes sufficient $Et_2NH_2^+$ to act as a catalytic species also is unlikely. The dissociation constant of diethylammonium ion in ethanol has been given as $10^{-9.15}$.[16] From this data and the autoprotolysis constant, $10^{-18.9}$,[17] we calculate that $[Et_2NH_2^+]$ in ethanol is 2.0×10^{-5} *M* at $[Et_2NH] = 1$ *M* (~5 mol %). Acetic acid (pK = 10 in ethanol)[13b] induces nucleophilic aromatic substitution in 20% yield when present at

(12) J. Murto, *Acta Chem. Scand.*, **18**, 1043 (1964); J. Hine and M. Hine, *J. Amer. Chem. Soc.*, **74**, 5266 (1952).

(13) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959: (a) Chapter X; (b) pp 43–46.

(14) G. Brière and F. Gaspard, *J. Chim. Phys.*, **64**, 1071 (1967).

(15) S. Arai and L. M. Dorfman, *J. Chem. Phys.*, **41**, 2190 (1964).

(16) P. Rumpf, G. Girault-Vexlearschi, and R. Schaal, *Bull. Soc. Chim. Fr.*, 554 (1955).

(17) K. Bowden, *Can. J. Chem.*, **43**, 2624 (1965).

1×10^{-3} *M*. Thus, it seems unlikely that catalysis by $Et_2NH_2^+$ can be responsible for the effect of diethylamine. In the absence of a satisfactory alternative explanation, we conclude that the solute diethylamine must effect the bulk solvent structure of ethanol in such a way that the solvolytic reaction pathway for **3** is favored relative to pure ethanol.

In conclusion, this work reports a new facet in the study of deoxygenations of aromatic nitroso compounds. While a qualitatively satisfactory mechanistic description of the aromatic nucleophilic substitution process seems to have been developed, several of the details and quantitative aspects of the data must, at present, be ascribed to rather ill-defined solvent effects.

Experimental Section

Procedure for Quantitative Glpc Analyses.—Quantitative analysis of product mixtures was carried out on a Varian Aerograph 204-1C instrument using a 10-ft copper column (1/8-in. o.d.) of 5% Apiezon L–5% potassium hydroxide on Chromosorb G. Column temperature was programmed 160–200° at 15° per min. The internal standard method of analysis was employed and detector responses for the various alkoxyanilines *vs.* biphenyl were determined experimentally with the following exceptions. The internal standard for the reaction in 2-methoxyethanol was *n*-amylbenzene. In the case of *o*-phenetidine, β-methoxy-*o*-phenetidine, *o*-isopropoxyaniline, and *o*-*tert*-butoxyaniline the yields were calculated using the detector responses obtained for the respective para isomers.

Deoxygenation of Nitrosobenzene (1) in Methanol.—A solution of 1 (2.0 g, 18.7 mmol) in benzene (80 ml) was added dropwise over a period of 3 hr to a cooled (0°) solution of TEP (9.4 mol, 55 mmol) in methanol (600 ml) under nitrogen. The methanol and benzene were then removed using a rotary evaporator, the residue was diluted with ether, and an aliquot was removed for quantitative glpc analysis. This analysis indicated yields of *o*- and *p*-anisidine of 10 and 49%, respectively. The main portion of the ether solution was extracted with dilute hydrochloric acid. The acidic extract was made alkaline with dilute sodium hydroxide and extracted with ether. After drying, concentration and chromatography on silicic acid (benzene-ether mixtures were used as the eluent solvent), there was obtained *o*-anisidine (0.14 g, 1.1 mmol, 7%) and *p*-anisidine (0.79 g, 6.4 mmol, 38%). Both compounds were identified by spectral comparison with authentic samples.

Deoxygenation of Nitrosobenzene in Ethanol.—The procedure was analogous to that described above for methanol. Quantitative glpc indicated no trace of *o*- or *p*-phenetidine under analytical conditions capable of detecting a 0.5% yield. Chromatography afforded no characterizable products.

Repetition of the experiment by adding nitrosobenzene (0.90 g, 8.4 mmol) in benzene (140 ml), dropwise over 2 hr, to TEP (4.2 ml, 24 mmol) in ethanol–acetic acid (272 ml, 1.0% acetic acid by volume) followed by the work-up described for methanol gave a glpc yield of 40% *p*-phenetidine. Chromatography on silicic acid using benzene-ether mixtures gave o-phenetidine (0.11 g, 0.8 mmol, 10%) and *p*-phenetidine (0.39 g, 2.8 mmol, 34%). Both compounds were identified by spectral comparison with authentic samples.

Deoxygenation of Nitrosobenzene in Methanol–Acetic Acid, Ethanol–Acetic Acid, and Methanol–Ethanol Mixtures.—The yield data for the solvent systems described in Figure I and Table II were obtained as follows. A solution of nitrosobenzene (0.45 g, 4.2 mmol) in benzene (20 ml) was added dropwise over a period of 1 hr to TEP (2.1 ml, 22 mmol) dissolved in the appropriate solvent (136 ml) at 0° under nitrogen. The solvent was then removed using a rotary evaporator and the residue was dissolved in ether and analyzed by glpc using the internal standard technique.

Solvent Isotope Effect in Methanol-*d*.—Two series consisting of three runs each were carried out, one series using methanol and the other using methanol-*d*. A solution of TEP (0.2 ml, 1.2 mmol) in methanol (8 ml) was cooled to 0°. A solution of nitrosobenzene (45 mg, 0.42 mmol) in methanol (5.6 ml) was added in one portion. The solution was then stirred for 1.5 hr. The solvent was evaporated and the residue was dissolved in ether and analyzed by glpc. The yield data for the individual runs are shown in Table III.

TABLE III
ANISIDINE YIELDS IN METHANOL AND METHANOL-*d*

Solvent	% yield *o*-Anisidine	% yield *p*-Anisidine
Methanol	10	60
Methanol	10	59
Methanol	11	62
Methanol-*d*	8	48
Methanol-*d*	8	46
Methanol-*d*	9	48

Deoxygenation of Nitrosobenzene in Methanol Containing Sodium Methoxide.—A solution of nitrosobenzene (0.45 g, 4.2 mmol) in benzene (20 ml) was added dropwise over a period of 1 hr to a cooled (0°) solution of TEP (2.1 ml) in 1.0 mol % methanolic sodium methoxide (prepared by adding 0.78 g of metallic sodium to 136 ml of methanol). The reaction mixture was concentrated and analyzed by glpc. The yield of *o*-anisidine was 5% and that of *p*-anisidine was 22%.

Deoxygenation of Nitrosobenzene in Other Alcohols.—In each case a solution of nitrosobenzene (0.45 g, 4.2 mmol) in benzene (15 ml) was added dropwise over a period of 1 hr to a cooled (0°) solution of TEP (2.1 ml, 12 mmol) in the alcohol (136 ml) containing acetic acid in the amounts shown in Table I. The solvents were removed using a rotary evaporator and the residues were analyzed by glpc. Yield data are shown in Table I. Product identification procedures are given below for each alcohol.

A. 2-Methoxyethanol.—The crude product was chromatographed on silicic acid (50 g). Benzene–ether (9:1) eluted β-methoxy-*o*-phenetidine[18] (30 mg): ir (CCl_4) 3500, 3410 cm^{-1} (NH_2); nmr (CCl_4) δ 3.41 (s, 3 H, OCH_3), 3.50–4.30 (m, 6 H, OCH_2CH_2O and NH_2), and 6.51–6.82 (m, 4 H, C_6H_4); mass spectrum *m/e* 167, 109 (base peak). Benzene–ether (4:1) eluted β-methoxy-*p*-phenetidine (0.21 g): ir (CCl_4) 3490, 3400 cm^{-1} (NH_2); nmr (CCl_4) δ 3.15 (broad s, 2 H, NH_2), 3.38 (s, 3 H, OCH_3), 3.48–4.10 (m, 4 H, OCH_2CH_2O), and 6.35–6.85 (m, 4 H, C_6H_4); mass spectrum *m/e* (relative intensity) 167 (47), 109 (100); hydrochloride mp 180–181 (lit.[19] mp 181°) after recrystallization from methanol-ether; acetyl derivative mp 116–117° (lit.[19] mp 117°) after recrystallization from hexane–ether.

B. 2-Propanol.—The crude product was chromatographed on silicic acid (50 g). Benzene–ether (9:1) eluted *o*-isopropoxyaniline[20] (60 mg): ir (CCl_4) 3500, 3400 cm^{-1} (NH_2); nmr ($CDCl_3$) δ 1.37 (d, 6 H, J = 7 Hz, $CHCH_3$), 3.5 (broad s, 2 H, NH_2), 4.58 [multiplet, $J \approx 7$ Hz, ~1 H, $CH(CH_3)_2$], 6.84 (s, 4 H, C_6H_4); mass spectrum *m/e* (relative intensity), 151 (24), 109 (100). Benzene–ether (4:1) eluted *p*-isopropoxyaniline (0.26 g): ir (CCl_4) 3470, 3390 cm^{-1} (NH_2); nmr ($CDCl_3$) δ 1.29 [d, 6 H, J = 7 Hz, $CH(CH_3)_2$], 3.15 (broad s, ~2 H, NH_2), 4.40 [m, J = 7 Hz, 1 H, $CH(CH_3)_2$], 6.75 (d, 4 H, C_6H_4); mass spectrum *m/e* (relative intensity) 151 (19), 109 (100); acetyl derivative mp 130–131° (lit.[21] mp 131°) after recrystallization from ethanol–water.

C. *tert*-Butyl Alcohol.—The crude product was chromatographed on silicic acid (50 g). Benzene–ether (9:1) eluted *o*-*tert*-butoxyaniline (50 mg): ir (CCl_4) 3480, 3390 cm^{-1} (NH_2); nmr ($CDCl_3$) δ 1.40 [s, 9 H, $C(CH_3)_3$], 3.96 (broad singlet, 2 H, NH_2), and 6.45–7.15 (m, 4 H, C_6H_4); mass spectrum *m/e* 165, 109 (base peak). Treatment with hydrochloric acid (20 min) followed by acetylation gave 2-hydroxyacetanilide, mp 205–206 (lit.[22] mp 209°), identified by spectral comparison with an authentic sample. Benzene–ether (4:1) eluted *p*-*tert*-butoxyaniline (73 mg): mp 64–64.5° (lit.[23] mp 73–74°) after recrystallization from hexane ir (CCl_4) 3480, 3390 cm^{-1} (NH_2); nmr ($CDCl_3$) δ 1.31 [s, 9 H,

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$C(CH_3)_3$]; 3.45 (broad s, ~2 H, NH_2), 6.67 (d, J = 9 Hz, 2 H), 6.93 (d, J = 9 Hz, 2 H); mass spectrum (relative intensity) 165 (6), 109 (100); acetyl derivative mp 131–132° (lit.[23] mp 130°). Treatment of the acetyl derivative with hydrochloric acid gave 4-hydroxyacetanilide, mp 164–165° (lit.[24] mp 166°), which was identified by spectral comparison with an authentic sample.

Deoxygenation of *p*-Nitrosotoluene in Methanol.—A solution of TEP (10.0 ml) in methanol (600 ml) was stirred at room temperature and a solution of *p*-nitrosotoluene (2.0 g, 16.5 mmol) was added dropwise over 3 hr. The solution was then stirred at room temperature for 1 hr followed by addition of water (50 ml). The resulting solution was concentrated at room temperature to about 100 ml with a rotary evaporator. The residue was diluted with water (500 ml) and thoroughly extracted with hexane. Evaporation of the hexane gave a mixture containing 0.3 g (17%) of 2-methoxy-4-methylaniline (**13**) by nmr analysis. A sample purified by glpc using an Apiezon–KOH column gave a pure sample: nmr (CCl_4) δ 2.15 (s, 3 H), 3.45 (broad, 2 H), 3.80 (s, 3 H), and 6.52 (s, 3 H). An acetyl derivative was prepared, mp 127–129° (lit.[25] mp 131°). The water solution remaining after hexane extraction was extracted with ether. Evaporation of the dried ether extract gave a mixture of triethyl phosphate and 4-methoxy-4-methyl-2,5-cyclohexadienone (**14**) containing 0.5 g of **14** (23%) by nmr analysis. Crystallization from hexane gave pure **14**: mp 61–63° (lit.[26] mp 62–63°); nmr (CCl_4) 1.48 (s, 3 H), 3.27 (s, 3 H), 6.35 (d, 2 H), and 6.85 (d, 2 H).

Deoxygenation of Nitrosobenzene in Methanol–Diethylamine Mixtures.—A solution of nitrosobenzene (0.45 g, 4.2 mmol) in benzene (20 ml) was added dropwise over a period of 1 hr to a cooled (0°) solution of TEP (2.1 ml, 12 mmol) in the methanol–diethylamine mixtures indicated in Figure 2. After the reaction was complete, the solvent was removed on a rotary evaporator and the residue was analyzed for *o*-anisidine, *p*-anisidine, and 2-diethylamino-3*H*-azepine by glpc. The glpc analysis indicated the presence of a fourth volatile product which was isolated by preparative glpc using a 5-ft 5% SE-30 on Chromosorb G column. Spectral data indicated this to be 1,1-diethyl-2-phenylhydrazine and the identification was confirmed by comparison with an authentic sample prepared by the procedure of Fratzl and Berger.[6] The hydrazine was not detected at concentrations below 5 mol % diethylamine. The maximum yield observed was 8% at 40 mol % diethylamine.

Deoxygenation of Nitrosobenzene in Ethanol–Diethylamine Mixtures.—The reaction procedure was identical with that described for methanol–diethylamine mixtures. Results of glpc analysis for *p*-phenetidine and 2-diethylamino-3*H*-azepine are shown in Figure 3. Traces of 1,1-diethyl-2-phenylhydrazine were detected by tlc.

Deoxygenation of Nitrosobenzene in Ethanol Containing Sodium Ethoxide.—A solution of nitrosobenzene (0.225 g, 2.1 mmol) in benzene (10 ml) was added slowly to ethanol (67 ml) containing sodium ethoxide (11.7 mmol, prepared by dissolution of 0.27 g of sodium) and TEP (1.0 ml). No *p*-phenetidine was detected by glpc using the standard conditions of analysis.

Photolysis of Phenyl Azide in Methanol, Ethanol, Methanol–Acetic Acid, and Ethanol–Acetic Acid.—A solution of phenyl azide (1.0 g, 8.4 mmol) was irradiated using a 200-W Hanovia mercury lamp (filtered through Pyrex) for 9 hr in 180 ml of the appropriate solvent. More than 90% of the azide decomposed in each run. The solvents were removed using a rotary evaporator and the residue was analyzed by glpc. The results for the four solvent systems are described individually below.

A. Methanol.—No *o*-anisidine or *p*-anisidine was detected. 2-methoxy-3*H*-azepine[27] was formed in 11% yield and identified by spectra data.

B. 9:1 (v/v) Methanol–Acetic Acid.—No *o*-anisidine or *p*-anisidine was detected. A 9% yield of 2-methoxy-3*H*-azepine was indicated by glpc.

C. Ethanol.—No *o*-phenetidine or *p*-phenetidine was detected. A volatile product, tentatively identified as 2-ethoxy-3*H*-azepine, on the basis of spectral data was detected, but the yield was not determined.

D. 9:1 (v/v) Ethanol–Acetic Acid.—No *o*- or *p*-phenetidine was detected. Qualitative glpc indicated that 2-ethoxy-3*H*-azepine had been formed, but the yield was not determined.

Registry No.—**1**, 586-96-9; triethyl phosphite, 122-52-1; **9a**, 67-56-1; **9b**, 64-17-5; **9c**, 109-86-4; **9d**, 67-63-0; **9e**, 75-65-0; **12**, 623-11-0.

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Structure–Reactivity Studies of Deoxygenation Reactions

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The rates of deoxygenation by triethyl phosphite in methanol have been measured for nitrosobenzene, six monosubstituted derivatives, and 2-nitrosomesitylene. The rate of deoxygenation is enhanced by electron-withdrawing substituents and correlated best (ρ = 1.83, r = 0.994) in the Hammett equation using σ^+ substituent constants. Nitrosomesitylene is slightly more reactive than nitrosobenzene and the lack of a steric hindrance to deoxygenation points to nucleophilic attack by phosphorus at oxygen. Rates of deoxygenation of nitrobenzene and eight derivatives are reported. The rate of deoxygenation is enhanced by electron-withdrawing substituents. The question of isolation of triethyl *N*-arylphosphorimidates from thermal deoxygenation reactions is considered in light of these rate data.

The deoxygenation of aromatic nitroso and nitro compounds by trivalent derivatives of phosphorus has attained important synthetic potential for the preparation of a variety of benzoazoles,[1] trialkyl *N*-arylphosphorimidates,[2] dialkyl *N*-arylphosphoramidates,[3] nucleophilic aromatic substitution products,[4] and several types of rearranged heterocyclic nitrogen system.[2,3] During the course of the investigations which have explored the synthetic scope of the deoxygenation reaction, there have been relatively few rate studies which could provide data for more detailed mechanistic discussion of the deoxygenation reaction. Cadogan has reported a comparison of the reactivity of *o*-nitrobiphenyl with its 4-bromo and 4′-methyl derivatives.[5] Half-

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lives of 50, 17, and 50 min, respectively, at 145.5° in triethyl phosphite (TEP) were reported. Cadogan and Cooper[6] have also reported a study of the rate of deoxygenation of *o*-nitrosobiphenyl by TEP in triethyl phosphate. Rate data in the temperature range 278–332°K led to values for E_a of 11.56 kcal mol^{-1} and $\Delta S^{\pm}$ of −29 eu at 298°K.

In the present work we have studied the rate of deoxygenation of eight substituted nitrosobenzenes by TEP in methanol and of nine aromatic nitro compounds in excess TEP. This study has provided the first quantitative data on the sensitivity of the deoxygenation reaction to ring substitution.

Results

The aromatic nitroso compounds reported in Table I were deoxygenated in methanol with sufficient excess of TEP to provide pseudo-first-order kinetics. The rates of disappearance of the nitroso compounds were followed by the decrease in absorbance at the absorbance maximum of the nitroso compound in the range 283–342 nm. The rate constants were evaluated from the absorbance data by the Guggenheim method.[7] A first-order dependence of [TEP] was established for nitrosobenzene and *p*-nitrosotoluene. The derived rate constants and relative reactivity of the compounds studied are shown in Table I.

TABLE I
RATES OF DEOXYGENATION IN METHANOL

R	Registry no.[a]	Max (nm)	$k\psi$ sec^{-1}[b] × 10^4	k_2 sec^{-1} mol^{-1} l. × 10^2	Relative rate
p-OCH_3	1516-21-8	345	0.33	0.868	0.057
p-CH_3	623-11-0	315	1.80	4.74	0.31
m-CH_3	620-26-8	286	3.83	10.1	0.67
H	586-96-9	283	5.75	15.1	1.00
m-CO_2CH_3	26960-97-4	283	36.3	95.6	6.3
m-Cl	932-78-5	282	37.5	98.7	6.5
p-CO_2CH_3	13170-28-0	286	76.6	202	13.3
2,4,6-Tri-CH_3	1196-12-9	321	7.47	19.7	1.30

[a] Registry no. are for nitrosobenzene with substituents. [b] Temperature 29.9°; [TEP] = 3.80 × 10^{-3} *M*.

Rate data recorded in Table II indicate the sensitivity of the deoxygenation of nitrosobenzene to changes of the solvent media to ethanol or ethanol containing

TABLE II
RATES OF DEOXYGENATION OF NITROSOBENZENE IN OTHER SOLVENTS

Solvent	$k\psi$ sec^{-1} × 10^4
MeOH	5.75
EtOH	5.40
EtOH–1% HOAc	5.80

1% acetic acid. Rate-temperature results for *p*-nitrosotoluene are reported in Table III. From this data a value of E_a of 9.7 kcal/mol and a $\Delta S^{\pm}$ of −35 eu are calculated at 30.0°. These activation data are quite comparable to the results Cadogan and Cooper[6] obtained for *o*-nitrosobiphenyl.

The nitroso compounds, with the exception of *p*-methoxynitrosobenzene, gave a satisfactory Hammett

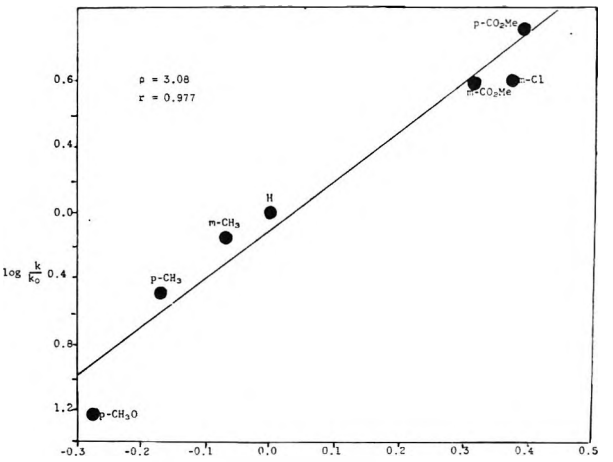


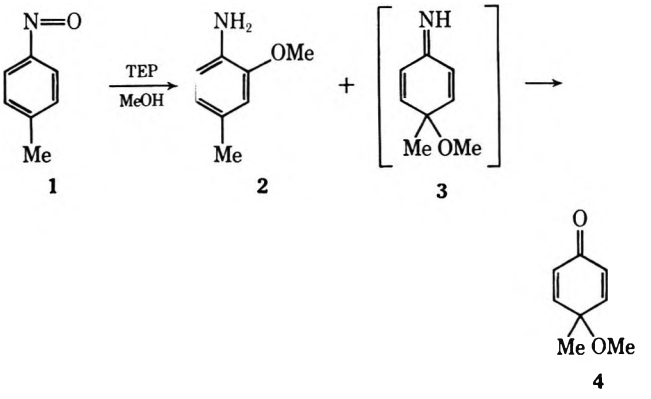
Figure 1.—Hammett correlation of rates of deoxygenation of nitrosoaromatics with σ.

TABLE III
TEMPERATURE DEPENDENCE OF DEOXYGENATION OF *p*-NITROSOTOLUENE

Temp, °C	$k\psi$ sec^{-1} × 10^4	k_2 sec^{-1} mol^{-1} l. × 10^2
24.0	1.29	3.39
27.0	1.56	4.10
29.9	1.80	4.74
34.7	2.25	5.92

correlation with σ, yielding a ρ value of 3.08. An excellent correlation, which included *p*-methoxynitrosobenzene, was found with σ^+ with ρ equal to 1.83. These correlations are shown in Figure 1 and 2, respectively.

The principal products of the deoxygenation of nitrosobenzene in methanol are *o*- and *p*-anisidine.[4c] The absorption spectrum found at the end of typical rate runs in consistent with the formation of *p*-anisidine as the major reaction product. The final absorption spectrum for *m*-nitrosotoluene is very similar indicating that 3-methyl-4-methoxyaniline is the major product in this reaction. The final absorption spectrum for *p*-nitrosotoluene is much different. Product isolation studies in this system have shown that 2-methoxy-4-methylaniline and 4-methoxy-4-methyl-2,5-cyclohexadienone are major products.[4c]



The final absorption spectrum [λ_{max} 228 nm (ϵ 13,600), 290 (s) (1120)] for the deoxygenation of *p*-nitrosotoluene is very similar to that reported for **4**,[8] indicating that **4**, or conceivably the precursor **3**, is the principal product formed under the conditions of the

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(7) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, p 49.
(8) E. Hecker and R. Lattrell, *Justus Liebigs Ann. Chem.*, **662**, 48 (1963).

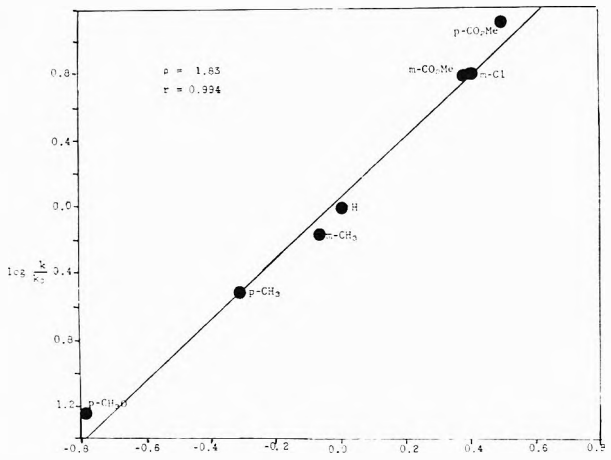


Figure 2.—Hammett correlation of rates of deoxygenation of nitrosoaromatics with σ^+.

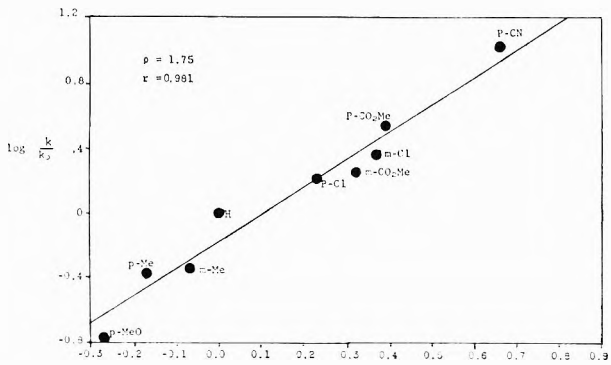


Figure 3.—Hammett correlation of rates of deoxygenation of nitroaromatics with σ.

kinetic experiment. The products formed from the other nitroso compounds have not been studied. The satisfactory Hammett relationship indicates that no change in the nature of the rate-determining step has occurred in the range of substituent groups studied, however.

The rate of deoxygenation of 2-nitrosomesitylene was studied in order to assess the steric effect of the two ortho substituents. Nitrosomesitylene was found to be surprisingly reactive toward deoxygenation as the reaction proceeded slightly faster than that of nitrosobenzene despite the presence of the electron-donating methyl substituents.

The rates of deoxygenation of the nitro compounds in triethyl phosphite were followed by gas chromatography. Pseudo-first-order rate constants were derived from the resulting data. These rates are summarized in Table IV.

Hammett plots of the rate data *vs.* σ and σ^+ are shown in Figures 3 and 4. The correlation with σ (correlation coefficient 0.981) is somewhat more satisfactory than with σ^+ (correlation coefficient 0.961).

In contrast to nitrosomesitylene, the deoxygenation of nitromesitylene is subject to some steric hindrance. It was not included in the present study but data from preparative runs give a half-life of about 4 hr at 156°.

The product mixtures obtained from thermal deoxygenations of nitro compounds in triethyl phosphite are complex and include triethyl *N*-arylphosphorimidates and products derived from them,[2,3] as well as products resulting from rearrangement of the original aromatic

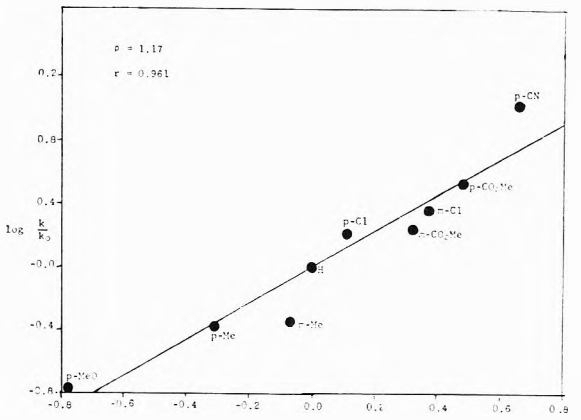


Figure 4.—Hammett correlation of rates of deoxygenation of nitroaromatics with σ^+.

TABLE IV

RATES OF DEOXYGENATION OF NITROAROMATICS IN TRIETHYL PHOSPHITE AT 130.0 ± 0.1°

R	Registry no.[a]	$k\psi$ (hr^{-1}) × 10	$t_{1/2}$ (hr)	Relative rate
p-MeO	100-17-4	0.80 ± 0.05	8.6	0.17
p-Me	99-99-0	2.11 ± 0.12	3.3	0.45
m-Me	99-08-1	2.33 ± 0.07	2.9	0.50
H	98-95-3	4.68 ± 0.40	1.5	1.00
p-Cl	100-00-5	8.14 ± 0.20	0.85	1.74
m-CO_2Me	618-95-1	8.79 ± 0.31	0.79	1.88
m-Cl	121-73-3	11.5 ± 0.2	0.60	2.46
p-CO_2Me	619-50-1	16.9 ± 0.3	0.41	3.61
p-CN	619-72-7	51.5 ± 1.1	0.13	11.0

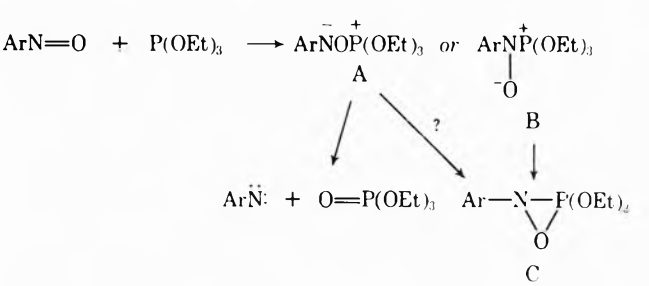
[a] Registry no. are for nitrobenzene with substituents.

ring.[2c,3] Although, as described in the discussion section, we have repeated some of our earlier product studies, no new product studies on the reaction were carried out in the course of this work.

Discussion

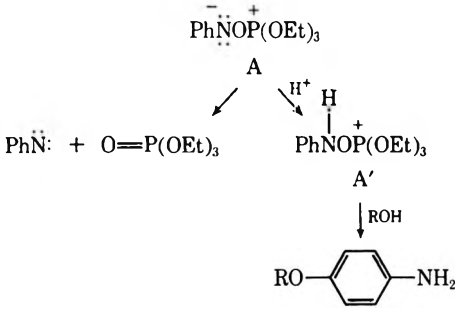
In the preceding paper,[4c] evidence was presented pointing to the existence of an intermediate in the deoxygenation of nitrosobenzene which could give either phenylnitrene by α elimination or aromatic nucleophilic substitution products. The intermediate was considered to be the zwitterion A (Scheme I). We can now consider this intermediate and its role in the deoxygenation reaction in terms of the rate studies presented in this paper.

SCHEME I



The response of the deoxygenation rates to substituents in the nitroso compounds shows that the rate of deoxygenation is accelerated by electron-withdrawing substituents. These data, along with studies of Cadogan and Todd[5] which have established that highly nucleo-

philic phosphorus compounds are the most reactive deoxygenating agents, indicate that nucleophilic attack by phosphorus on the nitroso compounds occurs in the deoxygenation reaction. The initial nucleophilic attack could conceivably be at oxygen or nitrogen. Furthermore, either of the resulting zwitterionic intermediates A and B might form the cyclic pentacovalent phosphorus intermediate C prior to expulsion of triethyl phosphate. Any of these schemes is compatible with the observed substituent effects, provided the initial nucleophilic attack by phosphorus is rate determining. The evidence that the deoxygenation eventually leads to aryl nitrenes has been discussed elsewhere.[1,2b-c,3,9] Our studies[4c] of the products of deoxygenation in alcoholic solvents have established that the type of products formed in the reaction is very sensitive to the nature of the reaction media. Changes in solvent media which would increase the rate of protonation of a dipolar intermediate, such as A, divert the reaction from its normal nitrenoid course and lead, instead, to nucleophilic aromatic substitution.[4c]

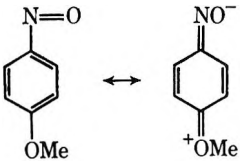


A dipolar intermediate such as A provides an attractive explanation for this feature of the reaction. Its conjugate acid A′ is an aniline derivative with an excellent leaving group, triethyl phosphate, bonded to nitrogen. Protonation of C could also lead to aromatic nucleophilic substitution, but protonation of the intermediate B would not be expected to lead directly to aromatic substitution although it could do so indirectly *via* a cyclic form.

The rate of deoxygenation of nitrosobenzene is relatively unaffected by changes in solvent which have a major effect on product composition. Nucleophilic aromatic substitution accounts for >60% of the nitrosobenzene in methanol, but less than 5% of the total product in ethanol.[4c] The rates of deoxygenation in the two solvents are within 10% of one another. Addition of acetic acid to ethanol induces nucleophilic aromatic substitution in >50% yield[4c] but increases the rate of deoxygenation by less than 10%. These results indicate that the product-determining step in deoxygenation, protonation, or α elimination, follows the rate-determining step which must be formation of A (or B or C).

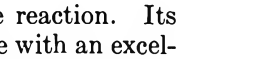
The insensitivity of the deoxygenation reaction to steric hindrance which is dramatically indicated by the fact that nitrosomesitylene is slightly more reactive than nitrosobenzene can not easily be reconciled with the formation of B in the rate-determining step of the reaction. Nucleophilic attack at nitrogen would be expected to be subject to large steric hindrance. Base-catalyzed hydrolysis of mesitoate esters, for example, is about 10^5 times slower than comparable hydrolyses of benzoate esters.[10,11] The reason for the small rate enhancement present in nitrosomesitylene is not entirely clear. It may be associated with steric inhibition of resonance in nitrosomesitylene. Such an effect is known to be present[12] and the resulting higher ground-state energy of the nitroso compound may result in increased reactivity.

The Hammett correlation for the nitroso deoxygenations is significantly improved by use of σ^+ values in place of σ values. This points to a high contribution from resonance interactions in the overall substituent effect.[13] The intermediate A cannot account for the large resonance effect associated with σ^+ correlations. However, the ground-state nitroso compounds present the opportunity for direct conjugation of the nitroso group with the substituents and such conjugation is known to significantly effect the spectral[14] properties of



the nitroso compounds. We suggest that the σ^+ correlation reflects the fact that this direct conjugation is decreased in the transition state leading to A.

In summary, we propose that the transition state for deoxygenation of aromatic nitroso compounds can be represented as D. A similar proposal has been made by Cadogan and Cooper[8] on the basis of their studies on *o*-nitrosobiphenyl. In accord with expectation for an



D

exothermic reaction with a low energy of activation,[15] the transition state probably occurs early on the reaction coordinate and there appears to be minimal steric resistence to the approach by phosphorus in the transition state. There is no evidence in the present data that indicates that the reaction proceeds to a cyclic intermediate C but the possibility can not be finally ruled out.

The electronic substituent effects in the nitro deoxygenations are generally similar to those observed with the nitroso compounds. There is a moderate steric effect observed in the deoxygenation of nitromesitylene. Although quantitative rate data were not obtained, preparative scale runs indicate a half-life of about 40 hr at 156° for nitromesitylene. The steric effect thus decreases the reactivity relative to nitrobenzene by a factor of roughly 100. Again, this seems much too small for a nucleophilic attack on nitrogen. The increase in steric sensitivity may reflect the fact that nitrogen is trisubstituted in the nitro system but only disubstituted

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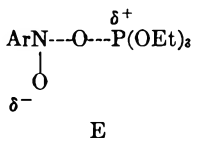
in the nitroso case. The transition state for deoxygenation of nitrobenzene may be represented as E. It is as-



E

sumed that the deoxygenation of nitroaromatics leads to nitroso compounds which are rapidly deoxygenated,[1,2b,16] but, as Cadogan[1] has pointed out, the evidence for this assumption is indirect at this point.

We believe that the rate data presented here affords a partial explanation for the differences in products reported in our studies of the deoxygenation of nitro compounds as compared with those of Cadogan. Cadogan has reported the deoxygenation of a number of alkyl and alkoxynitroaromatics and found dialkyl *N*-arylphosphoramidates and dialkyl *N*-alkyl-*N*-arylphosphoramidates as the major products.[3] In contrast, our studies of similar compounds have lead usually to the isolation of trialkyl *N*-arylphosphorimidates.[2a-c] Cadogan has noted this difference. We have confirmed the isolation of trialkyl *N*-arylphosphorimidates from deoxygenation of several representative (specifically *o*-ethylnitrobenzene, 3,4-dimethylnitrobenzene, and 2,3-dimethylnitrobenzene). We have usually[2b,c] isolated triethyl *N*-arylphosphorimidates by direct distillation of the reaction mixture after a *4–5-hr reflux* period. Cadogan's coworkers have used *11–17 hr* reflux periods. With half-lives of the nitrotoluenes in the range of 0.5–1.0 hr at 156° (the reflux temperature of triethyl phosphite), it is clear that the more extended reflux periods provide the opportunity for subsequent conversion of the initially formed *N*-arylphosphorimidates to the dialkyl *N*-arylphosphoramidates isolated by Cadogan and coworkers. We suspect that this difference in length of reflux contributes to the difference in product distribution noted in the two laboratories. In our hands[2c] only such unreactive compounds as *p*-nitroanisole and nitromesitylene give rise to much dealkylation of the phosphorimidate during the time required for deoxygenation. It should be noted that trimethyl *N*-arylphosphorimidates are quite thermally labile.[17]

Experimental Section

Nitrosoaromatics.—With the exception of *p*-nitrosoanisole, all of the nitroso compounds were prepared from the corresponding nitro compounds by reduction with zinc followed by oxidation of the crude arylhydroxylamine with ferric chloride.[18] 2-Nitrosomesitylene was prepared following the procedure of Bamberger and Rising.[19] We were able to prepare only impure *p*-nitrosoanisole from *p*-nitroanisole. Pure *p*-nitrosoanisole was obtained by oxidation of *p*-anisidine with persulfuric acid.[20] Potassium persulfate (57 g) was slowly added to cooled concentrated sulfuric acid (80 ml). A solution of *p*-anisidine (12 g) in water (1500 ml) was brought to pH 6 with 6 *N* acetic acid and cooled to 5°. The solution of persulfuric acid was poured on to ice, neutralized with potassium carbonate, and finally made slightly acidic with dilute acetic acid. This solution was added all at once at 5° to the solution of *p*-anisidine. After 0.5 hr, the precipitated nitroso compound was extracted with hexane. The hexane extract was diluted with methanol and a methanol–hexane azeotrope was removed (bp 50°). The concentrated hexane solution was steam distilled, yielding blue crystalline *p*-nitrosoanisole, contaminated with 15% *p*-nitroanisole. The product was purified by sublimation.

Triethyl Phosphite.—Commercial triethyl phosphite (Mobil Chemicals) was stored over sodium metal and then distilled through a Vigreux column under nitrogen at atmospheric pressure.

Kinetic Measurements on Nitroso Compounds.—Solutions of the nitroso compounds with absorbance of ~0.9 were prepared in methanol and exactly 3 ml was pipetted into a cell thermostated at 29.9° in a Beckman DU spectrophotometer. At $t = 0$, triethyl phosphite was added from a microsyringe and the cell was shaken. The cell was quickly returned to the thermostat and absorbance *vs.* time measurements were recorded for several half-life periods. Straight lines were obtained plotting log $(A_t - A_{t+c})$ *vs.* time according to the Guggenheim method.[7] The pseudo-first-order rate constants were evaluated from the slope of the line, slope $= -k/2.303$. Most runs gave good straight lines for two to three half-lives when subjected to standard first-order analysis but precise determination of A_∞ was difficult because of slow drift, and the Guggenheim method was used to circumvent this problem. The concentration of triethyl phosphite was calculated from the volume of triethyl phosphite delivered by the calibrated syringe (2–92 μl). The chloro- and carbomethoxy-substituted compounds were deoxygenated at [TEP] $= 3.80 \times 10^{-3}$ mol/l. The nitrosotoluenes were deoxygenated at several TEP concentrations ranging from [TEP] $= 1.52 \times 10^{-2}$ to 3.04×10^{-2} mol/l. and showed first-order dependence on [TEP] in this range. Nitrosobenzene was deoxygenated at [TEP] $= 3.80 \times 10^{-3}$ and 7.60×10^{-3} mol/l. and showed first-order dependence on TEP. For *p*-nitrosoanisole, [TEP] $= 1.52 \times 10^{-2} - 1.75 \times 10^{-2}$ mol/l. were used.

The procedures for studies in ethanol and solutions containing acetic acid were identical with those described for methanol.

Kinetic Measurements on Nitro Compounds.—Samples of 0.003–0.012 mol of the nitro compound were diluted to 25 ml with triethyl phosphite. The resulting solution was sealed in a series of 10–15 Pyrex ampoules. These were immersed in a oil bath at 130° and t_0 was taken at the point at which the bath and tubes had been at constant temperature (130 ± 0.1°) for 3 min. Tubes were removed at t_0 and subsequent time intervals, cooled in ice water, and stored for analysis at the end of the run. The amount of unreacted nitro compound was determined by the peak height method using a Wilkens A-90-P gas chromatograph and a 5-ft SE-30 column. Plots of log c_0/c *vs.* time showed first-order behavior and rate constants were obtained from the best least squares line using data for several half-life periods.

Preparative Thermal Deoxygenations.—Three nitroaromatics (2-ethylnitrobenzene, 3,4-dimethylnitrobenzene, and 2,3-dimethylnitrobenzene) were deoxygenated by refluxing with triethyl phosphite. The nitroaromatic (0.10 mol) was dissolved in triethyl phosphite (1.0 mol) and heated at reflux under nitrogen for 4–5 hr. Three fractions were collected by direct vacuum distillation of the reaction mixture. Recovered triethyl phosphite was obtained at 25–40° (0.1–0.2 mm), followed by triethyl phosphate, bp 55–65° (0.1–0.2 mm), and the trialkyl phosphorimidate, bp 120–140° (0.1 mm). Yields were 60, 78, and 79%, respectively, for the three nitro compounds (reported[2a] 44, 60, 79%, respectively). The infrared spectra showed no NH absorption. The nmr spectra were in accord with expectation and in particular the integration gave the expected values for the $-OCH_2CH_3$ and $-OCH_2CH_3$ signals indicating three ethoxy groups attached to phosphorus. There were no NCH_2CH_3 signals evident in the nmr. The only indication of any impurities is the presence of weak phosphoryl absorption in the infrared near 1250 cm^{-1}. Since phosphoramidates show strong absorptions in this region, the distilled samples are believed to be >90% pure.

Similar thermal deoxygenations of 2-nitromesitylene lead to substantial recovery of nitromesitylene (9 hr, 90% recovery; 43 hr, 52% recovery; 96 hr, 21% recovery). The products of such deoxygenations have been previously described.[2a]

Registry No.—Triethyl phosphite, 122-52-1.

Acknowledgment.—We acknowledge partial support of this work by National Institutes of Health Grant GM-14344.

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Synthesis of 5-Phenyl-2,3,4,5-tetrahydro-1,4-benzoxazepines and Corresponding 3-Ones

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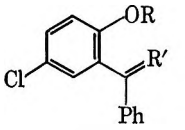
Received July 30, 1970

Preliminary, unsuccessful attempts to obtain di- and tetrahydro-5-phenyl-7-chloro-1,4-benzoxazepines through reactions of derivatives of 2-hydroxy-5-chlorobenzophenone oxime (**2a–d**) and of 2-(carboxymethoxy)-5-chlorobenzophenone and benzhydrol (**5–8**) are described. A successful route to the title compounds differing from existing methods for synthesis of (hydro) 1,4-benzoxazepines was found involving novel preparation of *o*-hydroxybenzhydrylamines **11** by reduction of *o*-hydroxybenzophenone imines **10**, O-alkylation with α-halo esters, and thermal closure to lactams **12a**, followed by N-alkylation and hydride reduction to the cyclic amines **13**.

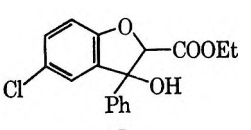
Tetrahydro-5-aryl-1,4-benzoxazepines such as **12** and **13** (Scheme I) might be of pharmacological interest, owing to their structural similarity to the well-known 5-aryl-3*H*-1,4-benzodiazepines.[1,2] Synthetic hydro-1,4-benzoxazepines, prepared starting from salicylaldehydes,[3,4] *o*-hydroxyacetophenones,[5,6] salicylamides with α-halo ketones and α-halo esters,[7] *N*-(*o*-hydroxybenzyl)-anilines,[8] or *o*-hydroxybenzophenones,[9] and tetrahydro-4,1-benzoxazepines, obtained from *o*-aminobenzhydrols,[10] have appeared recently, some of the reports attesting that compounds of this type are not easy to synthesize by classical methods.

Our initial attempts to arrive at **12**, starting from phenolic ketone **1a** and its oxime **2a**, failed for reasons which may be outlined briefly as follows. Diacetyl (**2b**) and chloroacetyl (**1b**, **2c**, **2d**) derivatives were labile, hydrolyzing or aminolyzing back to **1a** or **2a** readily. The carbonyl group of **1a** being relatively inert, **1a** did not condense with glycine ester (pyridine)[1] or ethyl cyanoacetate,[11] and even Perkin condensation giving 4-phenyl-6-chlorocoumarin[12] was difficult. With NaH (toluene) and ethyl bromoacetate, **1a** gave mainly benzofuran **4a** (structure confirmed by spectra and conversion to acid **4b** and amide **4c**) and, as a by-product, corresponding ketol **3**. Milder ethyl bromoacetate alkylation (K_2CO_3) of **1a** gave **5a** which was readily converted to amide **5b** by ammonolysis. Whereas sodium borohydride reduction of **5a** gave diol **6**, further indicating the highly reactive nature of the ester group, reduction of **5b** under the same conditions gave amide carbinol **7a**. This in turn with $SOCl_2$ gave chloroamide **7b**, but no seven-membered lactam could be prepared from **7b** by internal displacement. Products of the reaction of **7b** with sodium methoxide were identified as **8a**, **8b**, and NH_3.

We then sought a relatively facile way to introduce an amino group on the benzhydryl carbon at the onset.



1a, R = H; R′ = O
b, R = $COCH_2Cl$; R′ = O
2a, R = H; R′ = NOH
b, R = $COCH_3$; R′ = $NOCOCH_3$
c, R = $COCH_2Cl$; R′ = $NOCOCH_2Cl$
d, R = H; R′ = $NOCOCH_2Cl$



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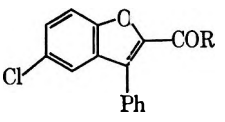
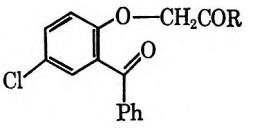
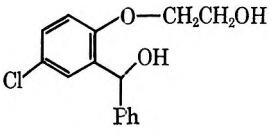


4a, R = OEt
b, R = OH
c, R = NH_2



5a, R = OEt
b, R = NH_2



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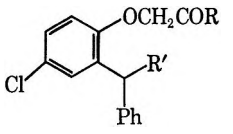

7a, R = NH_2; R′ = OH
b, R = NH_2; R′ = Cl
8a, R = NH_2; R′ = OCH_3
b, R = OH; R′ = OCH_3

o-Hydroxybenzhydrylamines have been reported as products of reduction of *o*-hydroxybenzophenone oximes[13] and 3-arylbenzisoxazoles,[14] and also as Curtius rearrangement products of azides from 3-phenylbenzofuran-2-ones,[15] but these routes do not seem practical for preparative work. On the other hand, although a number of *o*-hydroxy and otherwise substituted benzophenone imines have been prepared from nitriles with ArMgX reagents and their hydrolysis rates studied,[16] they have not been used as benzhydrylamine precursors. We found that *o*-hydroxy imine **10**, a relatively stable, bright yellow, highly chelated substance, could be prepared readily in quantity by action of excess ammonia on **1a** in ethanol. After some preliminary work, in which it was learned that large excesses of strongly

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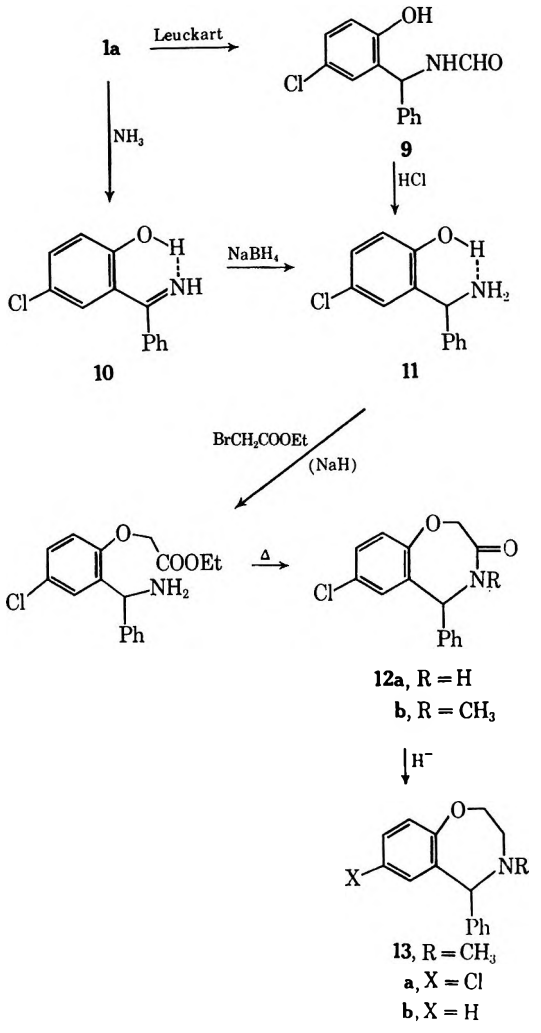
SCHEME I



basic reagents and overly vigorous conditions, leading to loss of NH_3, had to be avoided, it was possible to reduce **10** to the colorless aminophenol **11** with $NaBH_4$ in methanol.[17,18] Compound **11** (·HCl) was also prepared, more arduously, by Leuckart reaction of **1a** and acid hydrolysis of resulting **9**. With **11** in hand, one could try a variety of acylations and alkylations. Although certain acylations of **11** proved to be rather surprisingly complex, alkylations of the preformed phenolate anion were more straightforward. Thus **11** with ethyl bromoacetate (NaH) gave an oily mixture, probably owing to partial N-alkylation, consisting largely of the expected ethoxycarbonylmethoxy amine. This was evident during work-up and subsequent heating of the crude oil, when lactam **12a** crystallized and was isolated readily in 16% yield. In view of Luts' yield of 2.4% of demethyl **13a** from Leuckart reaction of **1** (R = CH_2CH_2Cl; R′ = O), hydrolysis, and closure,[9] these results represent significant improvement in the construction of this ring system.

Infrared and nmr spectra (see Experimental Section) having shown structure **12a** to be correct, further confirmation was adduced by first methylating **12a** to **12b** and reducing **12b** to the cyclic amine **13a** with $LiAlH_4$ in ether. This reduction had to be done gently to retain the chloro substituent, for under more vigorous conditions (refluxing tetrahydrofuran) there was partial dechlorination to give **13b**, also isolated and characterized.

Only moderate hypotensive (and no significant central nervous) effects were observed in pharmacological testing of compounds **12** and **13**.

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Experimental Section[19]

2-Hydroxy-5-chlorobenzophenone Oxime (2a).—Refluxing 41.5 g of 2 hydroxy-5-chlorobenzophenone (1a) and 20 g of hydroxylamine hydrochloride in 40 ml of pyridine and 250 ml of 90% ethanol (water) for 4 hr, evaporation, treatment with water, and recrystallization from aqueous methanol gave (100%) colorless crystals: mp 144–145.5°; base soluble, ferric chloride positive; ir 2.98, 6.12 μ; uv 276 nm (ε 12,080).

Anal. Calcd for $C_{13}H_{10}ClNO_2$: C, 63.04; H, 4.07; N, 5.66. Found: C, 63.08; H, 4.02; N, 5.66.

The corresponding *O,O′*-**diacetate (2b)**, obtained by heating a sample of the oxime 2 hr with excess acetic anhydride and evaporating, was recrystallized from methanol, mp 119–121°, ir 5.65 μ.

Anal. Calcd for $C_{17}H_{14}ClNO_4$: C, 61.54; H, 4.25; N, 4.22. Found: C, 61.65; H, 4.32; N, 4.07.

The corresponding *O,O′*-**bischloroacetate** (2c) was obtained by warming 2 g of the phenolic oxime with 11 ml of chloroacetyl chloride on steam cone 0.5 hr. The residue, after evaporation and treatment with water, crystallized in the presence of methanol: colorless crystals; mp 142–143.5°; ir doublet 5.59, 5.64 μ; uv 318 nm (ε 3380) and inflection 260 nm (ε 7890); ferric chloride negative.

Anal. Calcd for $C_{17}H_{12}Cl_3NO_4$: C, 50.96; H, 3.02; N, 3.50. Found: C, 51.20; H, 3.09; N, 3.44.

The corresponding **chloroacetyloximinophenol (2d)** was obtained by treating 10 g of the phenolic oxime with 20 ml of chloroacetyl chloride at room temperature. The reaction was nonexothermic, but much HCl was evolved. After standing 1.5 hr the solution was poured into cold water, and the product was collected, washed with water, and triturated with and recrystallized from ethanol to give 6.5 g of colorless crystals: mp 119.5–121°; ir 5.57 μ; uv 317 nm (ε 4150) with inflection 259 nm (ε 7650); ferric chloride positive (purple color).

Anal. Calcd for $C_{15}H_{11}Cl_2NO_3$: C, 55.57; H, 3.42; N, 4.32. Found: C, 55.53; H, 3.53; N, 4.26.

The monochloracetate reverted to the phenolic oxime on treatment with methanolic methylamine or sodium methoxide solutions.

2-(Chloroacetoxy)-5-chlorobenzophenone (1b).—Heating 40 g of 1a with 100 ml of chloroacetyl chloride at 100° for 2 hr, treatment of the cooled residue with water, and trituration of the resulting crude product with methanol gave 25 g of the recovered phenol and, from the filtrate, 4.5 g of chloroacetate: mp 88–90°, raised on further recrystallization (methanol) to mp 89.5–90.5°; ferric chloride negative; ir 5.63 and 6.01 μ; uv 221, 256, and 345 nm (ε 19,840, 11,770, and 3230, respectively). The chloroacetate reverted easily to the phenol on treatment with bases and gave imine **10** on treatment with ethanolic ammonia.

Anal. Calcd for $C_{15}H_{10}Cl_2O_3$: C, 58.27; H, 3.26. Found: C, 58.50; H, 3.38.

2-Hydroxy-5-chlorobenzhydrol.—A methanol suspension of 4 g of 1a or its chloroacetate was treated with excess sodium borohydride (*ca.* 10 g) in portions. The solution was heated (steam cone) 10 min, cooled, and treated with water, and the resulting solution acidified with HCl. The colorless oil was extracted with ether, the washed (water) and dried ($MgSO_4$) organic solution evaporated, and the residue recrystallized from cyclohexane, giving colorless crystals: mp 89–90.5°; ir 2.90, 3.10 μ; uv 286 nm (ε 2980).

Anal. Calcd for $C_{13}H_{11}ClO_2$: C, 66.53; H, 4.73. Found: C, 66.41; H, 4.54.

(19) Melting points were obtained using a Thomas–Hoover silicone oil bath, infrared spectra (Nujol mulls, unless otherwise noted) were recorded with Perkin-Elmer double-beam instrument, ultraviolet curves (methanol solutions) were measured by a Cary recording spectrophotometer, and nmr data were obtained using Varian A-60 60-Mc apparatus with TMS internal standard. We are indebted to Mr. Louis Dorfman, Mr. George Robertson, Mr. Rudolf Oeckinghaus, Miss Ruth Behnke, Mrs. Margaret Mulligan, and Mr. Charles Navarro for analytical and spectral data, and to Mrs. Angela Aretakis for literature search work.

2-Ethoxycarbonyl-3-phenyl-5-chlorobenzofuran (**4a**).—A stirred solution of 13.5 g of **1a** in 200 ml of warm toluene was treated with 2.5 g of 56% NaH (oil) and then 9 ml of ethyl bromoacetate, and the mixture was refluxed and stirred for 5.5 hr. After the mixture was cooled and treated with water, the ether-diluted, washed (water), and dried ($MgSO_4$) organic solution was evaporated to give yellow oil from which **4a** crystallized on standing (4.1 g), and was collected with the aid of a small amount of ethanol and recrystallized from ether: mp 105–106°; ir 5.80 μ; uv 216 and 286 nm (ϵ 29,170 and 15,950).

Anal. Calcd for $C_{17}H_{13}ClO_3$: C, 67.91; H, 4.36. Found: C, 67.92; H, 4.45.

2-Ethoxycarbonyl-3-hydroxy-3-phenyl-5-chloro-2,3-dihydrobenzofuran (**3**) crystallized from the mother liquor after removal of **4a**: crystals from ether; mp 134–137°; ir 2.91 (intense) and 5.77 μ; uv 289 nm (ϵ 3260).

Anal. Calcd for $C_{17}H_{15}ClO_4$: C, 64.05; H, 4.74. Found: C, 64.08; H, 4.71.

Compound **3** gave **4a** on warming with acids or PPA. Compound **4a** was further characterized by hydrolysis (10% sodium hydroxide, 1.5-hr reflux, dilution and acidification) to corresponding acid **4b**, recrystallized from ethanol: mp 254.5–256.5° slow dec; ir 5.95 μ.

Anal. Calcd for $C_{15}H_9ClO_3$: C, 66.07; H, 3.33. Found: C, 66.37; H, 3.50.

The acid was further converted to the corresponding acid chloride ($SOCl_2$) and thence, using concentrated NH_4OH and standard methods, to amide **4c**: crystals from ethanol; mp 186–188°; ir 2.88, 3.01, and 6.01 μ; uv 282 nm (ϵ 14400).

Anal. Calcd for $C_{15}H_{10}ClNO_2$: C, 66.30; H, 3.71; N, 5.16. Found: C, 66.15; H, 3.85; N, 5.27.

2-(Ethoxycarbonylmethoxy)-5-chlorobenzophenone (**5a**).—To a solution of 19.1 g of **1a** in 1400 ml of acetone was added 20 g of ethyl bromoacetate and 18.5 g of anhydrous potassium carbonate. The suspension was refluxed vigorously 7.5 hr and filtered, the filtrate was evaporated, the residue was taken into ether and clarified by another filtration, and the solvent again evaporated, to give crude, oily product. The keto ester was characterized as the 2,4-dinitrophenylhydrazone, red crystals from ethanol, mp 161–163°.

Anal. Calcd for $C_{23}H_{19}ClO_7N_4$: C, 55.37; H, 3.84; N, 11.23. Found: C, 55.61; H, 3.88; N, 11.48.

2-(β-Hydroxyethoxy)-5-chlorobenzhydrol (**6**).—Reduction of *ca.* 12 g of the preceding, crude keto ester **5a** was carried out in methanol with sodium borohydride (*ca.* 8 g) added in portions. After 15-min heating (steam cone) and evaporation of solvent, the cooled residue was treated with water. The colorless, crude product crystallized and was collected, washed with water, dried (yield 5.3 g), and recrystallized from ether: mp 124–125.5°; ir 3.12 μ (very broad, intense).

Anal. Calcd for $C_{15}H_{15}ClO_3$: C, 64.63; H, 5.42. Found: C, 64.82; H, 5.14.

2-Benzoyl-4-chlorophenoxyacetamide (**5b**) was prepared by saturating a solution of *ca.* 18 g of crude keto ester **5a** in 300 ml of ethanol with ammonia. After standing 3 days the alcoholic solution was evaporated, and the syrupy residue with the aid of methanol afforded 4.8 g of crystalline amide. Recrystallization from methanol gave colorless crystals: mp 184–186°; ir 2.90, 5.92 and 6.06 μ; uv 251 nm (ϵ 13,800) with inflection 312 nm (ϵ 2120).

Anal. Calcd for $C_{15}H_{12}ClNO_3$: C, 62.18; H, 4.18; N, 4.84. Found: C, 62.41; H, 4.17; N, 4.70.

2-(α-Hydroxybenzyl)-4-chlorophenoxyacetamide (**7a**) was obtained by sodium borohydride reduction of **5b** (4.5 g), following usual procedure of adding the excess reagent in portions to a methanol solution of the keto amide and thereafter warming 20–30 min on a steam cone and evaporating methanol. After treatment with water, the crude crystals were collected, water-washed, dried, and recrystallized (ether–methanol) to give (4.2 g) colorless crystals: mp 143–145°; ir 2.89, 2.97, 3.06, 3.17, and 5.94 μ; uv 280 nm (ϵ 2190).

Anal. Calcd for $C_{15}H_{14}ClNO_3$: C, 61.75; H, 4.84; N, 4.80. Found: C, 61.71; H, 4.87; N, 4.69.

2-(α-Chlorobenzyl)-4-chlorophenoxyacetamide (**7b**).—On treatment with excess thionyl chloride (50 ml) the hydroxyamide **7a** (2 g) reacted rapidly. The solution was warmed gently 15 min, the excess reagent was removed *in vacuo*, and the residual material was obtained in crystalline form (1.4 g) using ether: colorless crystals; mp 152.5–154.5°; ir 2.92, 3.20, and 5.93 μ; uv 281–287 nm (ϵ 2270).

Anal. Calcd for $C_{15}H_{13}Cl_2NO_2$: C, 58.08; H, 4.22; N, 4.52. Found: C, 57.78; H, 3.99; N, 4.43.

Methyl 2-(α-Methoxybenzyl)-4-chlorophenoxyacetate (**8a**) **and Methoxy Acid** (**8b**).—To a solution of 0.15 g of sodium in 40 ml of methanol was added 1.0 g of **7b**. After refluxing 1 hr, the methanol was evaporated *in vacuo* (NH_3 present, as evidenced by odor) and the cooled residue treated with water. Crystals of **8a** which separated were collected (0.25 g), washed with water, dried, and recrystallized from ether: mp 141–142°; ir 2.89, 3.20, and 5.89 μ; uv 281 nm (ϵ 2370).

Anal. Calcd for $C_{16}H_{16}ClO_3N$: C, 62.85; H, 5.28; N, 4.58. Found: C, 62.74; H, 5.40; N, 4.51.

Acidification (HCl) of the aqueous filtrate gave 0.45 g of **8b**. Recrystallization from ether gave a pure sample: mp 160–162°; ir 5.74–5.83 μ and bonded OH and carboxylate bands; uv 282 nm (ϵ 2420).

Anal. Calcd for $C_{16}H_{15}ClO_4$: C, 62.64; H, 4.93. Found: C, 62.83; H, 5.03.

2-Hydroxy-5-chlorobenzophenone Imine (**10**).—A brisk steam of anhydrous ammonia was passed into an uncooled suspension of 130 g of 2-hydroxy-5-chlorobenzophenone in 1.2 l. of EtOH for 1.8 hr. Within 1 hr the crystals of **1a** had dissolved and product began to separate. After standing overnight the suspension was filtered; the first crop of product, 69 g of orange-yellow crystals, had mp 134–136°, not raised on recrystallization (ethanol). Additional, less pure product (40 g) was obtained after concentrating the ammoniacal solution. The analytical sample, mp 134–136.5° from ethanol, was shiny, yellow flakes: ir 6.25 (sharp), bonded 3.19–3.27, and broad, dipolar bands 3.78–4.33 μ; uv 224, 336–350, and 421 nm (ϵ 18,180, 1220, and 6750, respectively) with inflections 236 and 272 nm. The compound was soluble in 10% hydrochloric acid (solution colorless), and gave strong ferric chloride test and precipitate with cupric acetate.

Anal. Calcd for $C_{13}H_{10}ClNO$: C, 67.39; H, 4.35; N, 6.05. Found: C, 67.09; H, 4.48; N, 6.20.

2-Hydroxy-5-chloro-α-aminodiphenylmethane (**11**).—The imine **10** (69 g) in 300 ml of warm (30°) methanol was treated (stirring) gradually (5 min) with 10–12 g of sodium borohydride, or *ca.* several grams in excess of the amount required to convert from yellow to colorless solution. After warming briefly and gently to ensure breakdown of any excess hydride, the solution was cooled and treated with 2 l. of water, and the crude amine extracted with ether (in some runs it crystallized directly and was collected). The ether solution was washed with water and extracted with 10% hydrochloric acid. The chilled, acid solution was neutralized carefully with cold, concentrated NaOH solution and the amine again either filtered or extracted with ether; the water-washed, dried ($MgSO_4$), and evaporated ether solution gave colorless crystals (44.8 g), mp 135–136° (solvated). Recrystallization from methanol gave a sample: mp 136.5–137.5°; ir 2.98, 3.05 μ and broad, moderately intense band centered *ca.* 4.03 μ, indicative of aminium phenolate form; uv 287 nm (ϵ 2820).

Anal. Calcd for $C_{13}H_{12}ClNO$: C, 66.81; H, 5.18; N, 5.99. Found: C, 67.13; H, 5.29; N, 5.96.

The corresponding hydrochloride, obtained from the aminophenol with alcoholic HCl or from its attempted chloroacetylation, and also from hydrolysis of **9** as described next, was recrystallized from ethanol–ether or methanol–ethyl acetate: colorless crystals; mp 218–220° dec; uv 288 nm (ϵ 3020).

Anal. Calcd for $C_{13}H_{12}ClNO \cdot HCl$: C, 57.79; H, 4.85; N, 5.19. Found: C, 57.57; H, 4.53; N, 5.04.

Both the aminophenol and its hydrochloride gave ferric chloride tests, but whereas that of the salt was blue and relatively permanent, that of the base itself was red and transient, indicating relatively facile oxidation of the benzhydrylamine moiety.

The corresponding *O,N*-**dibenzoate** was prepared by usual Schotten–Baumann method (benzoyl chloride and 5% sodium hydroxide solution) and after recrystallization from cyclohexane had mp 108–111°: ir 3.02, 5.74, 6.10, and 6.54 μ.

Anal. Calcd for $C_{27}H_{20}ClNO_3$: C, 73.38; H, 4.56; N, 3.17. Found: C, 73.60; H, 4.52; N, 3.27.

Other attempted acylations, with, *e.g.*, $ClCH_2COCl$, Ac_2O, AcCl, ClCOOEt, etc., appeared to be quite complex and did not afford crystalline, well-characterized derivatives.

Leuckart Reaction (**9**).—A solution of 20 g of **1a** and 30 g of ammonium formate in 100 ml of formamide and 75 ml of formic acid was distilled slowly until temperature of solution reached 175° and then refluxed 6 hr. The cooled solution was poured into ice water. The crude product was collected, triturated and

washed with water, dried (yield 20.3 g), and recrystallized from ethyl acetate–ether: colorless crystals; mp 169–171°; ir 2.99–3.07 and 6.06–6.12 μ; uv 286 nm (3100).

Anal. Calcd for $C_{14}H_{12}ClNO_2$: C, 64.25; H, 4.62; N, 5.35. Found: C, 64.48; H, 4.89; N, 5.46.

Hydrolysis of **9** (concentrated HCl, 4.5 hr reflux) gave a sample of **11** HCl, identical with that prepared *via* reduction of imine **10**.

5-Phenyl-7-chloro-2,3,4,5-tetrahydro-1,4-benzoxazepin-3-one (12a).—A stirred solution of 25 g of aminophenol **11** in 500 ml of toluene was treated with 4.8 g of 56% sodium hydride (oil) and 5–10 min thereafter with 12.5 ml of ethyl bromoacetate. The suspension was refluxed and stirred 4 hr. The cooled, filtered, and ether-diluted organic solution was washed with three portions of water, dried (K_2CO_3), and partly evaporated. Compound **12a** (2.7 g), crystallized from the solution, and collected and washed with ether, had mp 206–208°. The mother liquor, after evaporation while heating on steam cone, afforded 1.9 g of additional lactam **12a**, mp 204–206°, on trituration with ether, bringing the yield to 4.6 g (15.7%). Recrystallization from methanol gave a pure sample: mp 206.5–208.5°; ir 3.14, 3.27 (moderate), and 6.00 μ (intense); uv 272, 279, and 291 nm (ε 980, 990, and 210, respectively); nmr ($CDCl_3$) δ 7.35–6.9 (m, 8, aromatic protons), 5.71–5.65 (d, 1, benzhydryl proton coupled to NH, collapsed to δ 5.68 s when NH exchanged with D_2O), and 4.57 (s, 2, magnetically equivalent protons at position 2).

Anal. Calcd for $C_{15}H_{12}ClNO_2$: C, 65.82; H, 4.42; N, 5.12. Found: C, 65.93; H, 4.44; N, 4.98.

4-Methyl-5-phenyl-7-chloro-2,3,4,5-tetrahydro-1,4-benzoxazepin-3-one (12b).—Lactam **12a** (3.0 g) in toluene (200 ml) was treated with 1.5 g of 56% sodium hydride (oil) and then 20 ml of iodomethane, and the mixture was stirred and refluxed for 7 hr. After cooling, water treatment, and dilution with ether, the separated, washed (water), dried ($MgSO_4$), and evaporated organic layer afforded 2.8 g of colorless crystals, mp 177–181° (from ether). Recrystallization from methanol gave a sample: mp 180–182°; ir 6.13 μ; uv 280 nm (ε 1220) with inflections 271 nm (ε 1090) and 291 (500); nmr ($CDCl_3$) δ 7.43–6.88 (m, 8, aromatic protons), 5.31 (s, 1, benzhydryl proton), 4.95–4.14 (symmetric AB 1:2:2:1 quartet centered 4.54, J = 16 Hz, magnetically nonequivalent position 2 protons), and 3.28 (s, 3, *N*-methyl).

Anal. Calcd for $C_{16}H_{14}ClNO_2$: C, 66.78; H, 4.90; N, 4.87. Found: C, 66.51; H, 5.12; N, 4.88.

4-Methyl-5-phenyl-7-chloro-2,3,4,5-tetrahydro-1,4-benzoxazepine (13a).—Reduction of 3.5 g of *N*-methyllactam **12b** with 4 g of lithium aluminum hydride in 500 ml of ether with 1-hr stirring and reflux, followed by addition of 16 ml of water at 0°, 0.5-hr stirring at 26°, and filtration, gave a solution of crude base which was dried (K_2CO_3) and evaporated: yield 3.5 g of slightly greenish oil; soluble in dilute acids; ir devoid of C=O bands.

The corresponding hydrochloride was precipitated from ether with ethanolic HCl and recrystallized from ethanol–ether: colorless crystals; mp 231–233° dec; ir 4.08 μ (broad, intense); uv 269 nm (ε 940).

Anal. Calcd for $C_{16}H_{16}ClNO \cdot HCl$: C, 61.94; H, 5.53; N, 4.52. Found: C, 61.69; H, 5.66; N, 4.57.

The corresponding picrate was prepared in and recrystallized from ethanol: yellow crystals; mp 201.5–204° dec.

Anal. Calcd for $C_{22}H_{19}ClN_4O_8$: C, 52.54; H, 3.81; N, 11.14. Found: C, 52.84; H, 4.09; N, 11.10.

When 2.0 g of **12b** was reduced with lithium aluminum hydride (5 g) in tetrahydrofuran, and refluxing for 7.5 hr, the crude base (1.4 g) afforded a hydrochloride which, on crystallization from ethanol–ether, was obtained in two fractions, mp 224–228° dec and mp ca. 138–150° dec. Clarified, aqueous solutions of the lower melting, more soluble hydrochloride fraction, on dropwise treatment with 10% sodium hydroxide solution, gave amorphous, crude **deschloramine 13b** which, after isolation by ether extraction, drying (K_2CO_3), and evaporation, was also characterized by preparation of salts.

The corresponding hydrochloride, mp 151–155° dec (from ethanol–ether), apparently was a hydrate.

Anal. Calcd for $C_{16}H_{17}NO \cdot HCl \cdot H_2O$: C, 65.41; H, 6.86. Found: C, 65.17; H, 6.90.

The corresponding picrate was recrystallized from ethanol: yellow crystals; mp 190–192°; analytically devoid of chlorine.

Anal. Calcd for $C_{22}H_{20}N_4O_8$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.15; H, 4.49; N, 12.3.

Registry No.—**1b,** 23965-43-5; **2a,** 26965-44-6; **2b,** 27005-98-7; **2c,** 26965-45-7; **2d,** 27005-99-8; **3,** 26965-46-8; **4a,** 27006-00-4; **4b,** 26965-47-9; **4c,** 26965-48-0; **5a** 2,4-DNP, 26965-49-1; **5b,** 26965-50-4; **6,** 26965-51-5; **7a,** 26965-52-6; **7b,** 26965-53-7; **8a,** 26965-54-8; **8b,** 26965-55-9; **9,** 26965-56-0; **10,** 26965-57-1; **11,** 26965-58-2; **11** HCl, 26965-59-3; **11** *O,N*-dibenzoate, 26965-60-6; **12a,** 26965-61-7; **12b,** 26965-62-8; **13a** HCl, 26965-63-9; **13a** picrate, 26965-64-0; **13b** HCl, 26965-65-1; **13b** picrate, 26965-66-2; 2-hydroxy-5-chlorobenzhydrol, 26965-67-3.

Biologically Oriented Organic Sulfur Chemistry. VI. Uses of o-Carboxyphenyl o-Carboxybenzenethiolsulfonate with Thiols[1]

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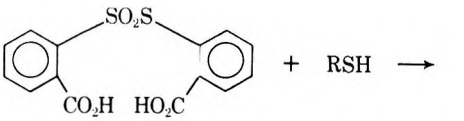
o-Carboxyphenyl o-carboxybenzenethiolsulfonate (4) was prepared easily in 77–92% yield from o-mercaptobenzoic acid in one step using chlorine or sulfuryl chloride. It reacted readily in ethanol or pH 7 buffer to give unsymmetrical o-carboxyphenyl disulfides (5–15), in yields exceeding 55%, with primary, secondary, and tertiary alkanethiols, an arenethiol, a heterocyclic thiol, and with mercapto amino acids. Other routes to these disulfides were inferior. The formation of o-carboxyphenyl disulfides affords a promising means of purifying and characterizing thiols, since typical compounds differ considerably in melting point and tlc R_f value, can be titrated with standard base, and can resist disproportionation well. Furthermore, the thiol can be regenerated by reduction either with sodium borohydride or dithiothreitol under mild conditions or recovered as the disulfide by disproportionation of the unsymmetrical disulfide. The o-carboxyphenylthio moiety seems promising for latentiating pharmacologically active thiols; it also reversibly blocks the sulfhydryl groups of an enzyme, although thus far it shows no advantages over Ellman's reagent.

Earlier work, in a continuing study of disulfides,[2] suggested that the o-carboxyphenylthio moiety, o-$HO_2CC_6H_4S$– (**1**), is a promising latentiating group[3] for radioprotective thiols.[5,6] It also suggested that salts of unsymmetrical disulfides containing moiety **1** showed an interesting instability.[5] While looking further into these matters, we realized that moiety **1** had attractive potentialities for latentiation of other medicinally significant thiols, for purification, characterization, or resolution of thiols, and for working with biochemically important thiol groups such as those of proteins. Relevant to many of these purposes were the presence of the carboxyl group and the probability of easy removal of moiety **1**. This paper reports a study of some of these potentialities.

We found earlier that o-mercaptobenzoic acid (**2**)[6] or its disulfide (**3**)[5] could be converted by chlorine–acetic acid–water in the Douglass–Farah reaction[7] to the thiolsulfonate (**4**). The **4** reacted with aminothiols to give compounds like **5**–**15** (eq 1).[5,6] With thiophenol as RSH, instead of an aminothiol, the reaction of eq 1 still proceeded cleanly, without added base at room temperature. As Table I shows, o-carboxyphenyl phenyl disulfide (**5**) precipitated in 85% yield. One recrystallization gave **5** of analytical purity in 74% yield.

Attempts to prepare **5** by treating o-carboxybenzenesulfenyl chloride (prepared from **2** with chlorine) with thiophenol gave **5** in 48% yield; o-carboxybenzenesulfenyl thiocyanate with thiophenol gave only impure **5** in 36% yield, at best.[8] In work by others, o-carboxybenzenesulfenyl chloride was prepared from *N*-chlorosuccinimide and thiol **2** and then was used to prepare an unsymmetrical disulfide;[9] in our hands this overall technique for the synthesis of **5** gave only symmetrical disulfides. Another approach was suggested by the well-known one for preparing disulfides by thioalkylating thiolates (RS^-) with thiosulfates (Bunte salts, $R'SSO_3^-$);[10] unfortunately, the attempted preparation of the pyridinium thiosulfate needed for synthesis of **5** was unsuccessful, *i.e.*, of o-$HO_2CC_6H_4SSO_3^-C_5H_5NH^+$,[11] and this route was not explored further.



(1)

5, R = C_6H_5
6, R = C_2H_5
7, R = n-C_3H_7
8, R = n-C_4H_9
9, R = n-$C_{12}H_{25}$
10, R = *trans*-2-ClC_6H_{10}
11, R = $(CH_3)_3C$
12, R = 2-benzothiazolyl
13, R = L-$CH_2CH(NH_2)CO_2H$
14, R = D-$C(CH_3)_2CH(NH_2)CO_2H$
15, R = DL-$C(CH_3)_2CH(NHAc)CO_2H$

With eq 1 thus the synthesis of choice for **5** as a model, the best means for preparing **4** was sought. Improvement was made on chlorinolysis of the thiol **2**,[6] but use of liquid chlorine makes this technique inconvenient. Use of sulfuryl chloride instead of chlorine is much

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(1) (a) Paper V: L. Field, J. L. Vanhorne, and L. W. Cunningham, *J. Org. Chem.*, **35**, 3267 (1970). (b) This investigation was supported by Public Health Service Research Grant AM11685 from the National Institute of Arthritis and Metabolic Diseases. (c) Reported in part at the Southeastern Regional Meeting of the American Chemical Society, Tallahassee, Fla., Dec 1968, Abstracts, p 98, and at the IVth "Symposium on Organic Sulphur," Venice, Italy, June 1970. (d) Abstracted from the Ph.D. Dissertation of P. M. G., Vanderbilt University, May 1970. (e) Compounds of the structure o-$HO_2CC_6H_4SSR$ usually are named in this paper as unsymmetrical disulfides. The alternative (and more proper) naming as 2-(alkyl- or aryldithio)benzoic acids fails to emphasize the disulfide function, that of principal interest in this paper, and leads to problems in the consistent treatment of related compounds and groups to be discussed. (f) We are indebted to Professor J. P. Danehy of the University of Notre Dame for helpful comment.

(2) (a) For leading references, see paper XXIX in the series entitled "Organic Disulfides and Related Substances."[2b] (b) N. E. Heimer and L. Field, *J. Org. Chem.*, **35**, 3012 (1970).

(3) One which converts a biologically active compound to a derivative which *in vivo* either liberates the parent or allows an active moiety of it to react at a biologically important site. *Cf.* ref 4 for elaboration.

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(8) The procedure was based on one of H. Lecher and M. Wittwer, *Ber.*, **55B**, 1474 (1922).

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(10) *Cf.* H. B. Footner and S. Smiles, *J. Chem. Soc.*, **127**, 2887 (1925).

(11) *Cf.* the method used to prepare $C_6H_5SSO_3^-C_5H_5NH^+$ developed by P. Baumgarten, *Ber.*, **63**, 1330 (1930).

TABLE I.—SYNTHESIS OF *o*-CARBOXYPHENYL DISULFIDES, *o*-$HO_2CC_6H_4SSR$

Compd	R	Time, hr (procedure)[a]	Yield, % (mp, °C)[b]	Mp, pure, °C[c]	C Calcd, %	C Found, %	H Calcd, %	H Found, %	S Calcd, %	S Found, %	Tlc R_f[d]	Neut equiv Calcd	Neut equiv Found[e]
5	C_6H_5	3 (A)	85 (190–195 dec)	197–198.5 dec	59.51	59.79	3.84	3.74	24.45	24.23	0.17	262	260
6	C_2H_5	3 (A)[f]	109 (112–116)	129–130	50.44	50.64	4.70	4.49	29.93	30.13	0.65[g]	214	214
7	n-C_3H_7	1 (A)[f]	93 (80–95 dec)	95–100 dec	52.60	52.74	5.30	5.26	28.09	27.84	0.74[g]	228	220
8	n-C_4H_9	1 (A)[f]	101 (75–80 dec)	89–90 dec	54.51	54.34	5.82	5.78	26.46	26.39	0.22	242	240
9	n-$C_{12}H_{25}$	3 (A)[f]	55 (89–92)	91–91.5	64.36	64.30	8.53	8.72	18.09	18.22	0.26	355	358
10	*trans*-2-ClC_6H_{10}	1.5 (A)[h]	97[i] (146–149)	155–156	51.56	51.62	4.99	5.13	21.18	21.36	0.37	303	303
11	$(CH_3)_3C$	1 (A)[f]	84 (156–159)	162–163	54.51	54.73	5.82	5.60	26.46	26.57	0.18	242	233
12	2-Benzothiazolyl	4 (A)	55[j] (172–175)	173–174	52.64	52.83	2.84	2.89	30.12	30.23	0.10	319	321
13	L-$CH_2CH(NH_2)CO_2H$[i]	3 (A)	70 (198–199 dec)	198–199 dec	43.94	43.91	4.06	4.38	23.46	23.29	...[k]	137	139[l]
		1 (B)	84[m] (198.5–199 dec)										
14	D-$C(CH_3)_2CH(NH_2)CO_2H \cdot {}^1/_2H_2O$[n]	18 (A)	69[o] (155–159 dec)	163–164 dec[p]	46.43	46.67	5.20	5.34	20.66	20.73	0.58[p]	155	146[l]
		1 (B)	36[r] (158–160 dec)										
15	DL-$C(CH_3)_2CH(NHAc)CO_2H$	1 (A)	87 (208–211)										
		1 (B)	96 (200–205 dec)	208–209 dec	48.96	48.92	4.99	5.07	18.67	18.79	0.29[p]	172	171

[a] Hours allowed for reaction; for procedures A and B, see Experimental Section. [b] Yield of the disulfides with the melting point reported, calculated on the basis of eq 1. [c] Melting point of analytically pure disulfide; recrystallized from aqueous EtOH or MeOH except where noted. [d] Eastman chromagram sheet was used, Type 6060 (silica gel); after development with 9:1 $CHCl_3$–EtOH, the sheet was exposed to I_2 vapor. [e] In 95% EtOH (25 ml), titrated to a phenolphthalein end point with standard 0.1 *N* NaOH (no blank was necessary). The value reported is an average with three samples. [f] Addition of water (50 ml) and cooling required to initiate precipitation. [g] The chromagram sheet was let stand for 10 min in $CHCl_3$ saturated with HCl prior to use. [h] Reaction mixture evaporated to dryness and residue recrystallized from EtOH–H_2O below 25°. [i] After one recrystallization from EtOH–H_2O below 25°. [j] Cysteine hydrochloride dihydrate was used, but **13** precipitated; see text. Recrystallization from H_2O (100°) did not alter the properties of **13**. [k] Sparing solubility led to meaningless results. [l] Formol technique; see Experimental Section. [m] After crude product had been washed with acetone (100 ml). [n] Ether (800 ml) added to initiate precipitation. [o] Recrystallized from H_2O (100°). [p] Brinkman MN Polygram (polyamide) was used, developed with MeOH containing 0.5 %HCO_2H; spots observed under uv light. [q] Calcd for $^1/_2H_2O$: 2.94%. Found: 4.26%, probably because of slight hygroscopicity. [r] Clear reaction solution concentrated to 0.25 vol to induce precipitation.

more convenient;[12] the yield of about 92% compares favorably with about 91% obtained using chlorine.

Typical classes of *o*-carboxyphenyl disulfides (**5–15**), shown in eq 1 and Table I, then were prepared in 95% ethanol without base (procedure A), or in ethanol–buffer (procedure B). In most instances procedure A was preferred. With compounds **13–15**, Table I shows that procedure B is not essential; it was included for biologically significant compounds with which it might be crucial. Although thiolsulfonate **4** is quite stable as a solid, it decomposes slowly in ethanol or buffer solution with precipitation of the disulfide **3**; this instability should be of little concern, ordinarily, since the low content of *o*-carboxyphenyl disulfide (**3**) in the products shows that the rate of thioarylation must compare favorably with that of decomposition of **4**.[13]

The reaction in eq 1 was general for a wide variety of types of thiols (eq 1 and Table I). Compounds **5–15** were obtained in crude yields of 55–100% and usually became virtually analytically pure after one recrystallization.

Primary aliphatic thiols such as ethanethiol, 1-propanethiol, 1-butanethiol, and even the long-chained 1-dodecanethiol gave disulfides with attractive properties (**6–9**, respectively; Table I). The nearly odorless disulfides formed quickly at room temperature. The three homologs **6–8** were prepared to test differences in melting points of homologs. The melts of **7** and **8** remained cloudy up to about 220°; for **7**, this fact and the broad melting range (Table I) were shown to be caused by disproportionation at about the melting point by isolating the symmetrical disulfides. The differences in melting points of these homologs suggest considerable promise in use of *o*-carboxyphenyl disulfides for characterization (*vide infra*). Sodium salts of disulfides **6** and **7** have been reported, but details were unavailable to us.[14]

Secondary and tertiary alkanethiols, *trans*-2-chlorocyclohexanethiol, and 2-methyl-2-propanethiol gave disulfides **10** and **11** without difficulty or indication of reduced rate; the products were easier to purify than some from the primary thiols; and there was no indication of disproportionation at the melting point.

Similarly, the heterocyclic thiol 2-mercaptobenzothiazole (**16**) gave the disulfide **12** without incident.

The mercapto amino acids L-cysteine, D-penicillamine, and DL-*N*-acetylpenicillamine gave disulfides **13–15**, although the synthesis of **13** had a surprising feature. The reaction of L-cysteine hydrochloride with **4** should have led to the hydrochloride of **13**. Instead, very sparingly soluble material precipitated from either 95% ethanol or buffer–ethanol that contained no halogen. Elemental analysis and neutralization equivalent (formol technique)[15] indicated that **13** is the correct structure. For insight into this unusual precipitation of a free base from its hydrochloride, the hydrochloride

(12) A method developed by J. D. Buckman, M. Bellas, H. K. Kim, and L. Field, *J. Org. Chem.*, **32**, 1626 (1967).

(13) As a measure of the decomposition of **4**, the sparingly soluble disulfide **3** was separated which precipitated under the usual reaction conditions, except for absence of thiol. In 95% ethanol the results for time in hours (% decomposition) were 0.1 (<1), 1 (10), 8 (60), and 24 (94). In 5:2 ethanol–pH7 phosphate buffer, the results were: 0.5 (24), 1 (51), 2 (68), and 10 (96).

(14) H. Sasaki, *Igaku Kenkyu*, **27**, 2679 (1957) [through indexes to *Chem. Abstr.*, **52**, 11266 (1958); the compounds are not mentioned in the abstract itself].

(15) R. H. A. Plimmer, "Practical Organic and Bio-chemistry," Longmans, Green and Co., London, 1918, p 145 (*cf.* Experimental Section).

of **13** was prepared by dissolving **13** in *dry* methanol containing dry hydrogen chloride and evaporating the solvent (**13** itself is insoluble in dry methanol alone). When this product was shaken with water **13** precipitated, and titration with alkali showed that 103% of the theoretical amount of hydrochloric acid remained in the water. The extremely low solubility of **13** may be a factor in this precipitation from its salt. Disulfides **14** and **15** behaved as one would expect.

Latentiation of mercaptoethylamine with moiety **1** led to *o*-(2-protoaminoethyldithio)benzoate (**17**),[16] which gave "good" protection against radiation;[5,16b] **17** has since shown activity as an antiinflammatory drug.[17] Disulfides **13**–**15** will be tested as antiradiation and antiinflammatory drugs, but penicillamine is of special interest to us because of its use in rheumatoid arthritis; unfortunately, its use often leads to problems of toxicity.[20] Latentiation with the moiety **1** to give **14** might lead to a more active or less toxic counterpart. The acetyl derivative **15** had no effect on the skin-tensile strength of rats,[21] but acetylpenicillamine does not affect collagen in the skin of rats.[22a] Disulfide **14** had virtually the same effect in reducing skin tensile strength (54–59% of the tensile strength of a control) as penicillamine (54%).[22b]

For assurance as to the structures of **5**–**15**, a typical disulfide was synthesized independently. The reaction of *o*-mercaptobenzoic acid (**2**) with ethyl ethanethiolsulfonate gave **6** in 83% yield (eq 2). Further structural

$$\underset{\mathbf{2}}{o\text{-}HO_2CC_6H_4SH} + EtSO_2SEt \longrightarrow \underset{\mathbf{6}}{o\text{-}HO_2CC_6H_4SSEt} + EtSO_2H \quad (2)$$

evidence was provided by neutralization equivalents (Table I) and ir spectra. In common with past experience,[23] the ir spectra are not merely summations of those of the two symmetrical disulfides, although they usually resemble a summation. Not only are some bands in the symmetrical disulfides absent in the unsymmetrical one, but bands present in neither symmetrical one appear. The most characteristic ir bands are at 1670, 1300–1250, 900, 740, 690, and 650 cm^{-1}, although in **13**–**15** some were shifted somewhat. All of the disulfides were too sparingly soluble for good nmr spectra.

Disproportionation conceivably could become troublesome with disulfides resembling **5**–**15** (eq 3). Fortunately, disproportionation usually can be recognized easily in four ways. (1) The disulfide **3** is so sparingly soluble that it generally remains as a readily recognizable residue upon recrystallization (a feature which aids purification, as does the fact that RSSR usually either fails to dissolve or remains in solution if it does dissolve). (2) The other disulfide (RSSR), unless it has a carboxyl group, will be evident when the unsymmetrical one is dissolved in dilute aqueous base, as when the neutralization equivalent is determined. (3) Melting point depression usually is clear if there is contamination by either symmetrical disulfide. (4) Tlc results in **3** left at the origin if much **3** is present. Thus, with **10** and **11** presence of as little as 1% of **3** is apparent by tlc. None of the disulfides **5**–**15** showed presence of **3** by tlc after one or two recrystallizations, and all gave single spots except **13**, which was too sparingly soluble for tlc (Table I); in eight instances, disulfides corresponding to RSSR were done simultaneously and were reasonably distant from the tlc spot reported in Table I. Some tendency to disproportionate in tlc was observed with **6** and **7** (9:1 chloroform–ethanol; three spots were seen); this behavior was circumvented by prior washing of the tlc sheet with chloroform containing dry hydrogen chloride.

$$2\underset{\mathbf{3}}{o\text{-}HO_2CC_6H_4SSR} \longrightarrow (o\text{-}HO_2CC_6H_4S)_2 + RSSR \quad (3)$$

Under most circumstances, the *o*-carboxyphenyl disulfides studied resist disproportionation in solution well. For example, **5** was recovered in 96–98% yield after 21–119 hr at 100° in H_2O, 1,4-dioxane, or AcOH; that it then contained negligible **3** was shown by tlc and melting point.

The sodium salt of **5** in water, on the other hand, disproportionated completely in 1 hr at 68° and to the extent of 13% in 20 hr at about 25° (25% in ambient light). This unusual behavior of the *salt* is more a virtue than a blemish. It furnishes a useful means for recovery of a thiol as its symmetrical disulfide. Thus **5** gave phenyl disulfide in 96% yield after 5 min with *ca.* 12 equiv (to accelerate disproportionation) of aqueous alkali at *ca.* 25°; the symmetrical disulfide **3** was recovered in 98% yield by acidification. Although aryl disulfides undergo decomposition to sulfinic acids and thiols in the presence of base,[24] no such behavior was apparent with **5**, in conformity with observations that the disulfide **3** is by far the least reactive of the dithiodibenzoic acids in alkaline solution.[25] Symmetrical disulfides often afford a convenient means of storing thiols; they can be used in a wide variety of reactions without reconversion to the thiol.

Although conversion of an *o*-carboxyphenylthio derivative to the symmetrical disulfide should prove useful, regeneration of the thiol by reduction should be more so. In establishing the feasibility of mild reductions, the benzothiazolyl disulfide **12** was used as a model because 2-mercaptobenzothiazole (**16**) is easily isolated. Sodium borohydride (**18**), which has been used for reduction of disulfides,[26] reduced **12** in either 1,4-dioxane or dilute aqueous alkali to the thiol **16** in 82–85% yield (eq 4).

$$\underset{\mathbf{12}}{o\text{-}HO_2CC_6H_4SSC_7H_4NS} \xrightarrow[\text{DTT (19)}]{NaBH_4\ (18)\ \text{or}} \underset{\mathbf{16}}{HSC_7H_4NS} + 2 \quad (4)$$

(16) (a) Nomenclature suggested by F. Y. Wiselogle. See F. G. Bordwell, M. L. Peterson, and C. S. Rondestvedt, Jr., *J. Amer. Chem. Soc.*, **76**, 3945 (1954). (b) *Cf.* L. Field and P. M. Giles, Jr., *J. Med. Chem.*, **13**, 317 (1970).

(17) We are indebted to Drs. N. G. Brink and C. G. Van Arman of the Merck Sharp and Dohme Research Laboratories for the following unpublished results: Carrageenin foot-edema assay,[18] 10 mg/kg (32%), 30 mg/kg (40%); adjuvant arthritis,[19] inactive at 50 mg/kg.

(18) Procedure of C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962); responses to standard agents are reported.

(19) Procedure of H. C. Stoerk, T. C. Bielinski, and T. Budzilovich, *Amer. J. Pathol.*, **30**, 616 (1954).

(20) I. A. Jaffe, *Arthritis Rheum.*, **8**, 1064 (1965).

(21) We are indebted to Dr. I. A. Jaffe, of the New York Medical College and Flower and Fifth Avenue Hospitals (New York, N. Y.), for these tests using means referred to previously.[4]

(22) (a) M. E. Nimni, K. Deshmukh, N. Gerth, and L. A. Bavetta, *Biochem. Pharmacol.*, **18**, 707 (1969); (b) I. A. Jaffe, P. Merryman, and D. Jacobus, *Science*, **161**, 1016 (1968).

(23) *Cf.* ref 6.

(24) R. Schiller and R. Otto, *Ber.*, **9**, 1637 (1876).

(25) (a) S. Smiles and J. Stewart, *J. Chem. Soc.*, **119**, 1792 (1921); (b) S. Smiles and D. C. Harrison, *ibid.*, **121**, 2022 (1922); (c) J. P. Danehy and K. N. Parameswaran, *J. Org. Chem.*, **33**, 568 (1968).

(26) (a) C. R. Stahl and S. Siggia, *Anal. Chem.*, **29**, 154 (1957); (b) W. D. Brown, *Biochim. Biophys. Acta*, **44**, 365 (1960).

The *o*-mercaptobenzoic acid (**2**) also formed was removed easily by washing with aqueous sodium bicarbonate. Dithiothreitol (**19**, Cleland's reagent, DTT) also is a mild elegant reductant,[27] a particularly popular one for sensitive systems. One molar proportion of **19** reduced one of **12** to the thiol **16** in 35% yield. Since the reduction by **19** presumably is an equilibrium process, use of a larger excess of **19** (which is costly, however) should increase the yield of **16**; this trend is reflected by an increase in the yield of **16** to 66% with use of 2 molar proportions of **19**.

The ease of preparing, purifying and characterizing *o*-carboxyphenyl disulfides, then of conversion to a desired disulfide or thiol, suggests several uses other than latentiation. One use is for the characterization of thiols for which few good means are available. Some common derivatives, such as mercuric mercaptides, nitro thiol esters, α-anthraquinone sulfides, *p*-nitrophenyl sulfones, and 2,4-dinitrophenyl sulfides or sulfones, often exhibit unsatisfactory melting points or have a small range of melting points,[28a] although *N*,*N*-diphenylthiocarbamates seem promising.[28b] Some are not applicable to thiols which contain other functional groups. *o*-Carboxyphenyl disulfides generally not only lack these shortcomings but have several features which further enhance their value (*cf.* Table I). (1) They are easy to prepare and purify from **4**, a cheap, readily accessible reagent. (2) The carboxyl group permits determination of the neutralization equivalent and is valuable for isolation and purification. (3) The tlc R_f values vary considerably. (4) The melting points fall in a desirable temperature range, are usually rather well separated and differ even for homologs (*i.e.*, **6**–**8**). (5) A thiol can be either regenerated or recovered directly as its disulfide.

Another attractive use (not verified experimentally) would seem to be in the resolution of thiols. Conversion of a thiol to its disulfide by eq 1 could be followed by resolution with optically active amines, regeneration of the *o*-carboxyphenyl disulfide from its salt, and conversion of the unsymmetrical disulfide to the optical active thiol or disulfide.

A third possible application was attractive, that of using eq 1 for analysis or reversible "blocking" of the sulfhydryl (–SH) moieties of proteins.[29] Creatine kinase, an enzyme, after reaction with **4** showed total loss of enzymatic activity, indicating conversion of –SH to disulfide. No distinctive uv absorption useful for analysis of –SH was observed. Ellman's reagent reacted with creatine kinase more rapidly;[30] the reaction could be followed by uv absorption. Reduction of either inactivated product with excess **19** gave a 95–100% recovery of enzymatic activity, indicating regeneration of –SH. The thiolsulfonate **4** seems rather unpromising for assay of –SH and seems to have no advantage over Ellman's reagent for reversible blocking, unless its slower reaction could provide greater selectivity for different –SH groups, or unless its lack of color makes it useful in masking SH where the color from Ellman's reagent might interfere with other colored reagents.

Experimental Section[31]

Materials.—*o*-Mercaptobenzoic acid (**2**, Aldrich Chemical Co.) was dissolved in 95% EtOH at *ca.* 60°, treated with decolorizing carbon, and filtered while hot. Water was added to incipient turbidity. Cooling and filtration gave fine yellow crystals having mp 165–166° (lit.[32] mp 163–164°). *trans*-2-Chlorocyclohexanethiol[33] had bp 95° (30 mm) and $n^{26}D$ 1.4986 [lit.[33a] bp 83° (20 mm); $n^{20}D$ 1.5015]. Ethyl ethanethiolsulfonate was kindly provided by Dr. Michael Bellas.[12] All other reagents were used as purchased.

Preparation of *o*-Carboxyphenyl *o*-Carboxybenzenethiolsulfonate (4). A. Using Cl_2.—In an improvement of earlier procedures,[5,6] Cl_2 (20.9 g, 13.5 ml, ~0.3 mol) was condensed and then introduced slowly (1 hr) into a stirred mixture of the thiol **2** (30.2 g, 0.196 mol) and AcOH (5.6 ml, ~0.1 mol) in CH_2Cl_2 (110 ml) at −2° to +2°. Moisture was carefully excluded from the system by means of drying tubes containing $CaCl_2$. The suspension was stirred (20 min) at −2° to +2°, after which H_2O (3.6 ml, 0.2 mol) was added slowly (15 min). After 16 hr at *ca.* 25°, crude **4** was separated by filtration, washed with cold H_2O (200 ml), and dried under reduced pressure: yield of **4**, 30.2 g (91%); mp 200–210° dec. The **4** was taken up in 95% EtOH (*ca.* 1 g/10 ml) at *ca.* 25° and filtered. Water was added to incipient turbidity. Cooling (*ca.* 0°) and filtration gave **4** as a tan powder (25.6 g, 77%), mp 220–225° dec, unchanged by further crystallization (lit. mp 218–222° dec,[5] 215–223° dec).[6]

Anal. Calcd for $C_{14}H_{10}O_6S_2$: C, 49.69; H, 2.98; S, 18.95. Found: C, 49.58; H, 3.37; S, 18.86.

Thin layer chromatography of compound **4** on Brinkmann MN Polygram Sheet (polyamide) developed with MeOH containing 0.5% HCO_2H showed only one spot under uv light (R_f 0.20). The **4** thus obtained was identical (ir) with authentic **4**.[5] A sample of **4** was unchanged (ir, mp) after 5 years.

B. Using SO_2Cl_2.—In a procedure resembling one reported,[12] SO_2Cl_2 (81.00 g, 0.60 mol) was added slowly (1.5 hr) to a rapidly stirred solution of the thiol **2** (61.68 g, 0.40 mol) and AcOH (12.00 g, 0.20 mol) in CH_2Cl_2 (400 ml) at −2° to −2°. The reaction mixture was allowed to warm (during *ca.* 1 hr) to *ca.* 25°. Heating (40°, 3 hr) then resulted in evolution of copious amounts of gas. Water (7.30 g, 0.41 mol) was added slowly (0.5 hr) and heating was continued for 5 hr more. Tan solid was separated, washed first with cold H_2O (400 ml) and then with cold CH_2Cl_2 (100 ml), and then dried to give **4**, 62.38 g (92%), mp 210–216° dec. Thiolsulfonate **4** at this point was nearly always satisfactory for preparing **5**–**15**, even though the melting point was occasionally 200–220° dec. Unsuitability, suggesting the recrystallization described next, was determined easily by a significant residue of **3** when the 10% solution of **4** used for such preparations was prepared in EtOH. Recrystallization of a 10-g sample from aqueous EtOH as above gave 8.4 g (84%) of **4** having mp and mmp 220–224° dec, identical (ir) with authentic **4**.[5]

Longer reaction times without heating gave **4** in only 30% yield, mp 220–222° dec.

Synthesis of *o*-Carboxyphenyl Disulfides 5–15 *via* Eq 1.—Except for variations noted in Table I, procedures A and B were as illustrated below.

Procedure A. *o*-Carboxyphenyl Phenyl Disulfide (5).—Thiophenol (1.65 g, 15 mmol, often in a little EtOH) was added to a stirred solution of **4** (5.06 g, 15 mmol) in 95% EtOH (50 ml). Precipitation of **5** began in *ca.* 5 min. Filtration after 3 hr gave **5** (3.00 g, 76%), mp 190–195° dec. A second crop was collected (0.36 g, 9%), mp 190–195° dec. The crude **5** (1 g) was dissolved in EtOH (50 ml) at *ca.* 25°, and water was added to incipient

(27) W. W. Cleland, *Biochemistry*, **3**, 480 (1964).

(28) (a) E. E. Reid, "Organic Chemistry of Bivalent Sulfur," Vol. I, Chemical Publishing Co., New York, N. Y., 1958, p 162; (b) R. G. Hiskey, F. I. Carroll, R. F. Smith, and R. T. Corbett, *J. Org. Chem.*, **26**, 4756 (1961).

(29) We are much indebted to Dr. L. W. Cunningham and Dr. C. S. Brown for these unpublished results and for their gracious permission to summarize them here. The Ph.D. Dissertation of C. S. B., Vanderbilt University, Jan 1970, may be consulted for details.

(30) 5,5′-Dithiobis(2-nitrobenzoic acid); see G. L. Ellman, *Arch. Biochem. Biophys.*, **82**, 70 (1959).

(31) Melting points are corrected. Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Ir spectra were done using a Beckman Model IR-10 with KBr pellets of all samples; s signifies a strong absorption band (others reported were medium). Unless otherwise stated, reactions were carried out at room temperature. Solvents were removed under reduced pressure with a rotary evaporator.

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

(33) (a) Prepared according to C. C. J. Culvenor, W. Davies, and N. S. Heath, *J. Chem. Soc.*, 282 (1949); (b) E. E. van Tamelen, *J. Amer. Chem. Soc.*, **73**, 3444 (1951), reported that the product obtained is the trans isomer.

turbidity. Cooling and filtration gave 0.87 g (87% recovery, 74% yield) of **5** as fine white crystals having mp 197–198.5° dec; ir (KBr) 3200–2500, 1670 (s), 1420, 1320, 1280, 1260, 900, 740, 690, and 650 cm^{-1}.

D-Penicillamine did not dissolve quickly in the reaction medium, but finely ground penicillamine did so during a long reaction period of 18 hr. Ether then was added to the clear solution to effect precipitation. Disulfide **14** had $[\alpha]^{25}D$ +181° (*c* 1 in glacial acetic acid).

Procedure B. DL-*o*-(1,1-Dimethyl-2-carboxy-2-acetamidoethyldithio)benzoic Acid (15).—DL-*N*-Acetylpenicillamine (1.91 g, 10 mmol) was suspended in commercial phosphate buffer (pH 7, 0.2 *M*, 20 ml), and the mixture was added to a stirred solution of **4** (3.38 g, 10 mmol) in 95% EtOH (50 ml). After 1 hr, the heterogeneous reaction mixture was cooled, and the **15** was removed by filtration, yield 3.28 g (96%), mp 200–205° dec. Recrystallization from MeOH–H_2O gave material having mp 208–209° dec; ir (KBr) 3360, 3200–2300, 1695 (s), 1625, 1540, 1250 (s), 900, and 740 cm^{-1}.

The formol titration technique[15] is illustrated for disulfide **13**. Commercial formalin (10 ml) was diluted with H_2O (20 ml) and neutralized with 0.1 *N* NaOH using phenolphthalein as an indicator. This neutral formalin was added to a suspension of **13** (0.2133 g, 0.78 mmol) in 95% EtOH (10 ml). Titration with NaOH (0.0994 *N*, 15.40 ml) indicated a neutralization equivalent of 139 (calcd, 137).

Comparative Syntheses of 5 by Other Means. A. *Via* **o-Carboxybenzenesulfenyl Chloride.**—Chlorine (7.09 g, 4.58 ml, 0.10 mol) was condensed (Dry Ice) and then was added slowly (0.5 hr) to a stirred suspension of **2** (15.42 g, 0.10 mol) in CH_2Cl_2 (55 ml) at *ca.* 0°. After 10 min more at 0°, PhSH (11.01 g, 0.10 mol) was added slowly (15 min). The reaction mixture was allowed to warm to *ca.* 25°, and the solvent was removed under reduced pressure. Recrystallization of crude **5** from EtOH–H_2O as before gave **5** (12.5 g, 48%) with mp 190–198° dec, identical with authentic **5** by ir.

B. *Via* **o-Carboxybenzenesulfenyl Thiocyanate** (*Cf.* **Ref 8**).—The thiol **2** (1.54 g, 10 mmol) in Et_2O (50 ml) was added slowly (1 hr) to a stirred solution of $(SCN)_2$ (1.33 g, 11 mmol) in Et_2O (55 ml) at *ca.* 0°. After 1 hr, PhSH (1.10 g, 10 mmol) in Et_2O (10 ml) was added rapidly. The solution was stirred for 10 min more at *ca.* 0° and for 3 hr at *ca.* 25°. The Et_2O solution was washed with H_2O until colorless and then dried ($MgSO_4$). The Et_2O was removed to give crude **5**; the ir was similar to (but not identical with) that of authentic **5**. Recrystallization as usual gave 0.95 g (36%) of **5** having a broad melting point of 145–180° dec. It might be added that, although the use of excess $(SCN)_2$ is standard,[8] use of smaller amounts might be advantageous here.

Independent Synthesis of o-Carboxyphenyl Ethyl Disulfide (6).—Ethyl ethanethiolsulfonate (1.54 g, 10 mmol) and **2** (1.54 g, 10 mmol) were stirred (1 hr) at *ca.* 25° in 95% EtOH (50 ml). Addition of H_2O (50 ml) and cooling gave 1.78 g (83%) of **6**, mp 125–128°. Recrystallization from MeOH–H_2O as usual gave 1.60 g (75%) of **6**, mp and mmp 129–130°, ir identical with that of **6** synthesized by procedure A.

Reactions of o-Carboxyphenyl Disulfides. A. Disproportionation.—Carefully weighed samples of **5** (*ca.* 1 mmol) were dissolved in 10 ml of solvent (see Table II) in 15-ml ampoules. The ampoules were wrapped with aluminum foil to protect the contents from light. They were immersed to their necks in an oil bath and were maintained at 25, 68, or 100° for the designated time intervals. The ampoules then were withdrawn and chilled in ice. The extent of disproportionation was determined either by isolating phenyl disulfide which was formed, or by recovering disulfide **5**. The phenyl disulfide, isolated by filtration from all experiments involving the sodium salt of **5** in H_2O, was washed with H_2O (100 ml) and carefully dried (identity established by melting point and tlc). In all other instances the solvent was removed under reduced pressure and phenyl disulfide was separated by washing the residue with hexane (100 ml). The recovered **5** (hexane insoluble) was identical with authentic material (ir, melting point). "Disproportionation, %" was calculated as usual;[34] the results are given in Table II.

TABLE II

DISPROPORTIONATION OF 5 OR OF ITS SALT

Time, hr	Temp, °C	Solvent	%[a]
20	25	H_2O[b]	13
25	25	H_2O[b]	25[c]
79	25	H_2O[b]	69
0.25	68	H_2O[b]	42
0.75	68	H_2O[b]	83
1.00	68	H_2O[b]	100
0.1	25	H_2O[d]	96[e,f]
24	100	1,4-Dioxane	<3[f]
119	100	AcOH	<2[f]
21	100	H_2O[g]	<4[f]
24	25	95% EtOH	0[f]

[a] Disproportionation, %; see ref 34. [b] Containing 1 molar proportion of NaOH. [c] Exposed to ambient light. [d] Containing 12 *M* proportions of NaOH. [e] 98% of the theoretical amount of disulfide **3** also was recovered. [f] Determined by isolation of disulfide **5**. [g] Sample did not dissolve even at 100°. The **5** was completely dissolved in all the other experiments reported in Table II.

B. Reduction with $NaBH_4$ (**18**).—A solution of **18** (0.67 g, 17.70 mmol) and disulfide **12** (1.14 g, 3.57 mmol) in dry 1,4-dioxane (50 ml) was warmed on a steam bath for 3 hr. The solution then was acidified carefully (pH 1, 10% HCl). After filtration to remove solids, the solvent was removed under reduced pressure. The solid residue was rubbed with 5% $NaHCO_3$ (100 ml) and H_2O (50 ml) and then dried to give 0.49 g (82%) of yellow crystalline **16**, mp and mmp 180–181°, ir identical with that of authentic **16**.

A similar reaction using 0.1 *N* aqueous NaOH as the solvent gave **16** in 85% yield, identified by melting point and ir.

C. Reduction with Dithiothreitol (**19**).—A solution of disulfide **12** (0.32 g, 1.0 mmol) and **19** (0.31 g, 2.0 mmol) in pH 10 buffer (0.2 *M* carbonate, 20 ml) was stirred for 20 min. Acidification to pH 1 (concentrated HCl) and cooling gave yellow **16**, which was separated and washed with 5% $NaHCO_3$ (100 ml) and H_2O (50 ml). The residue of crude **16** (0.16 g, 96%; mp 160–165°) was recrystallized from EtOH–H_2O to give 0.11 g (66%) of **16**, identified by ir, mp and mmp 180–181°.

When 1.0 mmol of **19** was used, 0.06 g (35%) of **16** was recovered, identified by melting point and ir.

Registry No.—**4**, 1906-41-8; **5**, 26929-62-4; **6**, 26929-63-5; **7**, 26893-47-0; **8**, 26893-48-1; **9**, 26893-49-2; **10**, 26885-61-0; **11**, 26893-50-5; **12**, 26893-51-6; **13**, 26885-62-1; **14**, 26885-63-2; **15**, 26885-64-3.

(34) L. Field, T. C. Owen, R. R. Crenshaw, and A. W. Bryan, *J. Amer. Chem. Soc.*, **83**, 4414 (1931).

The Reaction of Monohalonaphthalenes with Potassium *tert*-Butoxide and *tert*-Butyl Alcohol in Dimethyl Sulfoxide[1a]

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The reaction of monoiodo-, monochloro-, and monofluoronaphthalenes with potassium *tert*-butoxide in a *tert*-butyl alcohol–dimethyl sulfoxide medium at 140° has been examined; the results are compared to the reaction of the monobromonaphthalenes under the same conditions. The major products observed in the bromo-, iodo-, and chloronaphthalene reactions were 1- and 2-*tert*-butyl naphthyl ethers (IV and V), 1- and 2-naphthols (XIII and XIV), and 1-methylmercapto-2-naphthol (XI). Other products were found in minor yields. The mole per cent ratio of 1-substituted products (IV and XIII) to 2-substituted products (V and XIV) was found to be 0.35 ± 0.03 in every case suggesting that 1,2-dehydronaphthalene is an intermediate in each of these reactions. The fluoronaphthalenes were found to undergo only direct nucleophilic substitution with no formation of 1,2-dehydronaphthalene. The order of addition of potassium *tert*-butoxide and *tert*-butyl alcohol to DMSO seems to be critical in this reaction. When *tert*-butoxide is added first, the major products are not compounds IV, V, XI, XIII, and XIV, but are 1- and 2-methylthionaphthalene (XV and XVI).

Bromobenzene is known to react with potassium *tert*-butoxide to form *tert*-butyl phenyl ether by way of an aryne mechanism.[2-4] In another paper,[5] we report the reaction of 1- and 2-bromonaphthalene with potassium *tert*-butoxide in a *tert*-butyl alcohol–dimethyl sulfoxide mixture.[6] We found that the major products formed in this reaction were 1- and 2-*tert*-butyl naphthyl ethers (IV and V), 1- and 2-naphthols (XIII and XIV), and 1-methylmercapto-2-naphthol (XI). Ten other identifiable products were also observed. The reaction was studied under a variety of conditions and it was found that the ethers were formed in higher yields when less base concentration, lower temperature, and shorter reaction times were used. This was a result of the base-catalyzed decomposition of the ethers to give the corresponding naphthols and isobutylene under the reaction conditions. Maximum yields of the ethers were obtained at 80° with a molar ratio of 1:2:3:15 for the following reactants: bromonaphthalene–potassium *tert*-butoxide–*tert*-butyl alcohol–DMSO.[5] The mole per cent ratio of 1-substituted products to 2-substituted products was found to be 0.36 ± 0.02 under all conditions except when the initial concentration of base was greatly reduced or when the initial concentration of alcohol was eliminated. The fact that this ratio was obtained with both 1- and 2-bromonaphthalene indicated that 1,2-dehydronaphthalene was an intermediate in that reaction.[5]

We now report on the reaction of 1- and 2-iodo-, -chloro-, and -fluoronaphthalenes with potassium *tert*-butoxide in a *tert*-butyl alcohol–DMSO solvent mixture and compare the results found with those of the bromonaphthalene reaction.[5] The iodo- and chloronaphthalene reactions were found to be very similar to the bromonaphthalene reactions. However, the fluoronaphthalene reactions were found to proceed by way of direct nucleophilic substitution rather than the aryne mechanism.

Results

The halonaphthalene was rapidly added to the potassium *tert*-butoxide–*tert*-butyl alcohol–DMSO mixture maintained at 140°. The 1-halonaphthalene compounds were added as the neat liquids while a DMSO solution of the solid 2-halonaphthalene compounds was used. The reactions with the bromo- and iodonaphthalenes were more exothermic than those with the chloro- and fluoronaphthalenes. After 8 min, the reaction mixture was added to water and the neutral products (I–X in Scheme I) and acidic products (XI–XIV in Scheme I) were separated by extraction with ether and analyzed by vapor phase chromatography (vpc) as described previously.[5]

The results of the various runs are shown in Table I. Runs 1 and 2 are from ref 5 and are reproduced here to compare with runs 3–9. Although our previous work[5] showed that the conditions for maximum yield of the *tert*-butyl naphthyl ethers (IV and V) from 1-bromonaphthalene was at 80°, an initial reaction of 1-chloronaphthalene at 80° showed only a trace of ether formation. Therefore, all runs were made at 140° for comparison purposes. Even at this temperature only an 86% conversion was observed for the chloronaphthalenes with a lower conversion taking place for the fluoronaphthalenes.

Table I shows that a particular set of reaction conditions which maximize the yield of ethers (IV + V) over naphthols (XIII + XIV) produced from one halonaphthalene do not show the same result with other halonaphthalenes (compare runs 1–4 with 5–9). The formation of naphthols XIII and XIV is presumed in each case to be from the base-catalyzed decomposition of ethers IV and V.[5]

All products I–XIV (Scheme 1) were identified as described previously.[5] In addition to these, two additional products were observed in the 1-chloronaphthalene reaction (run 6). They were identified as 1-methylthionaphthalene (XV), 1.0%, and 2-methylthionaphthalene (XVI), 0.5%, from their nmr spectra, which matched exactly those given by Zweig and coworkers,[8] and from their ir spectra which were consis-

(1) (a) Nuclear magnetic resonance spectra were obtained on a Varian A-60A spectrometer purchased under the National Science Foundation Grant GP-6837. (b) National Defense Education Act Fellow, 1967–1970. (c) To whom inquiries should be addressed.

(2) D. J. Cram, R. Rickborn, and G. R. Knox, *J. Amer. Chem. Soc.*, **82**, 6412 (1960).

(3) J. I. G. Cadogan, J. K. A. Hall, and J. T. Sharp, *J. Chem. Soc. C*, 1860 (1967).

(4) M. Kise, T. Asari, N. Furukawa, and S. Oae, *Chem. Ind. (London)*, 276 (1967).

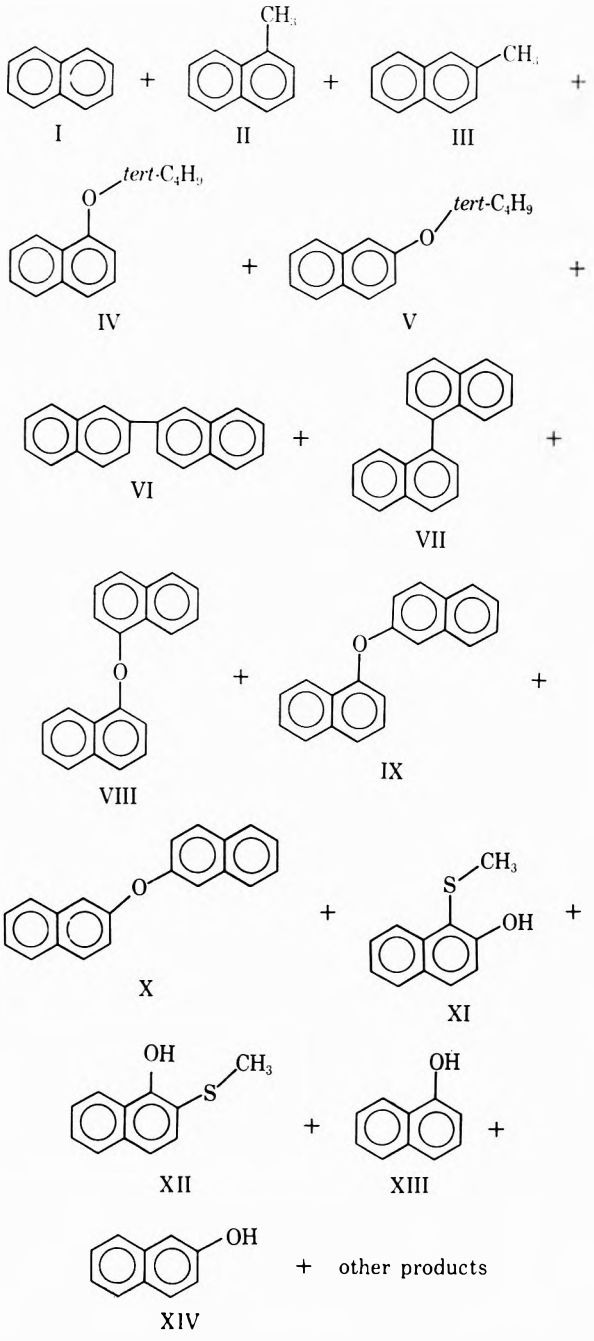
(5) J. S. Bradshaw and R. H. Hales, *J. Org. Chem.*, **36**, 318 (1971).

(6) We used the procedure of Sahyun and Cram.[7]

(7) M. R. V. Sahyun and D. J. Cram, *Org. Syn.*, **45**, 89 (1965).

(8) A. Zweig, J. E. Lancaster, and M. T. Neglia, *Tetrahedron*, **23**, 2577 (1967).

SCHEME I



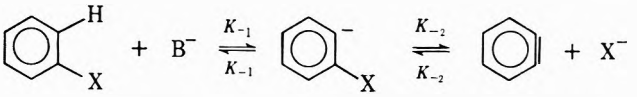
tent with these structures. In addition, compound XV was found to be identical with 1-methylthionaphthalene which was isolated from the reaction of methylsulfinyl carbanion with 1-bromonaphthalene.[5] Compounds XV and XVI were not noticed in any other run except run 7 where only trace amounts were formed. However, in a preliminary run with 1-chloronaphthalene, greater yields of compounds XV and XVI were produced (6.4 and 2.9%, respectively) while only small amounts of ethers IV and V (total 1.6%) and naphthols XIII and XIV (total 9.4%) were formed.

Upon examination of the experimental procedure of these two experiments (run 6, Table I, and the preliminary 1-chloro run), it was determined that both reactions were run exactly the same except for one point. In the preliminary run, the potassium *tert*-butoxide was added to hot DMSO. After the *tert*-butoxide dissolved, the *tert*-butyl alcohol was added and the temperature raised to 140°. In run 6 (Table I), the *tert*-butyl alcohol was added first to the hot DMSO followed by addition of potassium *tert*-butoxide. When both the 1-bromonaphthalene and 2-iodonaphthalene experiments were repeated with potassium *tert*-butoxide being added *before* *tert*-butyl alcohol, similar results were found in that the major neutral fraction products were compounds XV and XVI.

Discussion

The mole per cent ratio of 1-substituted products (IV and XIII) to 2-substituted products (V and XIV) of 0.36 ± 0.02 found previously[5] for 1-bromonaphthalene under a variety of conditions indicated that these products were being formed through a 1,2-dehydronaphthalene intermediate. The fact that a ratio of 0.34 was found for 2-bromonaphthalene at 80° confirmed this deduction.[5] From Table II we see that the mole per cent ratio of 1-substituted products to 2-substituted products at 140° is 0.35 ± 0.03 for not only the 1- and 2-bromonaphthalene reactions, but also for the 1- and 2-iodonaphthalene and 1- and 2-chloronaphthalene reactions as well. This value is within experimental error of that obtained previously[5] and would indicate that 1,2-dehydronaphthalene is indeed an intermediate in the reaction of the monohalonaphthalenes with potassium *tert*-butoxide in a *tert*-butyl alcohol–DMSO medium when the halogen is either chlorine, bromine, or iodine.

The fact that the bromo- and iodonaphthalenes are more reactive than the chloronaphthalenes under our experimental conditions (100% conversion compared to 86% conversion) is to be expected in view of the mechanism proposed for the generation of dehydrobenzene from aryl halides.[5,9] In the simplified representation shown below for the formation of dehydrobenzene from



an aryl halide by means of the 2-halophenyl anion, the order of reactivity in K_1 should be F > Cl > Br > I, because the removal of the ortho hydrogen would be enhanced by the increased electronegative properties in going from iodine to fluorine. The order of reactivity for K_2, however, is known to be I > Br > Cl > F.[10] Step 1 is normally assumed to be the rate-determining step due to the extreme instability of the 2-halophenyl anion. However, as soon as step 1 becomes reversible, *e.g.*, when operating in a protic medium, the ratio $K_2/(K_2 + K_{-1}[BH])$ codetermines the rate.[11] When $K_2 < K_{-1}[BH]$, K_2 may become rate determining. For the amination of aryl halides in liquid ammonia the two opposing halogen reactivity sequences for K_1 and K_2 are superimposed[12] and the resulting order of reactivity of halobenzenes and 3-halotoluenes were found to be C_6H_5Br–C_6H_5I–C_6H_5Cl = 20:8:1[13] and $CH_3C_6H_4Br$–$CH_3C_6H_4I$–$CH_3C_6H_4Cl$ = 13.5:5:1[14] with the corre-

(9) R. W. Hoffmann "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967, p 58.
(10) Reference 9, p 43.
(11) Reference 9, p 15.
(12) J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr., and L. A. Carlsmith *J. Amer. Chem. Soc.*, **78**, 601 (1956).
(13) F. W. Bergstrom, R. E. Wright, C. Chandler, and W. A. Gilkey, *J. Org. Chem.*, **1**, 170 (1936).
(14) F. W. Bergstrom and C. H. Horning, *ibid.*, **11**, 334 (1946).

TABLE I

RESULTS OF THE REACTION OF 1- AND 2-HALONAPHTHALENE WITH POTASSIUM *tert*-BUTOXIDE IN *tert*-BUTYL ALCOHOL–DMSO AT 140° FOR 8 MIN[a]

			Products[c]						
Run	ArX	Conversion	I	II	III	IV	V	VI	VII
1[b]	1-Br	100	2.3	0.5	0.1	8.5	27.8	0.2	0.2
2[b]	1-Br	100	2.6	0.5	0.1	8.3	28.1	0.2	0.2
3	2-Br	100	1.0	0.4	<0.1	6.2	27.5	0.1	<0.1
4	1-I	100	4.6	0.2	<0.1	8.8	25.5	0.1	0.2
5	2-I	100	2.2	0.1	<0.1	5.6	14.4	0.2	<0.1
6	1-Cl	86.0	6.5	1.5	<0.1	2.1	9.8	0.1	0.3
7	2-Cl	85.6	4.2	1.4	<0.1	1.9	9.1	0.3	0.1
8	1-F	80.3		0.5	<0.1	39.6			
9	2-F	72.8		0.5	<0.1		48.3		

	Products[c]						
Run	VIII	IX	X	XI	XII	XIII	XIV
1	0.8	2.7	2.5	7.4	1.1	4.8	8.5
2	0.8	2.9	2.6	7.7	1.2	5.2	9.7
3	0.8	2.8	2.8	6.1	1.4	6.2	10.6
4	0.8	2.8	2.4	8.6	1.6	2.4	6.2
5	3.0	3.6	3.3	10.6	1.2	6.0	18.1
6	1.1	3.6	2.8	5.6	0.9	6.1	13.9
7	1.6	2.8	2.6	4.7	1.4	5.3	13.4
8						58.3	
9							49.6

[a] Molar ratio of ArX–KO-*tert*-C_4H_9–HO-*tert*-C_4H_9–DMSO is 1:2:3:15 in each case. [b] From ref 5. [c] Mol % yields.

TABLE II

MOLE PER CENT RATIO OF 1-SUBSTITUTED PRODUCTS (IV AND XIII) TO 2-SUBSTITUTED PRODUCTS (V AND XIV)

Run[a]	Mole per cent ratio (IV + XIII/V + XIV)
1	0.37
2	0.36
3	0.33
4	0.35
5	0.36
6	0.35
7	0.32
8	Only 1
9	Only 2

[a] See Table I for reaction conditions and halonaphthalene used.

sponding fluoro compounds being inert. Although a difference between iodonaphthalene and bromonaphthalene could not be observed in our case, chloronaphthalene was much less reactive. This indicates that the presence of *tert*-butyl alcohol in our reaction mixture must have a similar effect in our reaction.

The fact that only *tert*-butyl 1-naphthyl ether and 1-naphthol were found in run 8 (Table I) and *tert*-butyl 2-naphthyl ether and 2-naphthol were found in run 9 (Table I) indicates that only a direct nucleophilic substitution mechanism takes place in the case of the fluoronaphthalenes. Apparently, step 2, in the mechanism shown above, is very much less than -1 when X = F, and the presence of *tert*-butyl alcohol in the reaction mixture reverses the metalation step and enhances the chance for direct substitution. This effect was observed in the reaction of lithium piperidide in ether with both 1-fluoronaphthalene and 1-fluoro-4-methylnaphthalene.[15,16] The mechanism of the reactions was seen to change from complete aryne mechanism to a predominance of nucleophilic substitution as the concentration of piperidine was increased from zero. In our system, the initial *tert*-butyl alcohol is causing only nucleophilic substitution to take place. Cram and coworkers[2] found that the reaction of *o*-fluorotoluene with potassium *tert*-butoxide in DMSO at 100° produced *o*-cresol which contained less than 3% *m*-cresol while *o*-bromotoluene produced a mixture of four parts of *m*-cresol to one part of *o*-cresol. It appears that the reaction of monofluoronaphthalene with potassium *tert*-butoxide in a *tert*-butyl alcohol–DMSO medium is a very good procedure for preparing pure *tert*-butyl 1- and 2-naphthyl ethers. Studies are presently being carried out on the reaction of monofluoronaphthalenes with other alkoxide–alcohol systems, as well as with mercaptide–mercaptan systems, in DMSO to determine the generality of this procedure.

The yields of naphthalene (I, Table I), methylnaphthalenes (II and III), binaphthyls (VI and VII), dinaphthyl ethers (VIII, IX, and X), and methylthionaphthols (XI and XII) were found to be very similar in the iodo- and chloronaphthalene reactions (runs 4–7) as compared to the bromonaphthalene reactions (runs 1–3).[17] Only a small amount of 1- and 2-methylnaphthalenes were found in the fluoronaphthalene runs (run 8 and 9, Table I). The presence of naphthalene in either the fluoronaphthalenes used as starting materials or those recovered from runs 8 and 9 (Table I) could not be determined by vpc analysis because a column could not be found which would separate naphthalene from 1- and 2-fluoronaphthalene. However, an ir spectrum of either the starting materials or the recovered fluoronaphthalenes did not show any naphthalene to be present.

Naphthalene was believed to be produced by the action of methylsulfinyl carbanion on the halonaphthalene to form naphthyl anion.[5,18] The fact that more naphthalene was formed from the reaction of the 1-halonaphthalenes than from that of the 2-halonaphthalenes (compare runs 1, 2, 4, and 6 with 3, 5, and 7, Table I)

(15) J. Sauer, R. Huisgen, and A. Hauser, *Chem. Ber.*, **91**, 1461 (1958).
(16) R. Huisgen, J. Sauer, W. Mack, and I. Ziegler, *ibid.*, **92**, 441 (1959).
(17) For a brief discussion of the mechanism of formation of these products, see ref 5.
(18) J. F. Bunnett and R. R. Victor, *J. Amer. Chem. Soc.*, **90**, 810 (1968).

when the halogen was Cl, Br, or I would lend support for the mechanism which involves an intermediate aryl anion.[5] Shatenshtein has reported that naphthalene underwent a base-catalyzed deuterium exchange reaction in the 1 position more than twice as fast as the 2 position.[19] Similar results were observed in the detritiation of naphthalene.[20] Thus, the 1-naphthyl anion is more stable than the 2 anion.

Apparently, the order of mixing of the solvent, alcohol, and base in these reactions is critical. When the potassium *tert*-butoxide is added first to the hot DMSO followed by addition of the *tert*-butyl alcohol the major neutral fraction products are 1- and 2-methylthionaphthalenes (XV and XVI). The ratio of compound XV to compound XVI under these conditions was 2.21 when 1-chloronaphthalene was used, 1.09 when 1-bromonaphthalene was used, and 0.34 when 2-iodonaphthalene was used. These α/β ratios indicate that compounds XV and XVI are being formed through both a 1,2-dehydronaphthalene and a direct nucleophilic substitution mechanism as was the case with the reactions of potassium *n*-butoxide and *n*-butyl alcohol with monobromonaphthalene.[5] The normal ratio of 1- and 2-substituted products from the 1,2-dehydronaphthalene mechanism is 0.50.[21]

The following mechanism is proposed to account for the above observations.

$$tert\text{-}C_4H_9O^- + CH_3SOCH_3 \rightleftharpoons tert\text{-}C_4H_9OH + CH_3SOCH_2^- \quad (1)$$

$$CH_3SOCH_2^- \longrightarrow CH_2 + CH_3SO^- \quad (2)$$

$$2CH_3SO^- \rightleftharpoons CH_3S^- + CH_3SO_2^- \quad (3)$$

$$CH_3S^- + C_{10}H_8 \xrightarrow{H^+} 1\text{-}CH_3SC_{10}H_7\ (2\text{-}CH_3SC_{10}H_7) \quad (4)$$

$$CH_3S^- + C_{10}H_7X \longrightarrow CH_3SC_{10}H_7 + X^- \quad (5)$$

The reaction of *tert*-butoxide with DMSO to form the methylsulfinyl carbanion (step 1) is amply precedented.[22,23] This step would occur much faster when no *tert*-butyl alcohol was initially present, *i.e.*, when *tert*-butoxide was added to the DMSO first. The thermal decomposition of the methylsulfinyl carbanion at temperatures above 80° in dimethyl sulfoxide has been shown to form the sulfenate ion (step 2) which disproportionates to the corresponding mercaptide and sulfinate ions (step 3).[24] The methyl mercaptide, being more basic than either of the other ions,[24] then reacts with either 1,2-dehydronaphthalene to give both XV and XVI (step 4) or with the halonaphthalene by direct nucleophilic substitution to give either XV or XVI (step 5). Both 2,4-dinitrochlorobenzene[25] and 1-bromonaphthalene[26] have been postulated to undergo nucleophilic substitution by decomposition products of DMSO to give the corresponding methylthio compounds. The fact that the ratio of 1- to 2-substituted methylthionaphthalenes is larger when 1-chloronaphthalene (2.21) was reacted than when 1-bromonaphthalene (1.09) was reacted indicates that more nucleophilic substitution took place with 1-chloronaphthalene than with 1-bromonaphthalene. This is consistent with the order of reactivity of activated aryl halides in nucleophilic substitution of $F \gg Cl > Br > I$ found in previous studies. This order was found when *o*- and *p*-nitrophenyl halides and 2,4-dinitrophenyl halides were reacted with sodium methoxide in methanol,[27] when *p*-nitrophenyl halides were reacted with sodium ethoxide in ethanol,[28] when 2,4-dinitrophenyl halides were reacted with ammonia in methanol,[29] and when 2,4-dinitrophenyl halides were reacted with amines in dimethylformamide.[30] This mechanism also accounts for the fact that the major product found by us in the reaction of methylsulfinyl carbanion with 1-bromonaphthalene was 1-methylthionaphthalene (XV).[5]

Experimental Section

Materials and Apparatus.—The following halonaphthalenes were obtained from the sources indicated and were used without further purification: 1-bromonaphthalene, Matheson Coleman and Bell; 2-bromo-, 1-chloro, 1-fluoro- and 1-iodonaphthalenes, Eastman Organic Chemicals; 2-chloronaphthalene, J. T. Baker Chemical Co.; 2-fluoronaphthalene, Aldrich Chemical Co.; and 2-iodonaphthalene, K and K Laboratories. Potassium *tert*-butoxide was used as received from MSA Research Corp. DMSO (J. T. Baker reagent grade) was passed through silica gel and stored over type 4A molecular sieves (Fisher Scientific Co.). Reagent grade *tert*-butyl alcohol (Eastman Chemical Co.) was distilled from potassium and stored over type 4A molecular sieves.

Authentic samples of the naphthalene compounds used to compare with the reaction products were either obtained commercially or synthesized in our laboratory as explained in our accompanying paper.[5] All reaction runs were analyzed on either a Varian Aerograph 202-B or 1720 temperature programming vapor phase chromatograph. Where possible, products were isolated on a Varian Aerograph 90-P3 vapor phase chromatograph. All infrared (ir) spectra were obtained on a Perkin-Elmer 457 spectrophotometer. A Varian A-60A spectrometer was used to obtain the nuclear magnetic resonance (nmr) spectra.[18]

The Reaction of Halonaphthalene and Base.—All runs were carried out using the procedure as described in our accompanying paper[5] for the reaction of 1-bromonaphthalene. The molar ratio of halonaphthalene–potassium *tert*-butoxide–*tert*-butyl alcohol–DMSO was 0.025:0.050:0.075:0.375, or 1:2:3:15, in each case. The work-up procedure was carried out exactly as described.[5]

Analysis of Products.—The neutral fraction products (I–X, XV, and XVI) were analyzed as described.[5] Results are listed in Table I. The retention times for compounds I–X were compared with those displayed by authentic samples of those compounds as well as with those shown by the same products obtained in the 1-bromonaphthalene reaction (runs 1 and 2, Table I). Compounds IV, V, XV, and XVI, as well as the recovered starting material from runs 6–9, were isolated from the vpc using a 5 ft by 0.25 in. column packed with 6% SE-30 and 6% Carbowax 20M on 60–80 mesh, acid washed Chromosorb G at 200–220°. Compound XV exhibited ir and nmr spectra identical with those for 1-methylthionaphthalene isolated from the reaction of methylsulfinyl carbanion with 1-bromonaphthalene.[5] Compound XVI exhibited an ir spectrum very similar to that for compound XV except that the bands characteristic for β-substituted naphthalenes were observed at 742 and 810 cm^{-1}. Compound XV exhibited bands characteristic for α substituted naphthalenes at 772 and 790 cm^{-1}. Also, the nmr spectrum of compound XVI,

(19) See A. I. Shatenshtein, *Advan. Phys. Org. Chem.*, **1**, 182 (1963).
(20) A. Streitwieser, Jr., and R. G. Lawler, *J. Amer. Chem. Soc.*, **85**, 2854 (1963).
(21) J. F. Bunnett and T. K. Brotherton, *ibid.*, **78**, 155, 6265 (1956).
(22) G. A. Russell and S. A. Weiner, *J. Org. Chem.*, **31**, 248 (1966).
(23) J. I. Brauman and N. J. Nelson, *J. Amer. Chem. Soc.*, **88**, 2332 (1966).
(24) C. C. Price and T. Yukuta, *J. Org. Chem.*, **34**, 2504 (1969).
(25) G. C. Finger and C. W. Kruse, *J. Amer. Chem. Soc.*, **78**, 6034 (1956).
(26) R. G. R. Bacon and H. A. O. Hill, *J. Chem. Soc.*, 1108 (1964).
(27) B. A. Bolto, J. Miller, and V. A. Williams, *ibid.*, 2926 (1955); G. P. Briner, J. Miller, M. Liveris, and P. G. Lutz, *ibid.*, 1265 (1954); A. L. Beckwith, J. Miller, and G. D. Leahy, *ibid.*, 3552 (1952).
(28) C. W. L. Bevan, *ibid.*, 2340 (1951).
(29) J. D. Reinheimer, R. C. Taylor, and P. E. Rohrbaugh, *J. Amer. Chem. Soc.*, **83**, 835 (1961).
(30) S. D. Ross, *ibid.*, **81**, 2113 (1959).

had peaks at δ 7.48 (m, 7) and 2.50 (s, 3), and was almost identical with that of compound XV except for the 1-proton multiplet at δ 8.29 assigned to the number eight hydrogen.[8] Not enough of this compound could be isolated for a carbon–hydrogen analysis.

The acidic fraction products (XI–XIV) were analyzed as described[5] for all runs except 6–9 where a 5 ft by 1/8 in. column packed with a mixture of 1% SE-30 and 1% Carbowax 20M on 80–100 mesh Varaport 30 using a program from 150 to 167° at a rate of 0.5° per min was used. Results are listed in Table I. The retention times for compounds XI–XIV were compared with those displayed by authentic samples of those compounds as well as with those shown by the same products obtained in the 1-bromonaphthalene reaction (runs 1 and 2, Table I).

Registry No.—1-Bromonaphthalene, 90-11-9; 2-bromonaphthalene, 580-13-2; 1-iodonaphthalene, 90-14-2; 2-iodonaphthalene, 612-55-5; 1-chloronaphthalene, 90-13-1; 2-chloronaphthalene, 91-58-7; 1-fluoronaphthalene, 321-38-0; 2-fluoronaphthalene, 323-09-1; potassium *tert*-butoxide, 865-47-4; *tert*-butyl alcohol, 75-65-0.

The Reaction of Bromonaphthalene with Potassium *tert*-Butoxide and *tert*-Butyl Alcohol in Dimethyl Sulfoxide[1a]

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The reaction of 1-bromonaphthalene with potassium *tert*-butoxide in a *tert*-butyl alcohol–dimethyl sulfoxide mixture has been extensively studied. The major products observed in this reaction were *tert*-butyl 1- and 2-naphthyl ethers (V and VI), 1- and 2-naphthols (XIV and XV), and 1-methylmercapto-2-naphthol (XII). Ten other identifiable products were also observed. The reaction was studied under a variety of conditions and it was observed that the desired ethers (V and VI) were obtained in greater yields when lower base concentration, lower temperatures, and shorter reaction times were employed. The mole per cent ratio of 1-substituted products (V and XIV) to 2-substituted products (VI and XV) was 0.36 ± 0.02 in every case. This ratio plus the fact that 2-bromonaphthalene reacted to give the same products and almost the same ratio (0.34) suggest that 1,2-dehydronaphthalene is an intermediate in this reaction.

The generation of arynes by reacting aryl halides with amide ions has been studied in detail.[2] Cram and coworkers have shown that the elimination of hydrogen bromide from bromobenzene can be effected using potassium *tert*-butoxide and that the reaction is greatly enhanced when dimethyl sulfoxide (DMSO) is used as a solvent.[3] More recently, Cram and Day[4] and Kise and coworkers[5] have found that aryne intermediates reacted with DMSO to yield 2-methylmercaptophenol-type products.

In connection with another study,[6] we have reported the preparation of *tert*-butyl 2-naphthyl ether from the reaction of 1-bromonaphthalene and potassium *tert*-butoxide in a *tert*-butyl alcohol–DMSO mixed solvent. At that time no *tert*-butyl 1-naphthyl ether was found and a mixture of 1- and 2-naphthols was the major product.[6] We now would like to report on the reaction of 1- and 2-bromonaphthalene with potassium *tert*-butoxide in a *tert*-butyl alcohol–DMSO solvent mixture. This reaction not only gave *tert*-butyl 1- and 2-naphthyl ethers and naphthols but also eleven other identifiable products (see Scheme I).

Results

Bromonaphthalene was rapidly added to the potassium *tert*-butoxide–*tert*-butyl alcohol–DMSO mixture at the appropriate temperature. The reaction proved to be exothermic. Upon completion of the reaction, the neutral and naphtholic products (Scheme I) were separated and the products were analyzed by vapor phase chromatography (vpc). The results of several runs are shown in Table I.

The hydrocarbons (I–IV) and naphthols (XIV and XV) were identified by comparing them with authentic compounds. The two *tert*-butyl ethers (V and VI) were identified as previously described[6] and by comparing them with authentic samples prepared by the method of Frisell and Lawesson.[7] The binaphthyls (VII and VIII) were not unequivocally identified; however, authentic samples exhibited the same vpc retention times. Authentic α,α′- and β,β′-dinaphthyl ethers (IX and XI) were prepared from the corresponding naphthols.[8] These authentic samples gave the same vpc retention times as compounds IX and XI. In addition, the product of reacting a mixture of 1- and 2-naphthols with sodium bisulfate at high temperatures[8] exhibited the same infrared spectrum as compounds IX to XI as collected in one combined sample from the vpc.

Compound XII exhibited the same infrared spectrum as that reported by Leysen and Van Rysselberge[9] for 1-methylmercapto-2-naphthol. The infrared band at 3375 cm^{-1} was unaffected by dilution which indicates the presence of a hydroxy group ortho to a methylmercapto group.[4] Compound XIII exhibited infrared and nuclear magnetic resonance spectra which were very similar to those of compound XII. This spectral similarity, as well as the probable source of

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(1) (a) Nuclear magnetic resonance spectra were obtained on a Varian A-60A spectrometer purchased under the National Science Foundation Grant GP-6837; (b) National Defense Education Act Fellow, 1967–1970.

(2) See R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967.

(3) D. J. Cram, B. Rickborn, and G. R. Knox, *J. Amer. Chem. Soc.*, **82**, 6412 (1960).

(4) D. J. Cram and A. C. Day, *J. Org. Chem.*, **31**, 1227 (1966).

(5) M. Kise, T. Asari, N. Furukawa, and S. Oae, *Chem. Ind. (London)*, 276 (1967).

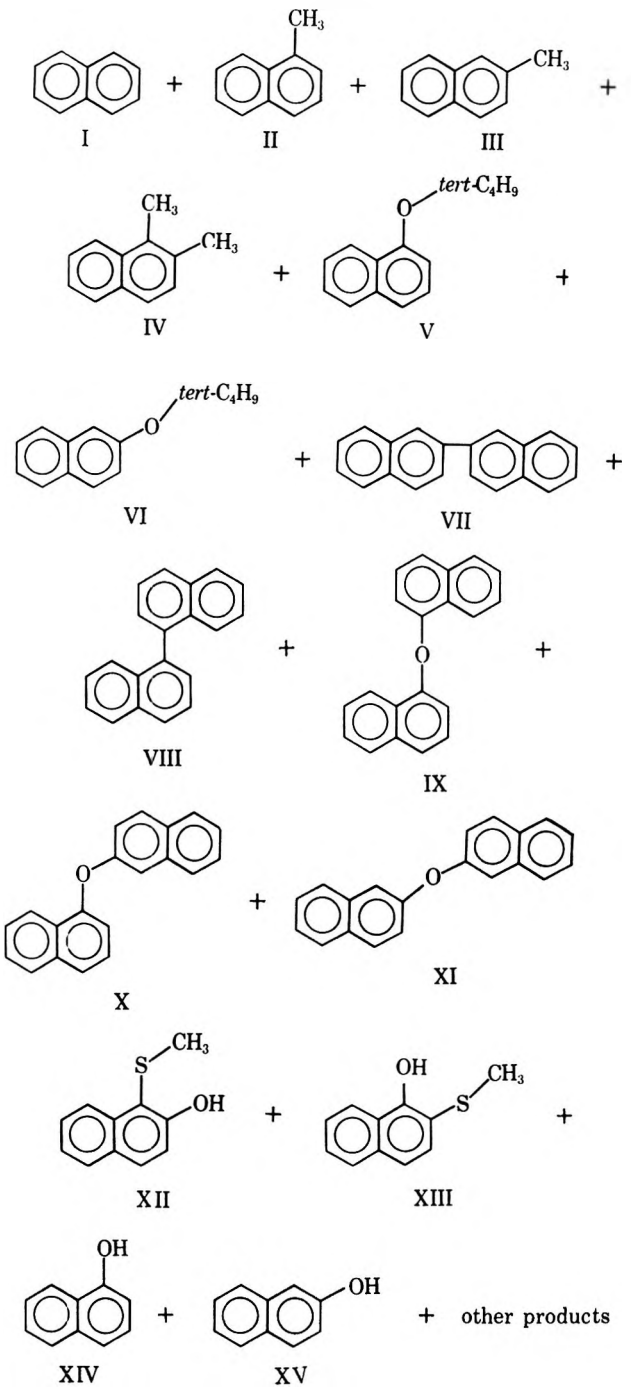
(6) J. S. Bradshaw, N. B. Nielson, and D. P. Rees, *J. Org. Chem.*, **33**, 259 (1968).

(7) C. Frisell and S. O. Lawesson, *Org. Syn.*, **41**, 91 (1961).

(8) W. M. Rodiodow and S. J. Manzow, *J. Soc. Chem. Ind., London, Rev. Sect.*, **42**, 509 (1923); see *Chem. Abstr.*, **18**, 981[7] (1924).

(9) R. Leysen and J. Van Rysselberge, *Spectrochim. Acta*, **22**, 777 (1966).

SCHEME I



both XII and XIII, suggests that compound XIII is 2-methylmercapto-1-naphthol.

The first reaction (run 1) was carried out using the conditions employed by Sahyun and Cram[10] for the bromobenzene reaction. In our case it was apparent that the conditions were too severe. When the amount of base was reduced, a much greater yield of the desired ethers (V and VI) was obtained and the yield of naphthols (XIV and XV) was greatly reduced (runs 1 and 2). A similar enhancement of yields was observed at lower temperatures (compare run 7 with run 2).

The higher ether, and correspondingly lower naphthol, yields can be attributed to a greater stability of the ethers in the less severe reaction conditions. We found that the *tert*-butyl naphthyl ethers decomposed to the corresponding naphthols under our reaction conditions. They were, however, much more stable at lower temperatures.

(10) M. R. V. Sahyun and D. J. Cram, *Org. Syn.*, **45**, 89 (1965).

Discussion

On reviewing the results in Table I, it becomes apparent that the same intermediate is leading to the major products in every experiment. The mole per cent ratio of 1-substituted products (V and XIV) to 2-substituted products (VI and XV) is 0.36 ± 0.02 in every case except runs 5 and 6 where either the base concentration is lower or the alcohol was eliminated (Table II). When 2-bromonaphthalene was reacted (run 8, Tables I and II), the mole per cent ratio of 1- and 2-substituted products was, within experimental error, the same as for 1-bromonaphthalene. These results clearly indicate that there is a common intermediate in these reactions. The greater preponderance of evidence concerning this and similar reactions[2-5] has shown the intermediate to be a 1,2-dehydroaromatic compound. In our case, this would be 1,2-dehydronaphthalene.

The ratio of 0.36 for 1 to 2 products is interesting. Most of the previous studies of 1,2-dehydronaphthalene, generated by a variety of methods, exhibited a ratio of 0.5 or higher except in cases where a bulky nucleophile was used.[11] In one case, the 1:2 ratio changed progressively from 0.64 to 0.075 when the base–nucleophile was changed from lithium diethylamide–diethylamine (0.64) to diisobutylamide–diisobutylamine (0.56), diisopropylamide–diisopropylamine (0.15), and dicyclohexylamide–dicyclohexylamine (0.075).[12] Our results indicate that *tert*-butyl alcohol is more bulky than diisobutylamine but less bulky than diisopropylamine. A less bulky alkoxide–alcohol system should give a higher ratio of 1- to 2-substituted products.

In an attempt to test this theory, we treated 1-bromo- and 2-bromonaphthalene with potassium *n*-butoxide in a 1-butanol–DMSO solvent mixture at 140° (same conditions as run 2, Table I). The ratio of 1- to 2-substituted products was 1.24 in the 1-bromonaphthalene reaction and 0.30 in the 2-bromonaphthalene reaction. A considerable amount (up to 28%) of naphthalene was observed in these reactions probably due to reductive processes observed by others.[13,14]

The fact that 1-bromonaphthalene gave the 2-ether and 2-bromonaphthalene gave the 1-ether suggests that at least some of the reaction in both cases is proceeding by a 1,2-dehydronaphthalene mechanism. Coupled with this is a direct nucleophilic substitution mechanism which would give mostly 1-ether from 1-bromonaphthalene and 2-ether from 2-bromonaphthalene.[15] A 2,3-dehydronaphthalene mechanism could also be possible in the reaction of 2-bromonaphthalene in the *n*-butoxide–1-butanol system. Work is in progress to sort out the various mechanisms in the *n*-butoxide system.

In any mechanistic scheme, the base–alcohol–DMSO system cannot be divorced from the intermediate. That

(11) Reference 2, p 139.
(12) R. Huisgen and L. Zirngibl, *Chem. Ber.*, **91**, 2375 (1958).
(13) J. F. Bunnett and T. K. Brotherton, *J. Amer. Chem. Soc.*, **78**, 6265 (1956).
(14) J. Sauer, R. Huisgen, and A. Hauser, *Chem. Ber.*, **91**, 1461 (1958).
(15) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951).

TABLE I
RESULTS OF THE REACTION OF 1- AND 2-BROMONAPHTHALENE WITH POTASSIUM *tert*-BUTOXIDE IN *tert*-BUTYL ALCOHOL–DMSO

	Mole ratios				Temp,	Time,		Products[d]			
Run	ArBr	KOR	HOR	DMSO	°C	min	Conversion	I	II	III	IV
1[a,b]	1	4.06	3.38	14.75	140	8	98.2	2.3	0.6	0.2	0.3
2[b]	1	2	3	15	140	8	100	2.3	0.5	0.1	
3[b]	1	2	3	15	140	8	100	2.6	0.5	0.1	
4[b]	1	2	3	15	100	5	86.3	3.0	0.2	0.1	
5[b]	1	1	3	15	100	5	34.2	1.8	0.1		
6[b]	1	2	0	15	100	5	99.9	3.2	1.2	0.2	0.3
7[b]	1	2	3	15	80	15	38.3	1.3			
8[c]	1	2	3	19.1	80	15	72.7	0.6	0.1		

	Products[d]										
Run	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XV
1	3.9	19.3	0.2	0.1	0.8	3.1	3.0	4.0	1.5	14.4	30.6
2	8.5	27.8	0.2	0.2	0.8	2.7	2.5	7.4	1.1	4.8	8.5
3	8.3	28.1	0.2	0.2	0.8	2.9	2.6	7.7	1.2	5.2	9.7
4	9.1	26.8	0.2	0.2	1.3	4.5	4.2	9.2	0.2	3.0	6.9
5	6.9	17.8	0.3	0.2	0.5	1.4	1.3	14.0	2.5	1.9	4.0
6	3.7	13.6	0.4	0.2	0.7	2.7	4.0	7.9	1.0	5.7	9.3
7	13.5	40.2	0.4	0.1	0.5	1.4	1.5	12.2	1.3	2.4	5.3
8	10.8	31.7	0.3		0.7	1.9	2.1	9.6	0.5	1.1	3.2

[a] Same condition as Sahyun–Cram reaction, see ref 10. [b] 1-Bromonaphthalene. [c] 2-Bromonaphthalene. [d] Mole per cent yields.

TABLE II
MOLE PER CENT RATIO OF 1-SUBSTITUTED PRODUCTS (V AND XIV) TO 2-SUBSTITUTED PRODUCTS (VI AND XV)

Run[a]	Mole per cent ratio (V + XIV:VI + XV)	Run[a]	Mole per cent ratio (V + XIV:VI + XV)
1	0.37	5	0.40
2	0.37	6	0.41
3	0.36	7	0.35
4	0.36	8	0.34

[a] See Table I for conditions.

alcohol is necessary is shown by the fact that without alcohol, a very poor yield of the desired ethers was obtained (see run 6 in Table I). A similar effect was observed by Huisgen and Sauer for the reaction of bromobenzene with lithium piperidide.[16] As they increased the amount of piperidine in the reaction, the overall rate of the reaction increased. They attributed this to a catalytic action of piperidine on the initial metalation step.[16] In our case, it should be a similar type of effect in the initial removal of the proton. 1,2-Dehydronaphthalene, produced in the fast loss of bromide ion, would then add either *tert*-butyl alcohol or more likely *tert*-butoxide ion. This addition is probably influenced by stereochemistry imposed by the peri hydrogen resulting in mostly 2-substituted naphthalene.

The *tert*-butyl ether decomposed in both acid[6] and base. In the base-catalyzed decomposition at higher temperatures, a gas was observed leaving the solution. In the initial experiment to generate 1,2-dehydronaphthalene the evolution of gas was very vigorous. This gas was not collected; however, Cram and Day observed similar results in their system and suggested that isobutylene and the corresponding phenol were formed by a simple elimination process.[4]

The presence of naphthalene in the products of the *tert*-butoxide system is somewhat surprising. This material may be produced by a mechanism similar to that postulated by Bunnett and Victor[17] for the dehalogenation of various trihalobenzenes. They proposed that methylsulfinyl carbanion produced in an equilibrium between *tert*-butoxide and DMSO was undergoing a nucleophilic displacement on the halogen forming an aryl anion.[17,18] The aryl anion then abstracts a proton from the solvent.

$$CH_3SOCH_3 + tert\text{-}C_4H_9O^- \rightleftharpoons CH_3SOCH_2^- + tert\text{-}C_4H_9OH$$

$$CH_3SOCH_2^- + ArBr \longrightarrow CH_3SOCH_2Br + Ar^-$$

$$Ar^- + tert\text{-}C_4H_9OH \longrightarrow ArH + tert\text{-}C_4H_9O^-$$

In an attempt to determine if this mechanism was appropriate for 1-bromonaphthalene, we treated 1-bromonaphthalene with sodium methylsulfinyl carbanion.[19] Only a minor amount of naphthalene (1.3 mol %) was produced in this reaction. The small amount of naphthalene produced when a large amount of the carbanion base was present suggests that the Bunnett–Victor mechanism is not appropriate in the naphthalene system.

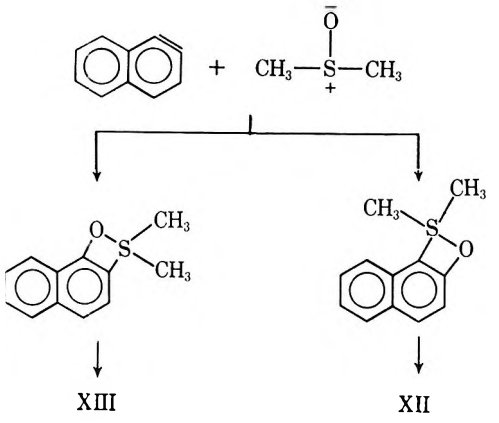
The methylnaphthalenes (II–IV) are probably being formed from naphthalene and methylsulfinyl carbanion as reported by Schriesheim and coworkers.[20] They found a ratio of 96% 1-methylnaphthalene to 4% 2-methylnaphthalene when naphthalene was treated with DMSO and potassium *tert*-butoxide in diglyme. We found that under our reaction conditions, naphthalene gave 1- and 2-methylnaphthalene in a similar ratio.

The formation of the dinaphthyl ethers (IX–XI) probably resulted from the reaction of 1- and 2-naphthoxide on 1,2-dehydronaphthalene. Similar results have been reported for the reaction of phenoxide with dehydrobenzene.[21–23]

The methylmercaptonaphthols (XII and XIII) were probably formed by a dipolar addition of DMSO to

(16) R. Huisgen and J. Sauer, *Chem. Ber.*, **92**, 192 (1959).
(17) J. F. Bunnett and R. R. Victor, *J. Amer. Chem. Soc.*, **90**, 810 (1968).
(18) See also C. G. Cardenas, A. N. Khafaji, C. L. Osborn, and P. D. Gardner, *Chem. Ind. (London)*, 345 (1965).
(19) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).
(20) P. A. Argabright, J. E. Hofmann, and A. Schriesheim, *J. Org. Chem.*, **30**, 3233 (1965).
(21) F. Scardiglia and J. D. Roberts, *Tetrahedron*, **3**, 197 (1958).
(22) Von W. Strubell, *J. Prakt. Chem.*, **14**, 60 (1961).
(23) R. W. Hoffmann, *Chem. Ber.*, **97**, 2772 (1964).

1,2-dehydronaphthalene as suggested by Cram and Day[4] and Kise and coworkers.[5] The resulting adduct is believed to eliminate methylene (in the form of polymethylene) to form the observed products.[4,5] The reasons for the observed preponderance of 1-methylmercapto-2-naphthol (XII) over the 2-1 isomer (XIII) is not readily apparent.



Experimental Section

Materials and Apparatus.—1-Bromonaphthalene was used as received from Matheson Coleman and Bell. Potassium *tert*-butoxide was used as received from MSA Research Corp. DMSO (J. T. Baker reagent grade) was passed through silica gel and stored over type 4A molecular sieves (Fisher Scientific Co.). Reagent grade *tert*-butyl alcohol and 1-butanol (Eastman Chemical Co.) were distilled from potassium and stored over type 4A molecular sieves. The naphthalene compounds used to compare with the reaction products were purchased from Aldrich Chemical Co. (naphthalene, 1-methylnaphthalene, 2-methylnaphthalene, 1-naphthol, and 2-naphthol) and K and K Laboratories (1,2-dimethylnaphthalene, 1,1′-binaphthyl, and 2,2′-binaphthyl). The *tert*-butyl perbenzoate was purchased from K and K Laboratories.

Authentic samples of *tert*-butyl 1-naphthyl ether and *tert*-butyl 2-naphthyl ether were prepared by the method of Frisell and Lawesson[7] using 1- and 2-bromonaphthalene (0.25 mol), magnesium (0.265 g-atom), and *tert*-butyl perbenzoate (0.15 mol). The yield of the *tert*-butyl 1-naphthyl ether was 34%, $n^{20}D$ 1.5759, bp 85–95° (2 mm) [lit.[24] $n^{20}D$ 1.5772, bp 87–88° (0.4 mm)]. The yield of *tert*-butyl 2-naphthyl ether was 67%, $n^{20}D$ 1.5788, bp 95–100° (2 mm) (lit.[6] $n^{20}D$ 1.5769).[6] Naphthalene was a by-product of these reactions.

1,1′-Dinaphthyl and 2,2′-dinaphthyl ethers were prepared by the procedure of Rodiodow and Manzow[8] from the 1- and 2-naphthols and sodium bisulfate. 2,2′-Dinaphthyl ether (40% yield) was purified by sublimation, mp 97.5–100.5° (lit.[25] mp 105°). 1,1′-Dinaphthyl ether (64% yield) was purified by recrystallization from 95% ethanol, mp 106–106.5° (lit.[25] mp 110°).

All reaction runs were analyzed and where possible the products were isolated using a Varian Aerograph 202-B temperature programming vapor phase chromatograph (vpc). All infrared (ir) spectra were obtained on a Perkin-Elmer 457 spectrophotometer. A Varian A-60A spectrometer[1a] was used to obtain the nuclear magnetic resonance (nmr) spectra.

Reaction of 1-Bromonaphthalene and Base (Run 1).—A mixture of 25 ml (0.3525 mol) of DMSO, 7.62 ml (5.99 g, 0.0808 mol) of *tert*-butyl alcohol, and 11.84 g (0.0970 mol) of potassium *tert*-butoxide was placed in a dry 100-ml three-necked round-bottom flask equipped with a thermometer, reflux condenser, and an addition funnel. A 1000-ml round-bottom flask with a male joint on the bottom was placed between the reaction vessel and the condenser. The potassium *tert*-butoxide dissolved when the stirred (magnetic stirring bar) reaction mixture was heated to 140°. 1-Bromonaphthalene (4.94 g, 0.0239 mol) was quickly added by means of the addition funnel. The reaction mixture turned black and vigorously foamed into the 1000-ml flask and condenser. After 8 min, the reaction mixture was added to 115 ml of ice water. The aqueous mixture was saturated with sodium chloride and extracted four times with 100-ml portions of ethyl ether. The combined ether extracts were washed with an aqueous 5% sodium hydroxide solution and dried over anhydrous magnesium sulfate. After the drying agent was filtered, the ether extract was evaporated leaving 2.11 g of a dark brown semisolid. This material was the neutral fraction.

The remaining aqueous DMSO reaction mixture was acidified to a pH of 1 with concentrated hydrochloric acid and extracted four times with 100-ml portions of ether. The combined ether extracts were washed with water and dried over anhydrous magnesium sulfate. After the drying agent was filtered, the ether extract was evaporated leaving 1.79 g of a dark yellow-green solid. This material was the acidic fraction.

The other reactions (runs 2–8, Table I) were carried out in the same manner using the listed ratios of reactants and solvents and the appropriate conditions. The reaction using potassium *n*-butoxide and 1-butanol was carried out by dissolving the required amount of potassium metal in enough 1-butanol to obtain a ratio of 2 mol of potassium *n*-butoxide to 3 mol of 1-butanol. The DMSO was then added and the reaction carried out as reported above. The analysis for all experiments was carried out as described below.

Analysis of the Neutral Fraction.—The neutral fraction was dissolved in 5 ml of benzene and subjected to vpc analysis using 1-bromo-4-methylnaphthalene as an internal standard.[26] The starting 1-bromonaphthalene was found to contain a minute amount of naphthalene. This was subtracted from the amount found in the products. The lower boiling compounds (V–VI) were analyzed on a 5 ft by 1/8 in. column packed with a mixture of 1% SE-30 and 1% Carbowax 20M on 60–80 mesh, Chromosorb G, acid washed, at 115°. The higher boiling fractions (VII–XI) were analyzed on a 5 ft by 1/8 in. column packed with 1.5% poly-*m*-phenoxylene (PMPE) on 80–100 mesh Varaport 30 using a program from 125 to 290° at a rate of 10° per min. A total of 27 peaks were observed. The retention times for compounds I–XI were compared with authentic samples of those compounds. Total amounts and yields were determined by the internal standard method.[26] Results are listed in Table I.

All the compounds in the neutral fraction except III, VII, and VIII were isolated from the vpc using a 5 ft by 0.25 in. column packed with 20% Carbowax 20M on 60–80 mesh, Chromosorb G, acid washed, for the lower boiling fraction and 1.5% PMPE on 80–100 mesh Varaport 30 for the higher boiling fraction. The compounds in the lower boiling fraction all exhibited ir spectra which were identical with those of authentic samples. Compounds IX–XI were isolated together and exhibited an ir spectrum which was exactly the same as that for an authentic sample prepared by reacting a mixture of 1- and 2-naphthols with sodium bisulfate.[8]

The *n*-butyl 1-naphthyl and *n*-butyl 2-naphthyl ethers exhibited ir and nmr spectra which were consistent with their assigned structures. The 2-substituted ether was also identical with that prepared previously.[6]

Analysis of the Acidic Fraction.—The acidic fraction (XII–XV) was dissolved in 3 ml of anhydrous ether and subjected to vpc analysis using a 5 ft by 1/8 in. column packed with a mixture of 1% SE-30 and 1% Carbowax 20M on 60–80 mesh, Chromosorb G, acid washed, at 175°. Five peaks were observed. The ir spectrum of the total material collected from the vpc was the same as the crude solid before it was subjected to analysis. Therefore, no internal standard was used; the area of each peak was used to determine the amount of that particular product. Results are listed in Table I.

Four of the five peaks were isolated from the vpc using a 5 ft by 0.25 in. column packed with 20% Carbowax 20M on 60–80 mesh, Chromosorb G, acid washed. Peak 2 exhibited an ir spectrum which was the same as that reported for 1-methylmercapto-2-naphthol (compound XII).[9]

Anal. Calcd for $C_{11}H_{10}OS$: C, 69.44; H, 5.30. Found: C, 69.30; H, 5.34.

Peak 3 exhibited the following major ir bands: 3385, 3060, 2925, 1629, 1621, 1590, 1573, 1506, 1460, 1438, 1390, 1360, 1320, 1268, 1249, 1205, 1153, 1136, 1073, 972, 886, 855, 808, 785, 778, 750, 724, and 668 cm^{-1}. The nmr spectrum had peaks at δ 7.76 (m, 6), 3.54 (s, 1), and 2.33 (s, 3). The ir spectrum was

(24) S. O. Lawesson, *J. Amer. Chem. Soc.*, **81**, 4230 (1959).

(25) R. C. Weast, Ed., "Handbook of Chemistry and Physics," 50th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1969–1970, p C-294.

(26) A. B. Littlewood, "Gas Chromatography, Principles, Techniques and Applications," Academic Press, New York, N. Y., 1962, p 246.

similar to that of vpc peak 2 (compound XII) and the nmr spectrum was identical. On this basis, peak 3 was believed to be 2-methylmercapto-1-naphthol (XIII). Not enough of this compound could be isolated for a carbon–hydrogen analysis. Vpc peaks 4 and 5 exhibited ir spectra which were identical with those of 1- and 2-naphthols, respectively.

Decomposition of *tert*-Butyl 1-Naphthyl Ether.—Mixtures of potassium *tert*-butoxide, *tert*-butyl alcohol, and DMSO of the appropriate ratio (same as in Table I) were heated to the desired temperature in a dry three-necked round-bottom flask equipped with a thermometer, addition tube, and condenser. *tert*-Butyl 1-naphthyl ether was added at once through the addition tube. After the desired reaction time, the reaction mixture was added to cold water and worked up as described above for the 1-bromonaphthalene reaction. The neutral and acidic fractions were analyzed as described above. In every case the ether decomposed to the naphthol. At high temperature only 5–10% of the ether was recovered; the other 90–95% was the naphthol. At lower temperatures (80–100°) most (60%) of the ether was recovered.

Reaction of Naphthalene with the Base–DMSO Solution.—Naphthalene (0.13 g, 0.001 mol) was added to a solution of 25 ml (27.5 g, 0.35 mol) of DMSO, 6.0 g (0.08 mol) of *tert*-butyl alcohol, and 11.8 g (0.10 mol) of potassium *tert*-butoxide at 140°. After 40 min, the reaction was added to ice water and worked up as reported above for the 1-bromonaphthalene reaction. No acidic fraction was observed. The neutral fraction was analyzed as reported above to yield 47.3% recovered naphthalene, 7.6% 1-methylnaphthalene, and 0.6% 2-methylnaphthalene. No 1,2-dimethylnaphthalene was observed.

Reaction of Methylsulfinyl Carbanion with 1-Bromonaphthalene.—Methylsulfinyl carbanion was prepared according to the procedure of Corey and Chaykovsky[19] from 124.83 g (1.6 mol) of DMSO and 4.5 g (0.19 mol) of sodium hydride. This mixture was placed in a dry 500-ml three-necked round-bottom flask equipped with a thermometer, condenser, addition funnel, and magnetic stirring. The temperature was raised to 80° and 19.5 g (0.09 mol) of 1-bromonaphthalene was added at once. The reaction mixture immediately turned black and the temperature rapidly increased to 150°. After 15 min (the temperature had lowered to 104°), the mixture was added to ice water and worked up as reported above. The acidic fraction was analyzed as reported above to yield 3.8% XII, 1.3% XIII, 0.3% XIV, and 0.5% XV. The neutral fraction yielded (analyzed as reported above) 1.3% I, 2.7% III, and 0.3% II. Another compound (11.4%) was observed and isolated. The nmr spectra of this compound was the same as that reported by Zweig and coworkers[27] for 1-methylthionaphthalene. The ir spectrum was consistent with this structure.

Anal. Calcd for $C_{11}H_{10}S$: C, 75.81; H, 5.79. Found: C, 75.94; H, 5.63.

Registry No.—1-Bromonaphthalene, 90-11-9; 2-bromonaphthalene, 580-13-2; potassium *tert*-butoxide, 865-47-4.

(27) A. Zweig, J. E. Lancaster, and M. T. Negia, *Tetrahedron*, **23**, 2577 (1967).

The Chemistry of Thiolsulfonates and Related Derivatives. Nucleophilic Reactions on Sulfenyl Sulfur[1a]

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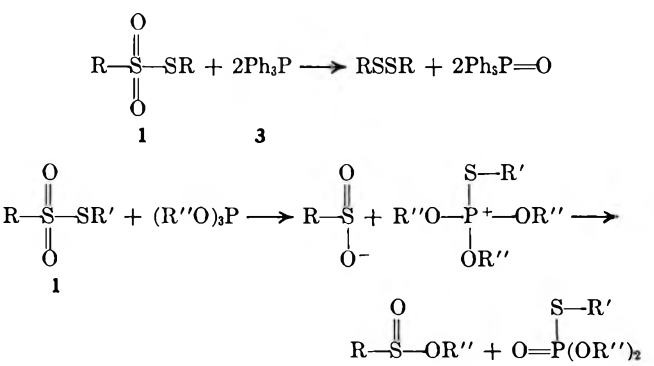
The reaction of thiolsulfonates with aminophosphines proceeds by nucleophilic attack on sulfenyl sulfur giving rise to sulfones and sulfinate esters as reaction products. This is in marked contrast to the reaction of triphenylphosphine (**3**) with thiolsulfonates where deoxygenation is observed. This dichotomy does not extend to the corresponding reaction of phosphines with sulfenylthiolsulfonates. Here, nucleophilic attack on sulfenyl sulfur is observed for both triphenylphosphine (**3**) and tris(diethylamino)phosphine (**4**). In addition, the desulfurization of cyclic thiosulfonates provides a new, general route to cyclic sulfinate esters.

As part of our continuing investigation of nucleophilic displacements on sulfenyl sulfur we have examined the reaction of a number of thiolsulfonates **1** and sulfenyl thiolsulfonates **2** with various trivalent phosphorus derivatives.

RSO_2SR (**1**) RSO_2SSR (**2**)

The behavior of trivalent phosphorus compounds toward disulfides and trisulfides has been shown to be a function of the type of substitution on the phosphorus atom (aminophosphines,[2,3] alkylphosphines,[3] arylphosphines,[3,4] and phosphites).[5]

Thiolsulfonates have been reported to undergo deoxygenation with triphenylphosphine[6] (**3**) or desulfurization with trialkyl phosphites.[7] In the latter reaction, the



sulfinate anion, presumably formed by nucleophilic displacement on sulfenyl sulfur, may react through oxygen to afford sulfinate esters or through sulfur to give sulfones. However, only products resulting from O-alkylation in an Arbusov-like rearrangement[8] are ob-

* To whom correspondence should be addressed.

(1) (a) Organic Sulfur Chemistry. IX. Part VIII: D. N. Harpp, D. K. Ash, T. G. Black, J. G. Gleason, B. A. Orwig, W. F VanHorn, and J. P. Snyder, *Tetrahedron Lett.*, 3551 (1970). (b) Holder of an NRCC Scholarship, 1968–1970. (c) Holder of an NRCC Bursary, 1969–1970.

(2) D. N. Harpp, J. G. Gleason, and J. P. Snyder, *J. Amer. Chem. Soc.*, **90**, 4181 (1968).

(3) D. N. Harpp, and D. K. Ash, *Chem. Commun.*, 811 (1970).

(4) (a) S. Safe and A. Taylor, *ibid.*, 1466 (1969); (b) F. Feher and D. Kurz., *Z. Naturforsch. B*, **23**, 1030 (1968); (c) S. Hayashi, M. Furukawa, J. Yamomoto, and K. Hamamura, *Chem. Pharm. Bull.*, **15**, 1310 (1967); (d) C. Moore and B. Trego, *Tetrahedron*, **19**, 1251 (1963); (e) A. Schonberg and M. Z. Barakat, *J. Chem. Soc.*, 892 (1949).

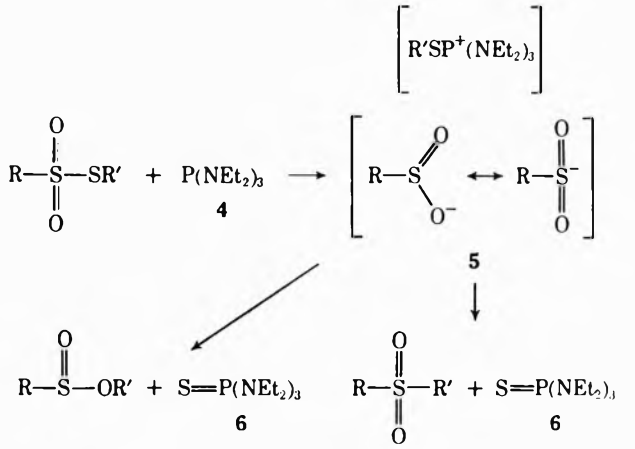
(5) H. I. Jacobson, R. G. Harvey, and E. V. Jensen, *J. Amer. Chem. Soc.*, **77**, 6064 (1955); C. Walling and R. Rabinowitz, *ibid.*, **81**, 1243 (1959).

(6) L. Horner and H. Nickel, *Justus Liebigs Ann. Chem.*, **597**, 20 (1955).

(7) J. Michalski, T. Modro, and J. Wieczorkowski, *J. Chem. Soc*, 1665 (1960).

(8) E. A. Arbusov, *Zh. Russ. Fiz.-Khim. Obshchest.*, **38**, 687 (1906).

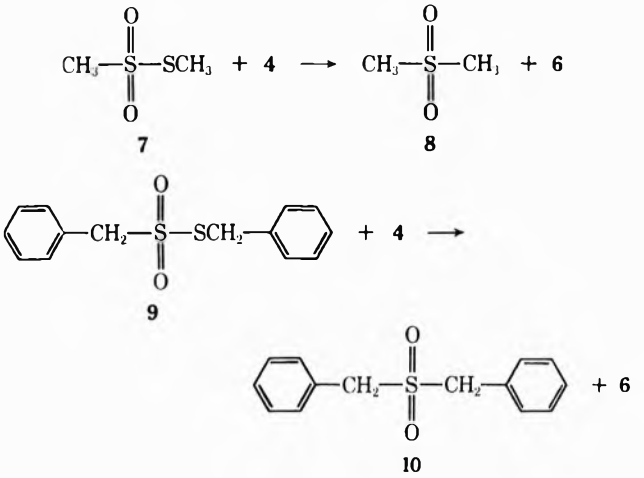
SCHEME I



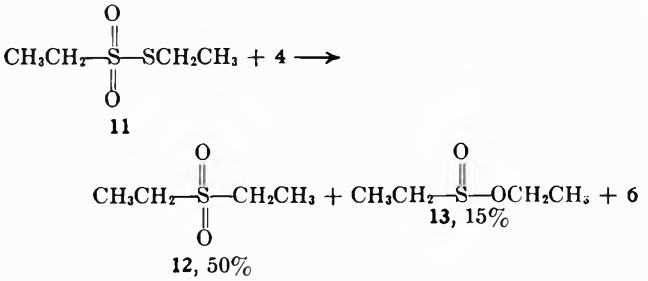
served. A highly nucleophilic aminophosphine such as tris(diethylamino)phosphine[9] (**4**) could be expected to react on sulfenyl sulfur displacing the ambident sulfinate anion **5** (Scheme I), an anion which may then undergo S- or O-alkylation giving rise to sulfone and/or sulfinate ester as products.

Results and Discussion

A variety of thiolsulfonates were prepared and treated with aminophosphine **4**. In most of the reactions investigated, sulfone was the only product observed. For example, methyl methanethiolsulfonate (**7**) and benzyl benzylthiolsulfonate (**9**) afforded dimethyl sulfone (**8**) and dibenzyl sulfone (**10**) in 80 and 70% yield, respec-



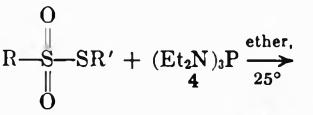
tively. In both reactions, the absence of sulfinate ester was demonstrated by vpc. In a few cases, sulfinate esters were observed as minor by-products (10–30%) of the desulfurization reaction. For example, ethyl ethanethiolsulfonate (**11**) afforded both diethyl sulfone

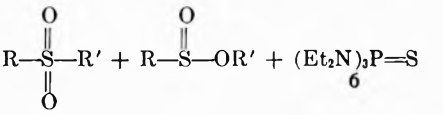


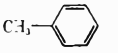
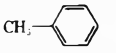
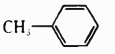
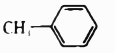
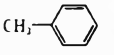
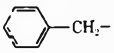
(9) R. G. Pearson, H. Sobel, and J. Songstad, *J. Amer. Chem. Soc.*, **90**, 319 (1968).

(**12**) (50%) and ethyl ethanesulfinate (**13**) (15%) on reaction with **4**. The results of these desulfurization reactions are summarized in Table I. In all cases, isolated yields were in excess of 65%; where only one product was formed, the absence of sulfinate ester was demonstrated by vpc analysis of the reaction mixture.

TABLE I





	R	R′	Product composition[a] R–S(=O)–R′	Product composition[a] R–S(=O)–OR′
14		$-CH_3$	66[b]	33[b]
15		$-C_6H_5$	61[c]	39[c]
16		$-CH_2-C_6H_5$	100	0
17		$-CH_2-C_6H_4-Br$	100	0
18		$-CH_2-C_6H_4-CH_3$	100	0
7	CH_3-	$-CH_3$	100	0
11	C_2H_5-	$-C_2H_5$	66	33
9		$-CH_2-C_6H_5$	100	0

[a] Product composition was determined by vpc analyses. Unless otherwise noted isolated yields of desulfurized products were better than 60%. [b] Low yields are due to separation difficulties. [c] No products were isolated.

The formation of both sulfone and sulfinate ester during desulfurization is indicative of the formation of an ambident sulfinate anion (Scheme I). Meek and Fowler[10] have demonstrated that O- and S-alkylation of the ambident *p*-toluenesulfinate anion is very sensitive to the structure of the alkylating agent. The sulfinate–sulfone distribution is consistent with the expected[11] behavior of such an ambident anion in that nucleophilic displacement by the sulfinate ion on a benzylic center (**16**, **17**, **18**) would proceed preferentially through the less electronegative atom (sulfur), while enhanced O-alkylation would be anticipated on an alkyl center (**14**, **15**). As is shown in Table I, this is, in fact, observed.[12]

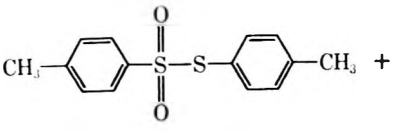
The reactions of diaryl thiolsulfonates with phosphines are of special interest since neither sulfone nor sulfinate ester would be expected. When phosphine **4** was added to an ethereal solution of *p*-tolyl *p*-toluene-

(10) J. S. Meek and J. S. Fowler, *J. Org. Chem.*, **33**, 3422 (1968).

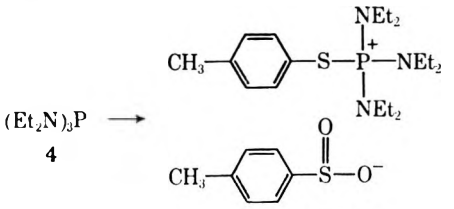
(11) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, p 296.

(12) This rationalization is not valid for compounds **7**, **9**, and **11** since in these cases both the sulfenyl (RS–) and sulfonyl (RSO_2-) radicals are varied.

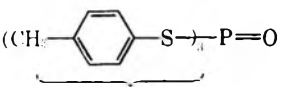
thiolsulfonate (19), a 1:1 thiolsulfonate–phosphine adduct 20 was isolated as a viscous, hygroscopic oil. The 60-MHz nmr spectrum of 20 exhibited a singlet and a



19



20, ^{31}P, δ −61.6



21, J_{PH} = 2.0 Hz

doublet (J_{PH} = 2.5 Hz) for the *p*-tolyl methyl resonances. The doublet results from seven-bond long-range coupling with the phosphorus nucleus. Analogous couplings have been observed in the spectrum of tri-*p*-tolyl phosphotrithioate (21) and for several other phosphines, phosphine oxides, and phosphonium salts.[13] The phosphonium salt structure of this adduct was confirmed by ^{31}P nmr spectroscopy in that adduct 20 exhibited a resonance at −61.6 ppm relative to H_3PO_4, consistent with that observed for other phosphonium salts (Table II).

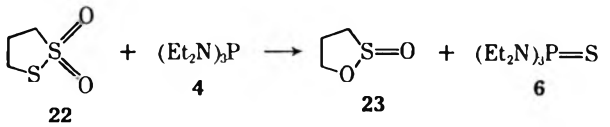
TABLE II

^{31}P NMR CHEMICAL SHIFTS

Compd	δ ^{31}P (relative to H_3PO_4)[a]
$(Et_2N)_3P$ (4)	−117.7
$(Et_2N)_3P{=}O$[b]	−23.5
$(Et_2N)_3P{=}S$ (6)	−78.5
$(Et_2N)_3\overset{+}{P}SCH_2Ph\ BF_4^-$[c]	−61.9
$(Et_2N)_3\overset{+}{P}SC_6H_4CH_3\ {}^-SO_2C_6H_4CH_3$[c]	−61.6

[a] Recorded in benzene solution. [b] M. M. Crutchfield, C. H. Dungan, J. H. Letcher, V. Mark, and J. R. Van Wazer, "Topics in Phosphorus Chemistry," Vol. 5, M. Grayson and E. J. Griffith, Ed., Interscience, New York, N. Y., 1967. [c] J. G. Gleason, Ph.D. Thesis, McGill University, June 1970.

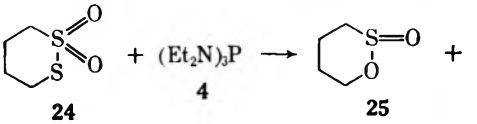
Cyclic thiolsulfonates, on treatment with aminophosphine 4, yield sulfinate esters and not sulfones.[14] The addition of 4 to a benzene solution of 1,2-ditholane 1,1-dioxide (22) effected an exothermic reaction which on distillation provided 1,2-oxathiolane 2-oxide (23) in 92% yield.



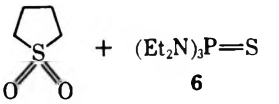
22 4 23 6

(13) G. Singh and H. Zimmer, *J. Org. Chem.*, **30**, 417 (1965).
(14) D. N. Harpp and J. G. Gleason, *Tetrahedron Lett.*, 1447 (1969).

Similarly the reaction of 1,2-dithiane 1,1-dioxide (24) with 4 afforded a mixture consisting of 10% thiolane 1,1-dioxide (26) and 90% 1,2-oxathiane 2-oxide (25).



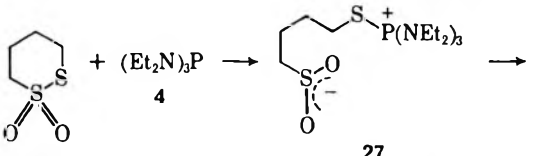
24 4 25



26 6

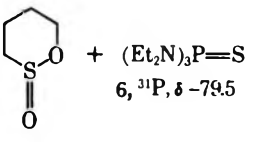
This alicyclic sulfinate ester was subsequently isolated in 64% yield.

The formation of both sulfone 26 and sulfinate ester 25 during desulfurization of 24 would indicate that the reaction proceeds *via* the phosphonium salt 27. This ionic intermediate was detected by ^{31}P nmr. Thus, when equimolar amounts of thiolsulfonate 24 and 4 were mixed in an nmr tube, an oil appeared immediately which exhibited a resonance at −62.1 ppm (relative to H_3PO_4), consistent with the phosphonium salt structure 27 (Table II). This signal slowly (5 min) disappeared and was replaced by a new resonance at −79.5 ppm, which is in good agreement with that observed for the aminophosphine sulfide 6 (Table II). Thus, it may be concluded that a phosphonium salt is formed as an intermediate in this reaction. The preferred formation of sulfinate ester appears to reflect the effect of ring size on the course of reaction.



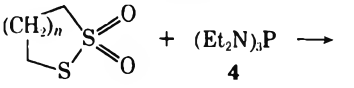
24 4 27

^{31}P, δ −62.1 ppm

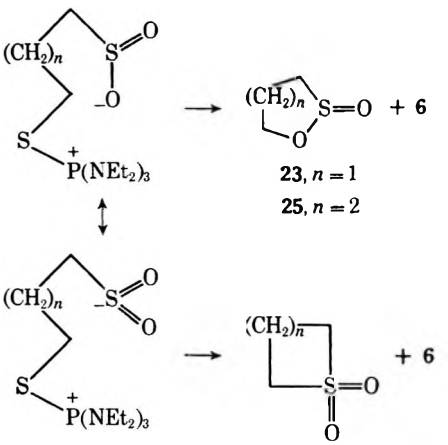


25 6

^{31}P, δ −79.5



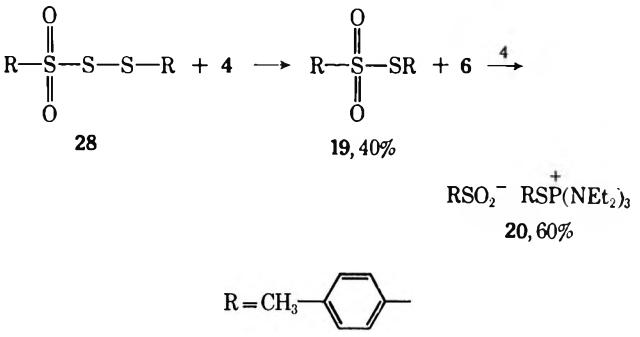
22, n = 1
24, n = 2 4



23, n = 1
25, n = 2

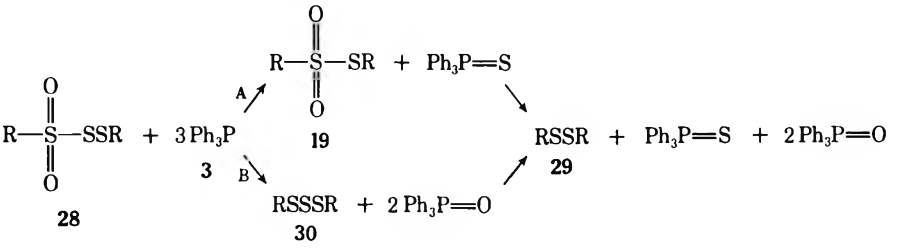
26, n = 2

The behavior of sulfenyl thiolsulfonates toward triphenylphosphine (**3**) and tris(diethylamino)phosphine (**4**) was also examined. The reaction of *p*-tolylsulfenyl *p*-toluenethiolsulfonate (**28**) with aminophosphine **4** afforded three products: *p*-tolyl toluenethiolsulfonate (**19**), phosphonium salt **20**, and phosphine sulfide **6**.



These observations are consistent with those obtained for the corresponding thiolsulfonate reaction.

In contrast, the reaction of sulfenyl thiolsulfonate **28** with 3 mol of triphenylphosphine (**3**) afforded only disulfide **29** (in addition to triphenylphosphine oxide and sulfide). The formation of disulfide in this reaction



may be rationalized in terms of two alternate pathways. Deoxygenation (path B) of **28** would afford the trisulfide **30** which is known[4b] to undergo rapid desulfurization to the disulfide **29**. Alternately, desulfurization of the sulfenyl thiolsulfinate prior to deoxygenation (path A) would also yield **29**.

When the reaction was performed with 1 molar equiv of triphenylphosphine (**3**), an 81% yield of thiolsulfonate **19** was realized. No trisulfide was observed. Thus, the reaction of **28** with triphenylphosphine proceeds *via* thiolsulfonate **19** as outlined in path A.

Experimental Section[15]

Preparation of Thiolsulfonates.—Benzyl phenylmethanethiolsulfonate[4c] (**9**), methyl methanethiosulfonate[16] (**7**), ethyl ethanethiolsulfonate[17a] (**11**), methyl,[17b] ethyl,[17a] benzyl,[4c] and *p*-tolyl[17c] *p*-toluenethiolsulfonates **14**, **15**, **16**, and **19** were prepared by reported procedures.

p-Bromobenzyl *p*-toluenethiolsulfonate (**17**) was prepared in 79% yield by the procedure of Boldyrev[18] from *p*-bromobenzyl bromide and potassium *p*-toluenethiolsulfonate, mp 84–85.5°.

Anal. Calcd for $C_{14}H_{13}BrO_2S_2$: C, 47.06; H, 3.67; S, 17.95. Found: C, 47.04; H, 3.76; S, 17.79.

p-Methylbenzyl *p*-toluenethiolsulfonate (**18**) was prepared in 60% yield by the procedure of Boldyrev[18] from *p*-methylbenzyl bromide and potassium *p*-toluenethiolsulfonate, mp 53–54°.

Anal. Calcd for $C_{15}H_{16}O_2S_2$: C, 61.63; H, 5.51; S, 21.94. Found: C, 61.35; H, 5.45; S, 21.77.

1,2-Dithiolane 1,1-Dioxide (**22**).—A solution of 20.1 g (200 mmol) of 1,3-propanedithiol in 450 ml of acetic acid was cooled to 5° and 60 ml (600 mmol) of a 35% aqueous hydrogen peroxide solution was added dropwise. The mixture was stirred overnight, the acetic acid removed under vacuum (below 40°), and the residue diluted with water and extracted with ethyl acetate. After neutralization with sodium carbonate, the extract was dried and concentrated under vacuum. The residue was crystallized from ethyl acetate–ether to afford 7.3 g (26%) of colorless crystals: mp 24.5–26°; ir (KBr) 1325 and 1110 cm^{-1}; nmr ($CDCl_3$) τ 6.25 (t, 2 H, J = 6.5 Hz), 6.53 (t, 2 H, J = 7 Hz), 7.46 (m, 2 H); mass spectrum parent ion at m/e 138, fragments at 46, 45, 74, and 64.

Anal. Calcd for $C_3H_6S_2O_2$: C, 26.07; H, 4.38; S, 46.40. Found: C, 26.09; H, 4.58; S, 45.96.

1,2-Dithiane 1,1-Dioxide (**24**).—A solution of 30.5 g (250 mmol) of 1,4-butanedithiol in 250 ml of acetic acid was cooled in an ice bath and 75 ml (770 mmol) of 35% aqueous peroxide solution was added slowly such that the reaction temperature did not rise above 35°. After stirring for 18 hr, the solvent was removed under vacuum, and the residue diluted with water, neutralized with sodium bicarbonate and extracted with benzene; the benzene extract was dried and the solvent removed under vacuum to yield a viscous oil which was crystallized from ether to provide 10.5 g (28%) of white crystals, mp 52–55°, which after two crystallizations from ether provided a pure sample: mp 54–56° (lit.[13] mp 54.5–55°); nmr (CCl_4) τ 7.0 (m, 4 H), 7.9 (broad multiplet, 4 H).

Desulfurization of Methyl Methanethiolsulfonate (**7**).—To a solution of 2.50 g (20 mmol) of **7** in dry ether was added 5.50 g (22 mmol) of tris(diethylamino)phosphine (**4**) in 20 ml of dry ether. An oil, which deposited immediately on mixing **7** with **4**, slowly crystallized. Filtration and recrystallization from ethanol afforded 1.5 g (80%) of dimethyl sulfone, mp 108–109° (lit.[20] mp 109°).

Similar desulfurization reactions were performed on thiolsulfonates **9**, **11**, **14**, **16**, **17**, and **18**. These results are summarized below (thiolsulfonate, product, yield, melting point or boiling point): thiolsulfonate **9**, dibenzyl sulfone **10**, 65%, mp 154–155° (lit.[21] mp 151°); thiolsulfonate **11**,[22] diethyl sulfone **12**, 50%, mp 70–73° (lit.[23] mp 74°), and ethyl ethanethiolsulfinate **13**, 15%, bp 61–63° (10 mm) [lit.[24] bp 62° (16 mm); thiolsulfonate **14**,[22] methyl *p*-tolyl sulfone, 6%, mp 85–87° (lit.[25] mp 86–87°), and methyl *p*-toluenesulfinate, 13%, bp 100–104° (0.1 mm), $n^{25}D$ 1.548 (lit.[26] $n^{25}D$ 1.543); thiolsulfonate **16**, benzyl *p*-tolyl sulfone, 70%, mp 140–141° (lit.[27] mp 145°); thiolsulfonate **17**, *p*-bromobenzyl *p*-tolyl sulfone, 72%, mp

(15) All melting points were recorded on a Gallenkamp melting point apparatus and are corrected. ^{31}P nmr spectra were measured on a Varian Associates DP-60 instrument at an oscillator frequency of 19.3 MHz. Analyses were performed by Organic Micro-analyses, Montreal, and Scandanavian Microanalytical Laboratories, Denmark.

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177–180° (lit.[28] mp 172°); thiolsulfonate **18**, *p*-methylbenzyl *p*-tolyl sulfone, 60%, mp 156–157° (lit.[29] mp 157°).

Desulfurization of Ethyl *p*-Toluenethiolsulfonate (15).—A solution of 2.16 g (10 mmol) of ethyl *p*-tolylthiolsulfonate (**15**) and 2.75 g (11 mmol) of the aminophosphine **4** in 10 ml of dry ether was stirred for 3 hr. The solvent was removed under vacuum and the residue was analyzed by vpc. By comparison of peak areas, the sulfone–sulfinate ester ratio was calculated to be 3:1. No pure products, however, were isolated from this reaction.

Attempted Desulfurization of *p*-Tolyl *p*-Toluenethiolsulfonate (19). Isolation of Adduct 20.—To a solution of 2.78 g (10 mmol) of *p*-tolyl *p*-toluenethiolsulfonate (**19**) in 10 ml of ether was added dropwise 2.50 g (10 mmol) of tris(diethylamino)phosphine (**4**). No heat was evolved; however, an oil precipitated immediately. The supernatant liquid was removed and the oil was washed eight times with fresh ether. The resulting oil was dried under vacuum for 24 hr to yield 5.0 g (92%) of adduct **20** as a tan, viscous, hygroscopic oil: nmr (benzene) τ 2.5 (m, 8 H, aromatic), 6.87 (m, 12 H, J_{HH} = 7 Hz, J_{PH} = 13 Hz), 7.60 (d, 3 H, J_{PH} = 2.5 Hz), 7.69 (s, 3 H), 8.85 (t, 18 H, J_{HH} = 7 Hz). The ^{31}P nmr of this adduct exhibited a strong resonance at −61.6 ppm relative to phosphoric acid.

Anal. Calcd for $C_{26}H_{44}N_3O_2PS_2 \cdot xH_2O$: C, 58.08; H, 8.63; N, 7.81; P, 5.76; S, 11.92. Found: C, 56.63; H, 8.93; N, 8.08; P, 5.45; S, 13.07. (Sample was reported to be highly hygroscopic.)

Desulfurization of 1,2-Dithiolane 1,1-Dioxide (22).—To a solution of 1.38 g (10 mmol) of 1,2-dithiolane 1,1-dioxide (**22**) in 25 ml of benzene was added dropwise 2.60 g (11 mmol) of tris(diethylamino)phosphine (**4**). An exothermic reaction occurred immediately upon addition of **4**. The mixture was stirred for 15 min, the solvent removed under vacuum, and the residue distilled under vacuum to yield 0.80 g (80%) of **23**: bp 48–49° (0.2 mm); n^{25}D 1.4862; ir (film) 1105 cm^{-1} (S=O); nmr ($CDCl_3$) τ 6.55 (m, 2 H), 8.65 (m, 4 H); mass spectrum parent ion at *m/e* 106, fragments at 43, 58, 42, and 78.

Anal. Calcd for $C_3H_6SO_2$: C, 33.93; H, 5.70; S, 30.19. Found: C, 33.08; H, 5.92; S, 29.36.

Desulfurization of 1,2-Dithiane 1,1-Dioxide (24).—A solution of 4.50 g (29.6 mmol) of 1,2-dithiane 1,2-dioxide (**24**) in 50 ml of dry benzene was cooled in an ice bath and 7.80 g (31.6 mmol) of tris(diethylamino)phosphine (**4**) was added slowly. After stirring the mixture for 10 min, the solvent was removed under vacuum and the residue fractionally distilled under vacuum to yield 2.25 g (64%) of **25** as colorless oil, bp 58–64° (0.2 mm), which on redistillation afforded an analytical sample: bp 60–61° (0.5 mm); n^{25}D 1.4862; ir (film) 1125 cm^{-1} (S=O).

Anal. Calcd for $C_4H_8O_2S$: C, 39.93; H, 6.70; S, 26.68. Found: C, 39.68; H, 6.73; S, 26.33.

***p*-Tolylsulfenyl *p*-Toluenethiolsulfonate (28).**—The method used was similar to that of Brooker, Child, and Smiles.[30] To a solution of 9.0 g (57 mmol) of *p*-toluenesulfenyl chloride[31] in 200 ml of anhydrous diethyl ether was added 13.3 g (59 mmol) of potassium *p*-toluenethiolsulfinate as a fine powder. The orange color of the sulfenyl chloride was discharged and a white precipitate of KCl formed. The reaction was stirred for 1.5 hr at room temperature and filtered, and the filtrate was evaporated to dryness. Crystallization of the crude solid from *n*-hexane gave 16.7 g (95%) of pale yellow crystals, mp 68.5–72.5°. Two recrystallizations from *n*-hexane afforded an analytical sample: mp 77.5–78.5°; ir (KBr) 1340 and 1140 cm^{-1} (–SO_2–); nmr (CCl_4) τ 2.15–3.0 (m, 8 H), 7.55 (singlet, 3 H), 7.65 (singlet, 3 H); mass spectrum parent ion *m/e* 310 fragments at 91, 123, 139, and 155.

Anal. Calcd for $C_{14}H_{14}O_2S_3$: C, 54.16; H, 4.54; S, 30.99. Found: C, 54.26; H, 4.49; S, 30.39.

Reaction of *p*-Tolylsulfenyl *p*-Toluenethiolsulfonate (28) with Tris(diethylamino)phosphine (4).—A solution of 0.25 g (1 mmol) of **4** in 25 ml of benzene was added slowly to 0.31 g (1 mmol) of **28** dissolved in 10 ml of benzene. The reaction was stirred for 6.5 hr at room temperature and the benzene was removed under vacuum. The residue was heated with *n*-hexane and an insoluble oil **20** (0.35 g) separated. The ^{1}H nmr of this oil was identical with that of **20** prepared by the reaction of **19** and **4**. The hexane soluble portion was chromatographed over silica gel. Elution with 1:1 hexane–chloroform afforded 0.10 g (40%) of *p*-tolyl *p*-toluenethiolsulfonate (**19**), which after crystallization from ethanol gave white crystals, mp and mmp 74–78° (lit.[32] mp 78.5–79.5°). Further elution gave 0.15 g of tris(diethylamino)phosphine sulfide (**6**).

Reaction of *p*-Tolylsulfenyl *p*-Toluenethiolsulfonate (28) with 3 Mol of Triphenylphosphine (3).—A solution of 2.36 g (9 mmol) of **3** in 50 ml of benzene was added over 1 hr to 0.93 g (3 mmol) of **28** dissolved in 50 ml of benzene. A precipitate formed and then redissolved after 2 hr. The reaction was stirred for 6 hr at room temperature, the benzene removed under vacuum, and the residue chromatographed over silica gel. Elution with 3:1 hexane–chloroform gave 0.50 g (68%) of di-*p*-tolyl disulfide (**29**) as a yellow oil which on crystallization from ethanol afforded white needles, mp 45.5–47.5° (lit.[4c] mp 47°). Elution with 1:1 hexane–chloroform provided, after crystallization from ethanol, 0.75 g (85%) of triphenylphosphine sulfide, mp 159–161.5° (lit.[4b] mp 161°). The use of 1:3 hexane–chloroform as eluent gave, after crystallization from diethyl ether, 0.95 g (57%) of triphenylphosphine oxide, mp 157–159° (lit.[13] mp 156°).

Reaction of *p*-Tolylsulfenyl *p*-Toluenethiolsulfonate (28) with Equimolar Triphenylphosphine (3).—A solution of 0.26 g (1 mmol) of **3** in 50 ml of benzene was added over 40 min to 0.31 g (1 mmol) of **28** dissolved in 50 ml of benzene. The reaction was stirred for 4 hr at room temperature, the benzene removed under vacuum, and the residue chromatographed over silica gel. Elution with 1:1 petroleum ether (30–60°)–chloroform gave a pale yellow solid, which, on crystallization from ethanol afforded 0.20 g (68%) of triphenylphosphine sulfide, mp 164–165° (lit.[4b] mp 161°). The filtrate was evaporated to dryness and crystallized from ethanol to produce 0.23 g (81%) of *p*-tolyl *p*-toluenethiolsulfonate (**19**), mp and mmp 71–75° (lit.[32] mp 78.5–79.5°).

Registry No.—**4**, 2283-11-6; $(Et_2N)_3P{=}O$, 2622-07-3; **6**, 4154-77-2; $(Et_2N)_3P^+SCH_2Ph\ BF_4^-$, 26893-33-4; **17**, 26885-97-2; **18**, 21668-99-5; **20**, 26885-99-4; **22**, 18321-16-9; **23**, 24308-28-9; **24**, 18321-15-8; **25**, 24308-29-0; **28**, 26886-04-4.

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Benzyne Reaction. IX.[1] Benzyne Reaction of o-Halobenzenes with Acetonitrile or Phenylacetonitrile in Organic Solvents

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The benzyne reaction of a number of ortho-substituted halobenzenes with acetonitrile or phenylacetonitrile was carried out, in various organic solvents together with the appropriate amines in the presence of sodium amide, to give the desired meta-substituted phenylacetonitriles together with meta-substituted amino compounds. When o-chloro- and o-methylhalobenzene were used in this reaction, a mixture of the corresponding 1,3- and 1,2-disubstituted benzenes was obtained.

In previous papers, we reported the syntheses of many compounds by application of the benzyne reaction.[1,3-9] We have also reported that syntheses of a number of aminoalkyl meta-substituted phenylacetates,[10] having anticholinergic activity, *via* phenylacetic acids obtained on the hydrolysis of the corresponding phenylacetonitriles (A). Furthermore, the syntheses of various isoquinolines using phenethylamines prepared by the reduction of the corresponding phenylacetonitriles have been reported.[11] Thus, phenylacetonitriles are considerably important intermediates in the syntheses of various kinds of medicinal substance since they are convertible to phenylacetic acids and phenethylamines on hydrolysis and reduction, respectively. Among the various methods available for the preparation of meta-substituted phenylacetonitriles, benzyne reaction[1,6] of o-halobenzenes with acetonitriles has been proved to be one of the most useful methods, notably in the syntheses of m-alkoxyphenylacetonitriles, using liquid ammonia as solvent. Since liquid ammonia is not suitable as solvent from the industrial point of view, it is of interest to reinvestigate the above reaction with the use of the other solvent. In general, aliphatic amines such as piperidine, morpholine, and dimethylamine, instead of liquid ammonia, in some cases, together with ether[12-14] have been used in the benzyne reaction as solvents. In these cases they were not only used as solvent but also as nucleophiles to the benzyne. Since only liquid ammonia has hitherto been used in the case of the compounds possessing active hydrogen such as alkylnitrile, we examined the benzyne reaction with the use of various kinds of organic solvents instead of liquid ammonia in the presence of sodium amide. We now wish to report these results.

The benzyne reaction of o-chloroanisole, o-benzyloxychlorobenzene, 1,2-dichlorobenzene, and o-chlorotoluene with acetonitrile and phenylacetonitrile was examined and found to give the meta-substituted phenylacetonitriles. All the products, if they were known, were identified with authentic specimens[1,6] by comparison of the spectroscopic data. If not, their structures were determined by the microanalyses and nmr and ir spectra. In some cases, 2,2-diphenylacetonitriles (B) were also formed as described in the Experimental Section. Among the products, m-aminobenzene derivatives, which would be formed by nucleophilic reaction, were also identified by their microanalyses and nmr and ir spectra. These result are shown in Table I.

As shown in Table I, in the benzyne reaction using amines as solvent, much more aminobenzenes (C) were formed than nitriles (A), the latter yield of which was less than 25%. The possible reason for this interesting feature would be due to the fact that the amines had reacted predominantly with benzyne as nucleophiles before the anion which formed from acetonitrile or phenylacetonitrile reacted with the benzyne. When N-methylmorpholine was used as solvent in the benzyne reaction of o-chloroanisole, 3-methoxy-N-methylaniline (XI) was obtained as unusual product in good yield. It is of interest that the heating of o-chloroanisole with N-methylmorpholine in tetrahydrofuran in the presence of sodium amide also afforded XI, whose structure was proved to be correct by comparison with an authentic sample prepared by methylation of 3-methoxyaniline.

When using tetrahydrofuran as solvent, 3-methoxyaniline was also obtained as in the case of liquid ammonia. In this case, this reaction seemed to occur due to the ammonia which formed during the reaction. In these series of benzyne reactions, when the substituent R_1 at the ortho position on the benzene ring was electron-attracting group such as methoxyl or benzyloxyl group, a cyanomethyl or amino group was introduced to the meta position to afford the meta-substituted benzenes However, with an electron-releasing group such as methyl, the reaction did not proceed with selectivity to give both compounds, ortho- and meta-substituted benzenes.[14] Among the compounds we prepared, the ratio of ortho-substituted benzene to meta isomer with V, VI, VIII, and XIV was investigated by gas chromatography, and the results are summarized in Table II.

As shown in Table II, when the substituent R_1 is methyl group, the ratio of ortho isomer to meta isomer is 1:1 and, when R_1 is chlorine group, the ratio of ortho

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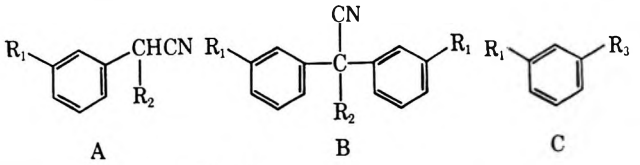
TABLE I

YIELDS OF BENZYNE REACTION PRODUCTS OF HALOBENZENES WITH NITRILES IN VARIOUS ORGANIC SOLVENTS



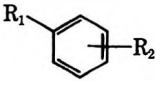
A B C

Starting material: Halobenzene	Starting material: Nitrile	Solvent (volume ratio)	Compd		Product: R_1	Product: R_2	Product: R_3	Yield, %
o-Chloroanisole	Acetonitrile	Piperidine	A	I	OCH_3	H		2.6
			C	IX	OCH_3			52.1
o-Chloroanisole	Acetonitrile	Morpholine	A	I	OCH_3	H		15.6
			C	X	OCH_3			51.1
o-Chloroanisole	Acetonitrile	Morpholine–triethylamine (1:1)	A	I	OCH_3	H		Trace
			B	XV	OCH_3	H		1.7
			C	X	OCH_3			48.5
o-Chloroanisole	Acetonitrile	Morpholine–triethylamine (2:1)	A	I	OCH_3	H		25.2
			B	XV	OCH_3	H		3.9
			C	X	OCH_3			45.5
o-Chloroanisole	Acetonitrile	*N*-Methylmorpholine	A	I	OCH_3	H		Trace
			B	XV	OCH_3	H		11.1
			C	XI	OCH_3		$NHCH_3$	40.0
o-Chloroanisole	Acetonitrile	Tetrahydrofuran	A	I	OCH_3	H		6.1
			B	XV	OCH_3	H		13.4
			C	XII	OCH_3		NH_2	9.2
o-Chloroanisole	Acetonitrile	Dioxane	A	I	OCH_3	H		Trace
			B	XV	OCH_3	H		5.5
			C	XII	OCH_3		NH_2	3.5
o-Chloroanisole	Phenylacetonitrile	Morpholine–triethylamine (2:1)	A	II	OCH_3	C_6H_5		26.7
			C	X	OCH_3			45.3
o-Chloroanisole	Phenylacetonitrile	Tetrahydrofuran	A	II	OCH_3	C_6H_5		54.8
o-Chloroanisole	Phenylacetonitrile	Dioxane	A	II	OCH_3	C_6H_5		27.4
2-Benzyloxy-1-chlorobenzene	Acetonitrile	Morpholine–triethylamine (2:1)	A	III	$OCH_2C_6H_5$	H		2.6
			C	XIII	$OCH_2C_6H_5$			40.7
2-Benzyloxy-1-chlorobenzene	Phenylacetonitrile	Tetrahydrofuran	A	IV	$OCH_2C_6H_5$	C_6H_5		58.5
1,2-Dichlorobenzene	Acetonitrile	Morpholine–triethylamine (2:1)	A	V	Cl	H		5.7[a]
1,2-Dichlorobenzene	Phenylacetonitrile	Tetrahydrofuran	A	VI	Cl	C_6H_5		20.6[a]
2-Chlorotoluene	Acetonitrile	Morpholine–triethylamine (2:1)	A	VII	CH_3	H		15.2[a]
			C	XIV	CH_3			47.1[a]
2-Chlorotoluene	Phenylacetonitrile	Tetrahydrofuran	A	VIII	CH_3	C_6H_5		48.9[a]

[a] This shows a total yield of ortho and meta isomers.

TABLE II

FORMATION RATIO OF THE ISOMERS IN THE BENZYNE REACTION OF HALOBENZENES WITH NITRILES



R_1	R_2	Compd	Solvent (volume ratio)	Yield, %	Isomer ratio ortho:meta
CH_3	CH_2CN	VII	Morpholine–triethylamine (2:1)	15.2	51.8:48.2
CH_3		XIV	Morpholine–triethylamine (2:1)	47.1	45.1:54.9
CH_3	C_6H_5CHCN	VIII	Tetrahydrofuran	48.9	23.5:76.5[a]
Cl	CH_2CN	V	Morpholine–triethylamine (2:1)	5.7	26.5:73.5
Cl	C_6H_5CHCN	VI	Tetrahydrofuran	20.6	19.1:80.9

[a] This ratio was measured by nmr spectral integration.

isomer to meta isomer becomes 1:4. Benzyne reaction with the use of morpholine–triethylamine as solvent between ortho-substituted halobenzenes and acetonitrile afforded meta-substituted phenylacetonitriles in moderate yields and, with phenylacetonitrile, tetrahydrofuran was found to be one of the best solvents.

Thus, two kinds of solvents, namely tetrahydrofuran and morpholine–triethylamine, were found to be available in the benzyne reaction of ortho-substituted halobenzenes with aliphatic nitriles.

Experimental Section[15]

3-Methoxyphenylacetonitrile (I). Benzyne Reaction of o-Chloroanisole. A.—To a stirred mixture of 30 ml of morpholine, 15.4 g of sodium amide, and 11.6 g of acetonitrile was added 10 g of *o*-chloroanisole. After the stirring had been continued for 3 hr at room temperature, the excess sodium amide was decomposed with water and extracted with ether. The extract was washed with 20% HCl to remove the basic product which was dried and evaporated. The residual oil was distilled *in vacuo* to give 1.6 g (15.6%) of I as a yellow oil, bp 116–119° (2 mm) [lit.[20] bp 124–128° (5 mm)], whose spectroscopic data were identical with those of authentic specimen. The above acidic washing was made basic with 30% NaOH and extracted with ether. The extract was washed with water, dried over Na_2SO_4, and evaporated. The remaining residue was distilled *in vacuo* to give 6.9 g (51.1%) of 3-methoxy-1-morpholinobenzene (X), bp 140–145° (0.5 mm) [lit.[21] bp 113° (0.15 mm)], whose picrate was recrystallized from ethanol–ether to give yellow prisms, mp 195–196° (lit.[21] mp 196–197°).

B.—To a stirred mixture of 100 ml of piperidine, 27.4 g of sodium amide, and 14.4 g of acetonitrile was added 25 g of *o*-chloroanisole. After the stirring had been continued for 5 hr at room temperature, the reaction mixture was worked up as above to give 0.5 g (2.6%) of 3-methoxyphenylacetonitrile and 17.1 g (52.1%) of 3-methoxy-1-piperidinobenzene (IX), bp 130–135° (0.5 mm) [lit.[21] bp 110° (0.2 mm)], whose picrate was recrystallized from ethanol–ether to afford yellow needles, mp 159–160° (lit.[21] mp 159–160°).

C.—To a stirred mixture of 30 ml of morpholine, 30 ml of triethylamine, 15.4 g of sodium amide, and 11.6 g of acetonitrile was added 10 g of *o*-chloroanisole and the stirring was continued for 4 hr at 40–45°. The reaction mixture was treated as above to give a trace of I, 0.3 g (1.7%) of bis(3-methoxyphenyl)-acetonitrile (XV), and 6.1 g (44.4%) of X.[21] All of them were identified by the comparison of their spectroscopic data with those of authentic specimens.

D.—To a stirred mixture of 40 ml of morpholine, 20 ml of triethylamine, 15.4 g of sodium amide, and 11.6 g of acetonitrile was added 10 g of *o*-chloroanisole. After the stirring had been continued for 4 hr at 30–40°, the reaction mixture was worked up as usual to give 2.6 g (25.2%) of I, 0.35 g (3.9%) of XV, and 6.3 g (45.5%) of X.[21] The compound (XV) was obtained by recrystallization of the residual substance obtained after removal of I by distillation *in vacuo*.

E.—To a stirred solution of 9.6 g of sodium amide and 5.8 g of acetonitrile in 70 ml of tetrahydrofuran was added 10 g of *o*-chloroanisole. After the stirring had been continued for 12 hr at room temperature, the reaction mixture was worked up as usual to give 0.63 g (6.1%) of I, 1.2 g (13.4%) of XV, and 0.8 g (9.2%) of 3-methoxyaniline, whose hydrochloride was identified by the mixture melting point test and comparison of the spectroscopic data with those of authentic specimen.

F.—To a stirred mixture of 70 ml of dioxane, 9.6 g of sodium amide, and 5.8 g of acetonitrile was added 10 g of *o*-chloroanisole, and the stirring was continued for 2 hr at room temperature. After refluxing for 5 hr, treatment of the reaction mixture as usual afforded a trace of I, 0.7 g (5.5%) of XV, and 0.3 g (3.5%) of XII.

G.—To a mixture of 20 ml of *N*-methylmorpholine, 8.2 g of sodium amide, and 5.8 g of acetonitrile was added 10 g of *o*-chloroanisole and the mixture was refluxed for 3 hr. After the reaction, treatment of the above mixture afforded a trace of I and 1 g (11.1%) of XV as a neutral substance. Washing with hydrochloric acid, obtained as for method A, was treated as above to give 3.2 g (40.0%) of 3-methoxy-*N*-methylaniline (XI) [bp 130–135° (3 mm); ir ν_{max}^{liquid} 3420 cm^{-1} (NH); nmr ($CDCl_3$) τ 7.26 (3 H, s, NCH_3), 6.28 (3 H, s, OCH_3), 6.37 (1 H, s, NH), 2.70–3.95 (4 H, m, aromatic protons)], whose hydrochloride was recrystallized from ethanol–ether to give colorless needles, mp 113–115°.

Anal. Calcd for $C_8H_{11}ON \cdot HCl$: C, 57.67; H, 7.39; N, 8.08. Found: C, 57.55; H, 7.45; N, 8.12.

This was identified by the comparison of the ir spectrum of the authentic specimen, which was prepared by the reduction of *N*-formyl-3-methoxyaniline with lithium aluminum hydride.

1-(3-Methoxyphenyl)-1-phenylacetonitrile (II). A.—To a mixture of 50 ml of morpholine, 25 ml of triethylamine, 9.6 g of sodium amide, and 16.4 g of phenylacetonitrile was added 10 g of *o*-chloroanisole. After the stirring had been continued at 28–35° for 5 hr, the mixture was treated as usual to give 4.2 g (26.7%) of II, bp 162–165° (2 mm) [lit.[1] bp 152–154° (1 mm)], whose ir and nmr spectra were identical with those of authentic specimen. From the acidic washing of I by method A, 6.2 g (45.3%) of X[21] was obtained.

B.—To a stirred mixture of 60 ml of tetrahydrofuran, 9.6 g of sodium amide, and 16.4 g of phenylacetonitrile was added 10 g of *o*-chloroanisole. The mixture was then refluxed for 4 hr and worked up as usual to afford 8.6 g (54.8%) of II.

C.—To a mixture of 60 ml of dioxane, 9.6 g of sodium amide, and 16.4 g of phenylacetonitrile was added 10 g of *o*-chloroanisole. After the stirring had been continued under reflux for 4 hr, the mixture was worked up as usual to give 4.3 g (27.4%) of II.

3-Benzyloxyphenylacetonitrile (III).—To a stirred mixture of 40 ml of morpholine, 20 ml of triethylamine, 15.4 g of sodium amide, and 11.6 g of acetonitrile was added 15.4 g of 2-benzyloxy-1-chlorobenzene. After the stirring had been continued at 35–40° for 6 hr, the reaction mixture was treated as usual to give 0.4 g (2.6%) of III as a pale yellowish oil [bp 170–175° (1 mm) [lit.[6] bp 188–190° (3 mm)]; ir ν_{max}^{liquid} 2250 cm^{-1} (C≡N); nmr ($CDCl_3$) τ 6.45 (2 H, s, CH_2CN), 5.09 (2 H, s, OCH_2), 2.65–3.42 (9 H, m, aromatic protons)] and 7.4 g (40.7%) of 3-benzyloxy-1-morpholinobenzene (XIII) [bp 180–185° (0.7 mm); nmr ($CDCl_3$) τ 7.01 (4 H, t, CH_2NCH_2), 6.26 (4 H, t, $-CH_2OCH_2-$), 5.08 (2 H, s, $OCH_2C_6H_5$), 2.63–3.80 (9 H, m, aromatic protons)], whose hydrochloride was recrystallized from ethanol–ether to give colorless needles, mp 173–174.5°.

Anal. Calcd for $C_{17}H_{19}O_2N \cdot HCl$: C, 66.75; H, 6.60; N, 4.58. Found: C, 66.92; H, 6.90; N, 4.61.

1-(3-Benzyloxyphenyl)-1-phenylacetonitrile (IV).—To a stirred mixture of 80 ml of tetrahydrofuran, 9.6 g of sodium amide, and 16.4 g of phenylacetonitrile was added 15.4 g of 2-benzyloxy-1-chlorobenzene. The mixture was refluxed for 4 hr and then treated as usual to give 12.4 g (58.5%) of IV as a pale yellowish oil: bp 200–205° (0.1 mm); ir ν_{max}^{liquid} 2220 cm^{-1} (C≡N); nmr ($CDCl_3$) τ 5.13 (2 H, s, OCH_2Ph), 5.13 (1 H, s, >CHCN), 2.61–3.41 (14 H, m, aromatic protons).

A Mixture of 1-(3-Chlorophenyl)-1-phenylacetonitrile and 1-(2-Chlorophenyl)-1-phenylacetonitrile (VI).—To a mixture of 60 ml of tetrahydrofuran, 9.6 g of sodium amide, and 16.4 g of phenylacetonitrile was added 10.3 g of 1,2-dichlorobenzene. The mixture was refluxed for 4 hr and then worked up as usual to afford 3.3 g (20.6%) of VI as a yellow oil [bp 161–164° (1 mm); ir ν_{max}^{liquid} 2230 cm^{-1} (C≡N); nmr ($CDCl_3$) τ 5.05 (s, >CHCN of 3-chloro derivative), 4.47 (s, >CHCN of 2-chloro derivative), 2.63–3.07 (m, aromatic protons)], whose Beilstein test was positive.

A Mixture of 3-Chlorophenylacetonitrile and 2-Chlorophenylacetonitrile (V).—To a stirred mixture of 40 ml of morpholine, 20 ml of triethylamine, 14.1 g of sodium amide, and 11.5 g of acetonitrile was added 10.3 g of 1,2-dichlorobenzene. After the stirring had been continued at 35–40° for 4 hr, the reaction mixture was worked up as usual to afford 0.6 g (5.7%) of V as an oil [bp 95–97° (1 mm); ir ν_{max}^{liquid} cm^{-1} 2230 (C≡N); nmr ($CDCl_3$) τ 6.37 (s, CH_2CN of 3-chloro derivative), 6.27 (s, CH_2CN of 2-chloro derivative), 2.60–2.90 (m, aromatic protons)], whose Beilstein test was positive.

A Mixture of 2-Methylphenylacetonitrile and 3-Methylphenylacetonitrile (VII).—To a mixture of 50 ml of morpholine, 25 ml of triethylamine, 17.1 g of sodium amide, and 13.1 g of acetonitrile was added 10 g of 2-chlorotoluene. After the stirring

(15) Melting points and boiling points were not corrected. Gas chromatography was taken with Hitachi K-23 or JGC-750 using 10% PEG-succinate on Celite 545, 5% OV-17 on Gas Chromosorb Q, and 30% Apiezon Grease L on Celite 545 as column; ir, and nmr spectra were determined on Shimazu spectrometer, and JNM-MH-60 with tetramethylsilane as internal reference, respectively. The authentic samples of ortho- and meta-substituted phenylacetonitrile used for the comparison of the gas chromatographic data were prepared by the methods in the literatures.[16-19]

(16) M. S. Newman, *J. Amer. Chem. Soc.*, **62**, 2295 (1940).

(17) O. Grummitt and E. N. Case, *ibid.*, **64**, 880 (1942).

(18) G. Lock and V. Rieger, *Chem. Ber.*, **86**, 74 (1953).

(19) R. A. Barnes and L. Gordon, *J. Amer. Chem. Soc.*, **71**, 2644 (1949).

(20) H. Tsukamoto and S. Toki, *Pharm. Bull.* (Tokyo), **3**, 239 (1955).

(21) H. Gilman and R. H. Kyle, *J. Amer. Chem. Soc.*, **74**, 3027 (1952).

had been continued at 35–40° for 4 hr, the reaction mixture was worked up as usual to give 1.5 g (15.2%) of VII as a colorless oil [bp 94–96° (3 mm); ir ν_{max}^{liquid} 2230 cm^{-1} (C≡N); nmr ($CDCl_3$) τ 7.83 (s, CH_3 of 2-methyl derivative), 7.80 (s, CH_3 of 3-methyl derivative), 6.60 (s, CH_2CN of the former), 6.57 (s, CH_2CN of the latter), 2.77–3.23 (m, aromatic protons)] and 6.2 g (47.1%) of XIV as a colorless oil, bp 114–116° (3 mm), both of which were separated to the following two components by the preparative gas chromatography. The first fraction afforded 2-methyl-1-morpholinobenzene [nmr ($CDCl_3$) τ 7.72 (3 H, s, CH_3), 7.18 (4, H, t, CH_2NCH_2), 6.20 (4 H, t, CH_2OCH_2), 3.71–2.65 (4 H, m, aromatic protons)], whose hydrochloride was recrystallized from ethanol–ether to give colorless needles, mp 185–186°.

Anal. Calcd for $C_{11}H_{15}ON \cdot HCl$: C, 62.08; H, 7.58; N, 6.59. Found: C, 62.12; H, 7.65; N, 6.60.

The second fraction gave 3-methyl-1-morpholinobenzene: mp 40.5–42° (from petroleum ether); nmr ($CDCl_3$) τ 7.70 (3 H, s, CH_3), 6.91 (4 H, t, CH_2NCH_2), 6.18, (4 H, t, CH_2OCH_2), 3.45–2.65 (4 H, m, aromatic protons).

Anal. Calcd for $C_{11}H_{15}ON$: C, 74.50; H, 8.52; N, 7.90. Found: C, 74.65; H, 8.61; N, 7.92.

A Mixture of 1-(2-Methylphenyl)-1-phenylacetonitrile and 1-(3-Methylphenyl)-1-phenylacetonitrile (VIII).—To a mixture of 60 ml of tetrahydrofuran, 9.6 g of sodium amide, and 16.4 g of phenylacetonitrile was added 8.9 g of 2-chlorotoluene. The reaction mixture was refluxed for 4 hr and worked up as usual to give 7 g (48.9%) of VIII as a pale yellowish oil: bp 141–143° (1 mm); ir ν_{max}^{liquid} 2230 cm^{-1} (C≡N); nmr ($CDCl_3$) τ 7.80 (s, CH_3 of 2-methyl derivative), 7.76 (s, CH_3 of 3-methyl derivative), 5.03 (s, >CHCN of 3-methyl derivative), 4.79 (s, >CHCN of 2-methyl derivative), 2.61–3.12 (m, aromatic protons).

Registry No.—IV, 26926-49-8; V, 1529-41-5; VI, 26926-51-2; VII, 2947-60-6; VIII, 26926-53-4; XI, 14318-66-2; XI hydrochloride, 26926-55-6; XIII, 26926-56-7; XIII hydrochloride, 26926-57-8; XIV, 7025-91-4; 2-methyl-1-morpholinobenzene hydrochloride, 26926-59-0; acetonitrile, 75-05-8; phenylacetonitrile, 140-29-4; *o*-chloroanisole, 766-51-8; 2-benzyloxy-1-chlorobenzene, 949-38-2; 1,2-dichlorobenzene, 95-50-1; 2-chlorotoluene, 95-49-8.

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Alkali Metal Reductions of Epoxides, Ketals, and Related Heterocycles. Intermediacy of Carbanions[1]

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Solutions of alkali metals in liquid ammonia reduce aromatic epoxides from the "most hindered" position to afford isomerically pure alcohols. Such reductions proceed *via* the most stable of two possible carbanions as demonstrated by alkylation and deuteration experiments. Aliphatic epoxides are likewise reduced to alcohols. Similar cleavages of aromatic, but not aliphatic, ketals and thioketals afford the corresponding hydrocarbons in good to excellent yield, though a deficiency of metal in such systems gives hydroxy ethers or their sulfur analogs. Monocarbanions, not *gem*-dicarbanions, have been shown to be intermediates in the reductions of ketals. Aromatic aziridines are reduced to give amines, but a reverse aldol-type condensation has been observed with one highly unsymmetrically arylated aziridine.

Although small heterocyclic ring systems such as epoxides and cyclic ketals have been reductively cleaved by a variety of reagents,[3] similar reactions effected by means of alkali metals in liquid ammonia and other inert solvents have been accomplished only in a few cases. For example, ethylene oxide,[4] indene oxide,[5] and propylene oxide[6] have been reduced by sodium in ammonia, but products were either not isolated or yields of alcohols were only fair. Certain steroidal epoxides have been cleaved by the more potent lithium–ethylamine system, but reduction of olefinic double bonds was also realized.[7,8] In similar, but unrelated studies, benzophenone diethylketal has been reported to afford a variety of products upon treatment with sodium or potassium in liquid ammonia.[9] Certain other ketals have been likewise cleaved in ammonia,[10,11] but alcohol coreagents were often present which led to concomitant reduction of aromatic rings; in addition, the yields in these reactions were only fair or not reported. Two related classes of compounds, aziridines and thioketals, appear not to have been reduced by alkali metals in ammonia. However, two bisthioketals were cleaved by lithium–ethylamine, but reduction of olefins occurred in one case,[12] and no yield was reported in the other.[13]

It has been suggested that dissolving metal reductions of epoxides and ketals proceed *via* carbanionic intermediates, but this has not been experimentally demonstrated. Indeed, one report[9] surprisingly postulates that *gem*-dialkali derivatives of diphenylmethane are intermediates in the reduction of benzophenone diethylketal in liquid ammonia.

Thus, it was the intent of the present research to not only determine the best conditions, and the scope and limitations of such reductions, but also to prove the intermediacy of carbanions. The latter was to be accom-

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(2) (a) Author to whom correspondence should be directed; (b) Undergraduate Research Participant.

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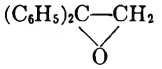
plished by performing appropriate trapping experiments. Of particular interest was the possibility that the small number of known *gem*-diorganometallics[14] might be expanded by reduction of ketals, especially in nonprotic solvents like THF or monoglyme. Finally, it was of interest to determine if aziridines might similarly be reduced to amines.

Results with Epoxides.—First, optimum conditions for the reduction of styrene oxide were established. Thus, treatment of this epoxide with 2 equiv of sodium in liquid ammonia cleanly afforded 2-phenylethanol (**1**) in 83% yield after only a 45-min reaction period. Similar amounts of alcohol **1** were obtained by employing lithium, sodium, or potassium in ammonia either at −33° or at −80°. Lower yields of **1** were obtained, though, using sodium–alcohol–ammonia or lithium–methylamine, perhaps because of ring opening by the more nucleophilic solvents. Interestingly, 1-phenylethanol (**3**), the alcohol obtained upon reduction of styrene oxide with lithium aluminum hydride,[3] was not observed in any of the above reductions. This fact suggests that the reductions of styrene oxide proceed *via* 1,3-dianion **2**, a relatively stable benzylic-type carbanion, rather than *via* the less stable **4**, a primary carbanion.

1, M = H
2, M = Na, K, Li

3, M = H
4, M = Na, Li, K

Similarly, *trans*-stilbene oxide and 1,1-diphenylethylene oxide (**5**) were reduced by sodium in ammonia to afford 1,2-diphenylethanol and 2,2-diphenylethanol (**6**) in yields of 77 and 89%, respectively. In the latter reaction, 1,1-diphenylethanol (**8**) was not observed indicating that this reaction apparently proceeds *via* dianion **7** rather than the less stable **9**.



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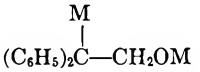
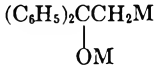
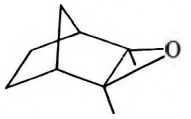


6, M = H
7, M = Na



8, M = H
9, M = Na

Next, strictly aliphatic epoxides were found to also undergo reduction by sodium in ammonia. Thus, cyclohexene oxide and *exo*-norbornene oxide (**10**) afforded cyclohexanol and *exo*-norbornanol (**11**) in yields of 60 and 82%, respectively. Likewise, 1,2-epoxybutane afforded 2-butanol in 55% yield.



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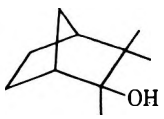

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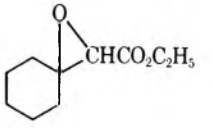
Finally, ethyl β,β-pentamethyleneglycidate (**12**), an epoxy ester, was reduced by 2 equiv of lithium in ammonia to afford hydroxy ester **13** in 46% yield; as above, the reaction apparently proceeded *via* the more stable resonance stabilized dianion **14** since no isomeric alcohol was observed. The use of sodium rather than lithium in the reduction of **12** was not satisfactory since a mixture of products was obtained which presumably arose from Claisen-type condensations.[15]



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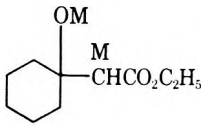
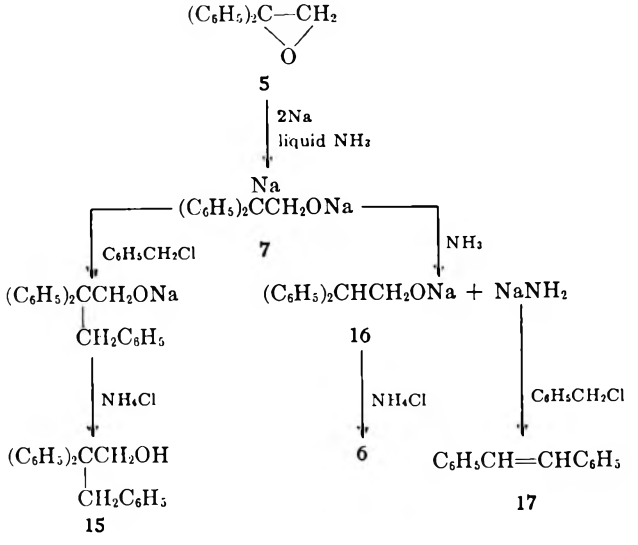


13, M = H
14, M = Li

Attention was then directed toward trapping intermediate 1,3-dianions in the reductions of epoxides by dissolving metals. 1,1-Diphenylethylene oxide (**5**) was selected as the model substrate since dianion **7**, its apparent reduction intermediate, was expected to be somewhat stable to ammonolysis. This was a reasonable assumption because related alkali alkyldiphenylmethides have a finite lifetime in this solvent.[16] Thus, when a mixture of epoxide **5** and benzyl chloride in ether was added to 2 equiv of sodium in ammonia, alkyl derivative **15** was indeed obtained in low yield; the remainder of the product consisted of alcohol **6** and stilbene (**17**). Such products can be rationalized by considering dianion **7** to undergo not only C-alkylation to afford **15**, but also rapid ammonolysis to give alkoxide **16** and sodium amide (Scheme I). It is well known that sodium amide reacts with benzyl chloride[17] to afford stilbene.

SCHEME I



Surprisingly, alkyl derivative **15** could not be obtained unless the epoxide and alkyl halide were simultaneously added to the reducing media; otherwise, only alcohol **6** and stilbene were realized. This would suggest that despite the fact that dianion **7** consists of a benzhydrylic carbanion, it is too basic to survive in liquid ammonia. This was verified by attempting the reverse reaction, *viz.*, treating alcohol **6** with 2 equiv of

(14) For example, see E. M. Kaiser, F. E. Henoch, and C. R. Hauser, *J. Amer. Chem. Soc.*, **90**, 7287 (1968); E. M. Kaiser and C. R. Hauser, *ibid.*, **88**, 2343 (1966).

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(17) C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Broadhag, *J. Amer. Chem. Soc.* **78**, 1653 (1956).

sodium amide in ammonia; however, no color developed and work-up gave only recovered 6 (eq 1).

$$(C_6H_5)_2CHCH_2OH + 2NaNH_2 \xrightarrow{\text{liquid } NH_3} (C_6H_5)_2\overset{\overset{Na}{|}}{C}CH_2ONa \quad (1)$$

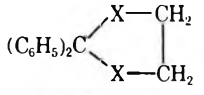
6 7

In order to avoid the ammonolysis described above, styrene oxide was reduced by 2 equiv of lithium in hexamethylphosphoramide–ether to afford an intense red solution. That a benzylic type carbanion was indeed present was demonstrated by treatment of the solution with deuterium oxide to afford α-deuterated 2-phenylethanol (eq 2); the nmr spectra of the compound indicated that it contained 0.8 benzylic deuterium atom per molecule.

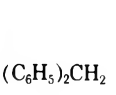
$$C_6H_5CH\text{—}CH_2 + 2Li \xrightarrow[\text{ether}]{\text{HMPA}}$$

$$\overset{\overset{Li}{|}}{C_6H_5CHCH_2OLi} \xrightarrow[\text{then } H_2O]{D_2O} \overset{\overset{D}{|}}{C_6H_5CHCH_2OH} \quad (2)$$

Results with Ketals and Related Compounds.—The results obtained in liquid ammonia will be discussed first. Benzophenone ethyleneketal (**18**) was cleaved by 4 equiv of sodium or potassium to afford diphenylmethane (**20**) in 60% yield; the yield of **20** was increased to 94% by the use of 5 equiv of metal during a 3-hr period. The latter conditions were also used to convert benzophenone ethylenethioketal (**19**) and dimethoxydiphenylmethane (**21**) to diphenylmethane in yields of 98 and 88%, respectively. Similar reduction of 1-naphthaldehyde ethyleneketal (**22**) gave 1-methylnaphthalene (**23**) in 58% yield; however, 2-nonanone ethyleneketal (**24**) failed to undergo reduction and only starting material was recovered.



18, X = O
19, X = S



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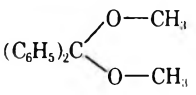

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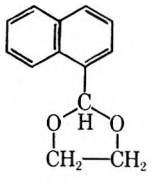

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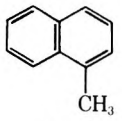
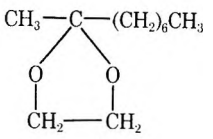


23



24

Incidentally, in contrast to previous reports,[10] reduction of ketal **18** under "Birch" conditions using 4 equiv each of sodium and ethanol gave diphenylmethane in about the same yield as obtained in the absence of the alcohol. Although an advantage the current method enjoys is that a large excess of reducing agent need not be employed as is often the case with Raney nickel,[3] at least stoichiometric amounts of metal must be used to avoid underreduction of the ketal functional group. Thus, treatment of **18** or of **19** with only 2 equiv of sodium in the absence of alcohol cleanly afforded hydroxy ether **25** and mercapto thioether **26** in good to excellent yields, respectively.

$(C_6H_5)_2CHOCH_2CH_2OH$ **25** $(C_6H_5)_2CHSCH_2CH_2SH$ **26**

Next, attention was directed toward trapping intermediate carbanions from these reductions in ammonia. Thus, ketal **18** was reduced by 5 equiv of sodium for 3 hr and the reaction mixture alkylated with *n*-butyl bromide to afford only 1,1-diphenylpentane (**27**); none of the dialkylated product **28** was present. This result implies that *gem*-dianion **29** was not present in the reaction mixture[14] and that the earlier workers[9] were probably in error by postulating the existence of such species in ammonia.

$(C_6H_5)_2CHC_4H_9$ **27** $(C_6H_5)_2C(C_4H_9)_2$ **28** $(C_6H_5)_2CNa_2$ **29**

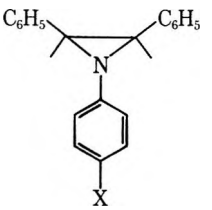
Similar trapping experiments were performed in ammonia on ketal **21** and on thioketal **19** using sodium and *n*-butyl bromide to also afford hydrocarbon **27**.

Two solvents related to ammonia were employed in the reduction of ketal **18** but neither one afforded the clean results realized in ammonia. Surprisingly, reduction of **18** by the more potent system, lithium in methylamine,[18] afforded only 17 and 31% of diphenylmethane (**20**) after 15 min and 3 hr, respectively; in the latter experiment, hydroxy ether **25** was obtained in 43% yield despite the use of 4 equiv of lithium. Reduction of **18** by the still more potent lithium–ethylamine system not only caused cleavage of the dioxalane ring, but also resulted in extensive reduction of the aromatic rings to give mixtures of olefinic compounds which were not further studied.

Next, certain reductions of ketals were performed in ethereal-type solvents in anticipation that *gem*-dicarbanions might be realized. However, reduction of ketal **18** by 4 equiv of lithium in THF for 4 hr afforded only hydroxy ether **25** in 73% yield. The yield of **25** was increased to 79% by allowing the reaction to proceed for 20 hr. Similarly, reduction of thioketal **19** by 4 equiv of lithium in monoglyme gave mercapto thioether **26** in 86% yield.

Finally, treatment of thioketal **19** with 4 equiv of lithium in hexamethylphosphoramide for 24 hr followed by excess deuterium oxide afforded deuterated diphenylmethane (**20**) in 70% yield. However, that deuterium was present only to the extent of 0.82 atom per molecule appears to indicate that the reduction proceeded *via* monolithiodiphenylmethane rather than dialkali salt **29** (M = Li).

Results with Aziridines.—Three arylated aziridines were likewise reduced by sodium in liquid ammonia. Thus, cleavage of 1,2,3-triphenylaziridine (**30**) and of *cis*-1-*p*-chlorophenyl-2,3-diphenylaziridine (**31**) by 2 and 4 equiv of sodium, respectively, gave 1-anilino-1,2-diphenylethane (**32**) in 66–73% yield (eq 3). The



30, R = H
31, R = Cl

$$\xrightarrow[\text{liquid } NH_3]{Na} \overset{\overset{NHC_6H_5}{|}}{C_6H_5CHCH_2C_6H_5} \quad (3)$$

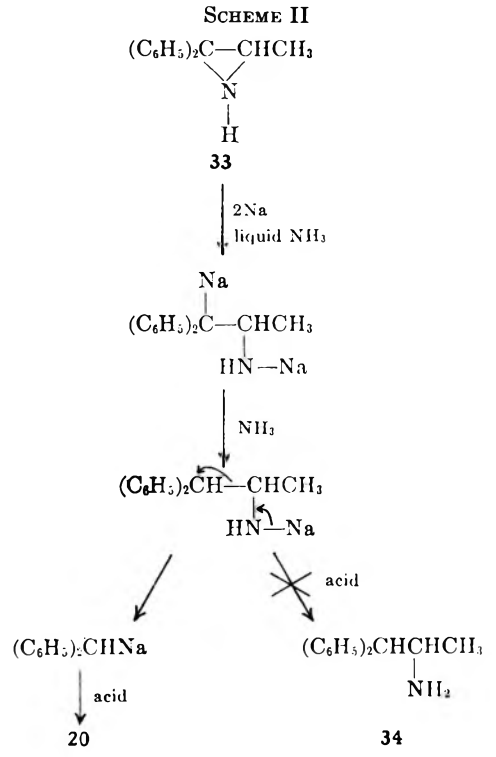
32

(18) For example, see R. A. Benkeser, R. K. Agnihotri, M. L. Burrous, E. M. Kaiser, J. M. Mallan, and P. W. Ryan, *J. Org. Chem.*, **29**, 1313 (1964).

excess sodium metal was successfully employed in the latter reduction to ensure complete removal of the aryl chlorine.

Similar cleavage of 2,2-diphenyl-3-methylaziridine (**33**), however, surprisingly gave diphenylmethane (**20**) rather than the expected amine **34**. Hydrocarbon **20** apparently arose *via* a reverse "aldol-type" condensation (Scheme II) despite the use of the inverse neutral-

SCHEME II



ization technique, a procedure which has previously been shown to minimize such reversions in liquid ammonia.[19]

In summary, it is now clear that aliphatic and aromatic epoxides, aromatic ketals and thioketals, and aromatic aziridines can be rapidly and conveniently reduced by alkali metals in liquid ammonia. Qualitatively, alkali metal reductions of epoxides and aziridines occur more easily than those of ketals as evidenced by more extensive cleavages of the former ring systems than of the latter during similar reaction periods. Also, and more importantly, strictly aliphatic epoxides, but not aliphatic ketals, readily undergo such reductions. These differences in reactivity can be ascribed to greater release of steric strain upon opening of the three-membered epoxides compared to the five-membered ketals. Such reductions appear to be quite general and presumably could be extended to a wide variety of other similar heterocyclic ring systems. Although the above reactions have been unequivocally shown to proceed *via* carbanion intermediates, no evidence for the existence of *gem*-dicarbanions was obtained either in ammonia or in ethereal-type solvents.

Experimental Section[20]

Reduction of Epoxides by Alkali Metals in Liquid Ammonia.—To a solution of 0.0125–0.5 mol of the epoxide in 300 ml of commercial, anhydrous, liquid ammonia, was added 2 equiv of sodium spheres as rapidly as caution permitted. After stirring until the blue color disappeared (35–90 min), the mixture was treated with excess solid ammonium chloride (directy neutralized) or poured into ammonia containing ammonium chloride, (inversely neutralized) and the ammonia was allowed to evaporate. The resulting residue was hydrolyzed (100 ml of 3 *N* HCl) and the aqueous layer extracted (ether). After drying ($CaSO_4$ or $MgSO_4$), the product was isolated by vacuum distillation or by recrystallization. Specific examples are listed in Table I.

Reductive Benzylation of 1,1-Diphenylethylene Oxide in Ammonia.—To a solution of 0.96 g (0.042 g-atom) of sodium in 300 ml of ammonia was added during 1 min, a solution of 4.0 g (0.021 mol) of 1,1-diphenylethylene oxide and 2.53 g (0.021 mol) of benzyl chloride in 100 ml of ether. After 30 min, the mixture was poured into 200 ml of ammonia containing 10 g of ammonium chloride, and the ammonia was allowed to evaporate. The residue was worked up as above to afford an oily material which was chromatographed on neutral alumina using ethanol–benzene solvent to give 0.85 g (22.5%) of stilbene, mp and mmp 123–124°, and 2.1 g (50%) of 2,2-diphenylethanol (**6**), mp and mmp 61–63°, mp and mmp of phenylurethan derivative 135–137°. The infrared spectra of the above compounds were identical with those of authentic samples. Also 0.9 g (15%) of 2,2,3-triphenyl-1-propanol (**15**) was obtained, mp 85–87° (lit.[21] mp 80°); the phenylurethan derivative was prepared: mp 170–173°, lit.[21] mp 169–170°; ir (mull) 3220 (OH), 775, 699 cm^{-1} (ArH); nmr ($CDCl_3$) δ 6.91 (m, 15, ArH), 3.90 (d, 2, CH_2O), 3.43 (s, 2, $ArCH_2$), 1.23 (s, 1, OH).

When the benzylation was repeated by adding the epoxide to the sodium–ammonia solution followed after 7 min, or after 30 sec, by the benzyl chloride, only stilbene and 2,2-diphenylethanol were obtained in yields of 83 and 85%, respectively.

Reductive Deuteration of Styrene Oxide in Hexamethylphosphoramide–Ether.—To a solution of 6.0 g (0.05 mol) of styrene oxide in 45 ml of hexamethylphosphoramide and 75 ml of ether was added 0.7 g (0.1 g-atom) of lithium wire cut into 1-cm pieces. Heat was applied and the mixture was gently refluxed for 2 hr. Upon cooling to 0°, the intensely red mixture was treated with 6 ml of deuterium oxide added all at once. After stirring briefly, the mixture was treated with 200 ml of ether and the resulting solution was washed with three 100-ml portions of water. Drying ($CaSO_4$), concentrating, and distilling the residue gave 1.5 g (24%) of 2-phenylethanol, bp 90–92° (3.5 mm). The nmr of the product indicated the presence of 0.8 benzylic deuterium atom per molecule.

Reduction of Ketals by Alkali Metals in Liquid Ammonia.—To a solution of 2–5 equiv of an alkali metal in 300 ml of liquid ammonia was added 0.025 mol of a given ketal dissolved in ethyl ether. After an appropriate time, the mixture was treated with excess solid ammonium chloride and the ammonia was allowed to evaporate. The residue was taken up into 100 ml each of water and ether, the aqueous layer was extracted with four 50-ml portions of ether, and the combined extracts were dried ($CaSO_4$) and concentrated. Products were purified by vacuum distillation or by recrystallization. Specific examples are listed in Table II.

Preparation of 3-Hydroxyethyl Benzhydryl Ether (25).—To 1.1 g (0.048 g-atom) of sodium in 300 ml of ammonia was added 5.65 g (0.025 mol) of benzophenone ethyleneketal (**18**). After stirring the resulting mixture for 3 hr, it was worked up as above to afford 3.3 g (58%) of β-hydroxyethyl benzhydryl ether (**25**): bp 148–150° (1 mm); ir (neat) 3280 (OH), 1105, 1055, and 1022 (COC), 735 and 695 cm^{-1} (ArH); nmr (CCl_4) δ 7.23 (m, 10, ArH), 4.08 (s, 1, OH), 3.4 (t, 2, CH_2), 2.26 (t, 2, CH_2).

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.90; H, 7.02. Found: C, 78.71; H, 6.93.

Hydroxy ether **25** was also prepared by stirring a mixture of 5.65 g (0.025 mol) of ketal **18** with 0.69 g (0.1 g-atom) of lithium in 75 ml of THF for 4 hr. At the end of this time, the mixture was hydrolyzed by 100 ml of water, worked up as above, and

(19) For example, see E. M. Kaiser and C. R. Hauser, *J. Org. Chem.*, **31**, 3316 (1966).

(20) All starting epoxides, ketals, thioketals, and aziridines were purchased from Aldrich Chemical Co., or prepared by standard methods. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 137 either neat or as Nujol mulls. Nmr spectra were obtained with a Varian Associates A-60 using tetramethylsilane as internal standard. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(21) M. Ramart and M. Amagat, *C. R. Acad. Sci., Ser. C*, **182**, 1342 (1926).

TABLE I

REDUCTION OF EPOXIDES BY ALKALI METALS[a]

Epoxide (mol)	Conditions (hr)	Product (%)	Nmr spectral data (δ)[b]
Styrene oxide (0.05)	2Na–NH_3 (0.75)	2-Phenylethanol (83)[c]	(neat) 7.08 (s, 5, ArH), 4.46 (s, 1, OH), 3.63 (t, 2, CH_2O), 2.70 (t, 2, CH_2)
trans-Stilbene oxide (0.0125)	2Na–NH_3 (1.0)	1,2-Diphenylethanol (77)[d]	($CDCl_3$) 7.0 (d, 10 ArH), 4.53 (t, 1, HCOH), 2.72 (d, 2, CH_2), 1.97 (s, 1, OH)
1,1-Diphenylethylene oxide (0.05)	2Na–NH_3 (1.0)[e]	2,2-Diphenylethanol (89)[f]	(CCl_4) 7.1 (s, 10, ArH), 3.91 (m, 2, CH_2O), 2.03 (t, 1, Ar_2CH)
Cyclohexene oxide (0.1)	2Na–NH_3 (0.75)	Cyclohexanol (60)[g]	
exo-2,3-Epoxynorbornane (0.05)	2Na–NH_3 (1.5)	*exo*-2-Norborneol (82)[h]	(CCl_4) 3.5 (s, 1, OH), 2.1 (m, 1, HCOH), 1.25 (m, 10, CH)
1,2-Epoxybutane (0.5)	2Na–NH_3 (1.0)	2-Butanol (55)[i]	
Ethyl β,β-pentamethyleneglycidate[j] (0.04)	2.2Li–NH_3 (0.8)	Ethyl 1-cyclohexanolacetate[k] (46)	(neat) 4.1 (q, 2, OCH_2), 3.65 (s, 1, OH), 2.43 (s, 2, CH_2CO), 1.5 (m, 10, $(CH_2)_5$), 1.23 (t, 3, CH_3)

[a] All reactions were directly neutralized unless otherwise indicated. [b] The ir spectra either were identical with authentic samples or were in agreement with the assigned structures. [c] Bp 69–70° (1.6 mm) [lit. bp 98–100° (12 mm)]: "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1965, p 2687. [d] Mp 62–63° (lit. mp 62°): see footnote *c*, p 1280. [e] Inversely neutralized. [f] Mp 61–63° (lit. mp 64–65°), phenylurethan, mp 134–136° (lit. mp 135–137°: see footnote *c*, p 1280. [g] Bp 160–161° (lit. bp 161°): see footnote *c*, p 785. [h] Mp 127–128° (lit. mp 126–127°), phenylurethan, mp 145–147° (lit. mp 146°): G. Komppa and S. Beckmann, *Justus Liebigs Ann. Chem.*, **512**, 172 (1934). [i] Bp 97.5–99.5° (lit. bp 100°): see footnote *c*, p 505. [j] Prepared by the method of R. H. Hunt, L. J. Chinn, and W. S. Johnson, *Org. Syn.*, **IV**, 459 (1963). [k] Bp 119–122° (17 mm) [lit. bp 143–146° (37 mm)]: E. H. Charlesworth, J. A. McRae, and H. M. MacFarlane, *Can. J. Res.*, **21B**, 37 (1943).

TABLE II

REDUCTION OF KETALS AND RELATED COMPOUNDS BY ALKALI METALS

Compd (mol)	Conditions (hr)	Product (%)[a]
Benzophenone ethyleneketal (0.025)	5Na–NH_3 (3.0)	Diphenylmethane (94)[b]
	4Na–NH_3 (0.25)	Diphenylmethane (60)[b]
	4K–NH_3 (0.25)	Diphenylmethane (60)[b]
	4Na–4C_2H_5OH NH_3 (0.25)	Diphenylmethane (63)[b]
Benzophenone ethylenethioketal (0.025)	5Na–NH_3 (3.0)	Diphenylmethane (98)[b]
Dimethoxydiphenylmethane (0.025)	5Na–NH_3 (3.0)	Diphenylmethane (88)[b]
Naphthaldehyde ethyleneketal (0.025)	5Na–NH_3 (3.0)	1-Methylnaphthalene (58)[c]
2-Nonanone ethyleneketal (0.025)	5Na–NH_3 (3.0)	2-Nonanone ethyleneketal (88%)[d]

[a] See footnote *b*, Table I. [b] Bp 84–85° (1 mm) [lit. bp 120° (10 mm)]: footnote *c*, Table I, p 1285. [c] Bp 77–78° (1 mm) [lit. bp 110° (12 mm)]: footnote *c*, Table I, p 2242. [d] Nmr (neat) δ 3.76 (s, 4, OCH_2CH_2O), 1.0 (m, 18, CH).

distilled to give 4.15 g (73%) of **25**, bp 148–150°. Similarly, the use of a 20-hr reaction period instead of a 3-hr one gave 4.5 g (79%) of this product, bp 148–150° (1 mm).

Preparation of β-Mercaptoethyl Benzhydryl Thioether (26).—To 1.15 g (0.05 g-atom) of sodium in 300 ml of ammonia was added 6.45 g (0.025 mol) of thioketal **19** to afford a red-brown mixture, the color of which changed to a bright red within 15 min. After 3 hr, the mixture was neutralized by the addition of 15 g of ammonium chloride and worked up in the usual fashion to give 5.7 g (88%) of β-mercaptoethyl benzhydryl thioether (**26**): bp 135–137° (2 mm); ir (neat) 733 and 695 cm^{-1} (ArH); nmr (CCl_4) δ 7.3 (m, 10, ArH), 5.0 (s, 1, Ar_2CH), 2.54 (m, 4, $-SCH_2CH_2S-$), 1.4 (m, 1, SH). The latter absorption was decreased upon mixing the sample with deuterium oxide.

Anal. Calcd for $C_{15}H_{16}S_2$: C, 69.23; H, 6.15; S, 24.62. Found: C, 69.27; H, 5.93; S, 24.67.

Compound **26** was also prepared by refluxing 0.69 g (0.1 g-atom) of lithium and 6.45 g (0.025 mol) of thioketal **19** in 75 ml of THF for 24 hr to give 3.1 g (48%) of the compound.

When the reaction was repeated by employing 4 equiv of lithium in refluxing monoglyme for 22 hr, the yield of **26** was increased to 5.6 g (86%).

Reductive Alkylation of Benzophenone Ketals in Ammonia.—To a solution of 2.88 g (0.125 g-atom) of sodium in 300 ml of ammonia was added 5.65 g (0.025 mol) of ketal **18**. After 3 hr, the mixture was treated with a solution of 3.8 g (0.0275 mol) of *n*-butyl bromide in 50 ml of ether. The resulting solution was then stirred for 1 hr before it was treated with excess ammonium chloride and worked up as above. Distillation of the crude product afforded 1.12 g (27%) of diphenylmethane (**20**), bp 84–85° (1 mm), and 3.3 g (60%) of 1,1-diphenylpentane (**27**), bp 125–127° (1 mm) [lit.[22] bp 80–81° (0.005 mm)]. The nmr of product **27** was identical with that of an authentic sample prepared by the method of Murphy and Hauser.[16]

When the reaction was repeated employing 6.45 g (0.025 mol) of thioketal **19** and 6.85 g (0.05 mol) of *n*-butyl bromide, 3.03 g (54%) of 1,1-diphenylpentane (**27**) was obtained, bp 125–127° (1 mm). Similarly, reduction of 5.76 g (0.025 mol) of ketal **19** followed by 3.8 g (0.0275 mol) of *n*-butyl bromide gave 3.95 g (71%) of 1,1-diphenylpentane (**27**), bp 125–127° (1 mm).

Reductive Deuteration of Benzophenone Ethylenethioketal (19) in Hexamethylphosphoramide.—A mixture of 6.45 g (0.025 mol) of thioketal **19** and 0.69 g (0.1 g-atom) of lithium in 50 ml of HMPA was stirred at room temperature for 24 hr. At the end of this time, the reddish mixture was treated with excess deuterium oxide, then washed with four 50-ml portions of water and worked up as usual to afford 2.95 g (70%) of diphenylmethane, bp 85–86° (1 mm). The nmr of the product indicated the presence of 0.82 benzhydrylic deuterium atom per molecule.

Reduction of Aziridines by Alkali Metals in Liquid Ammonia. A. 1,2,3-Triphenylaziridine (30).—To a solution of 0.115 g (0.005 g-atom) of sodium in 250 ml of ammonia was added 0.62 g (0.0025 mol) of solid aziridine **30** to afford, within 15 min, a yellow solution. After 1 hr, the solution was treated with 10 g

(22) H. Gilman and B. J. Gaj, *J. Amer. Chem. Soc.*, **82**, 6326 (1960).

of solid ammonium chloride, the ammonia was allowed to evaporate, and the crude product was worked up in the usual fashion to give 0.45 g (66%) of 1-anilino-1,2-diphenylethane (**32**), bp 168–170° (1 mm) [lit.[23] bp 168–170° (1 mm)]: hydrochloride, mp 198–199° (lit.[23] mp 192°); ir (neat) of **32**, 3115 (NH), 745, 728 and 689 cm^{-1} (ArH); nmr (CCl_4) of **32** δ 6.77 (m, 16, ArH, NCH), 4.08 (d, 2, $ArCH_2$), 3.67 (broad s, 1, NH).

B. *cis*-1-*p*-**Chlorophenyl-2,3-diphenylaziridine** (**31**).[24]—This reaction was effected essentially as described in part A by employing 0.92 g (0.04 g-atom) of sodium and 3.2 g (0.01 mol) of aziridine **31** to afford 2.2 g (73%) of 1-anilino-1,2-diphenylethane (**32**), bp 168–170°,[23] hydrochloride mp and mmp 198–199°. The ir and nmr of this product were identical with those in part A.

(23) M. Busch and A. Rinck, *Ber.*, **38**, 1761 (1905).
(24) Kindly provided by R. N. Loeppky and D. H. Smith.

C. 2,2-Diphenyl-3-methylaziridine (**33**).—This reaction was effected as described in part A by reducing 5.23 g (0.025 mol) of aziridine **33** by 1.15 g (0.05 g-atom) of sodium to give a reddish brown mixture which was, after 1 hr, poured into 200 ml of ammonia containing 15 g of ammonium chloride. The usual work-up gave 2.9 g (69%) of diphenylmethane, bp 84–85° (1 mm). The ir and nmr of this compound were identical with those of authentic samples.

Registry No.—Styrene oxide, 97-09-3; *trans*-stilbene oxide, 1439-07-2; **5**, 882-59-7; cyclohexene oxide, 286-20-4; **10**, 3146-39-2; 1,2-epoxybutane, 106-88-7; **12**, 6975-17-3; **18**, 4359-34-6; **19**, 6317-10-8; **21**, 2235-01-0; **22**, 26963-79-1; **24**, 14447-29-1; **25**, 26926-47-6; **26**, 26926-48-7.

A Stereochemical Reaction Cycle with Chiral Phosphorus[1]

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Cholesteryl and menthyl methylphenylphosphinates diastereomerically pure gave *N*-phenyl methylphenylphosphinic amide of the same rotation. The lithium salt of α-phenylethylamine with the same phosphinate esters gave the corresponding diastereomerically pure phosphinic amide of the same rotation. Treatment of these same esters with benzyl Grignard reagent gave benzylmethylphenylphosphine oxide of the same rotation. These results, coupled with reactions and configurational assignments of others, completed a three-reaction stereochemical cycle with three chiromers. The two reactions reported here proceed with inversion of configuration and high stereospecificity. Cholesteryl methylphenylphosphinate, absorbed on a solid support, failed to separate a series of racemates in a glc column.

From analogies drawn between the reactions of sulfinate[3,1b] and phosphinate esters, we anticipated the possibility that phosphinate esters might react with Grignard reagents and with substituted lithium amides to produce phosphine oxides and phosphinic amides, respectively. The stereochemical course of these reactions was of interest, particularly since they lead to compounds with phosphorus as the only chiral center. Indeed, since Horner and Winkler[4] had already demonstrated that benzylmethylphenylphosphine oxide was converted stereospecifically and with retention to *N*-phenyl methylphenylphosphinic amide, we envisioned closing a three-reaction stereochemical cycle by converting the same methylphenylphosphinate ester to these two substances. Finally, we planned to use these optically active compounds as liquid phases in attempts to resolve racemates by gas–liquid chromatography.

While our work was in progress, that of Korpium and Mislow[5a] appeared which established that in general, alkylarylphosphinate esters of menthol react with Grignard reagents to give phosphine oxides with high stereospecificity and inversion of configuration. In particular, they converted menthyl methylphenylphosphinate to benzylmethylphenylphosphine oxide. The absolute configuration of menthyl methylphenylphosphinate was known,[6] and that of the oxide was established.[5] Thus, by the time our work matured, the configurations of all three chiromers[7] II, III, and IV were in hand.

Initially, we failed to separate the diastereomers of menthyl methylphenylphosphinate, but successfully obtained pure one diastereomer of cholesteryl methylphenylphosphinate (I). Korpium and Mislow's[5a] recipe led us to the pure menthyl diastereomers (II). Treatment of either ester with benzylmagnesium Grignard reagent gave benzylmethylphenylphosphine oxide (IV) of essentially the same maximum rotation, a fact that establishes that both starting phosphinate esters possess the same configuration at phosphorus (*S*) (Scheme I). Both esters with lithium anilide gave *N*-phenyl methylphenylphosphinic amide (III) of the same sign and magnitude of rotation as that reported[4] by conversion of (+)-(*R*)-IV to (−)-(*S*)-III. These facts establish that the conversion of the phosphinic esters with lithium anilide proceeds with essentially complete inversion of configuration. The two, *three*-reaction stereochemical cycles are formulated. They are triligostatic (three ligands common to the three chiromers),[7] podal (number of chiromers equals the number of reactions),[7] contain no ligand metathesis,[7] and two of the reactions proceed with inversion and one with retention of configuration.

To determine the generality of the conclusion that lithium amides and phosphinate esters give phosphinic amides with high stereospecificity, (−)-(*S*)-I and (−)-(*S*)-II were treated with the lithium salt of optically

* To whom correspondence should be addressed.

(1) (a) This investigation was supported by the U. S. Public Health Service Research Grant No. GM 12640-04 from the Department of Health, Education and Welfare. (b) This work was reported in preliminary form: A. Nudelman and D. J. Cram, *J. Amer. Chem. Soc.*, **90**, 3869 (1968).

(2) This author thanks the Dow Chemical Co. and U. S. Rubber Co. for nonresident tuition grants.

(3) K. K. Andersen, *Tetrahedron Lett.*, 93 (1962).

(4) L. Horner and H. Winkler, *ibid.*, 3265 (1964).

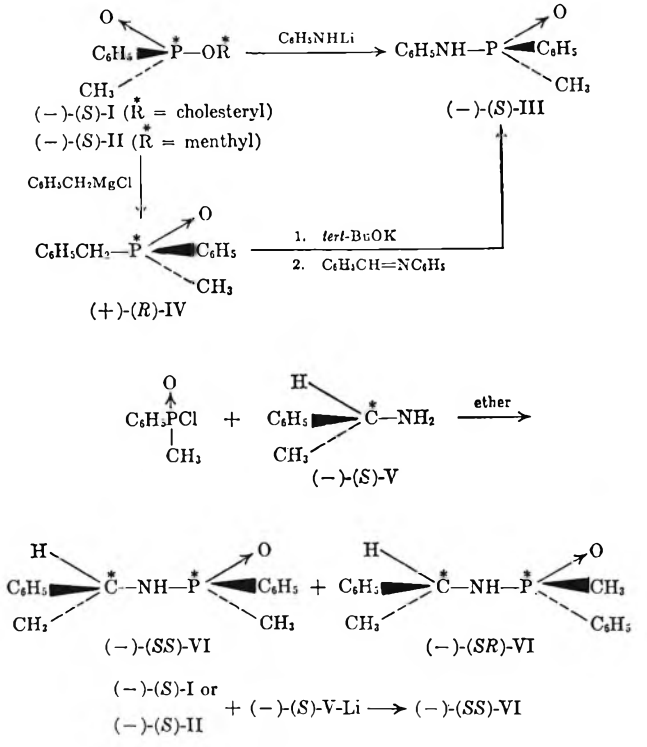
(5) (a) O. Korpium and K. Mislow, *J. Amer. Chem. Soc.*, **89**, 4784 (1967); (b) O. Korpium, R. A. Lewis, J. Chickos, and K. Mislow, *ibid.*, **90**, 4842 (1968).

(6) E. B. Fleischer and R. Dewar, unpublished results, referred to in ref 5b, coupled with the results of ref 5b.

(7) D. C. Garwood and D. J. Cram, *J. Amer. Chem. Soc.*, **92**, 4575 (1970).

pure (−)-(*S*)-α-phenylethylamine[3] [(−)-(*S*)-V] and gave a single diastereomer of VI, very probably (−)-(*SS*)-VI. The same diastereomer [(−)-(*SS*)-VI] and its epimer at phosphorus [(−)-(*SR*)-VI] were obtained and separated by treating 2 mol of (−)-(*S*)-V with 1 mol of methylphenylphosphinic chloride in ether. The difference in nmr spectra of these diastereomers was used to demonstrate the absence of less than 5% diastereomeric impurity in each sample, and tlc experiments decreased the value to less than 2%.

SCHEME I



The feasibility of using phosphine oxides as the liquid phase in glc experiments was tested with racemic *o*-dodecyloxyphenylmethylphenylphosphine oxide, which was synthesized by conventional reactions. A column successfully separated a series of compounds of similar structure (see Experimental Section). However, a glc column with (−)-(*S*)-cholesteryl methylphenylphosphinate [(−)-(*S*)-I] as the stationary liquid phase failed to separate a number of racemates (see Experimental Section). These columns were vastly shorter than those used in Gil Av's successful experiments[9] with peptides as the liquid phase.

Experimental Section

Cholesteryl Methylphenylphosphinate [(−)-(*S*)-I].—Cholesterol (74 g, 0.192 mol) and pyridine (15.2 g, 0.19 mol) were dissolved in 350 ml of dichloromethane under dry conditions and under nitrogen. To this stirred solution was added dropwise 33.6 g (0.192 mol) of methylphenylphosphinic chloride[10] dissolved in 50 ml of dichloromethane. The mixture (heavy white precipitate) was stirred for 12 hr at 25° and shaken with ice-cold dilute sulfuric acid. The organic phase was washed with water, dried, and evaporated to a viscous oil, wt 94.5 g, which was chromatographed on 1200 g of silica gel. The unreacted cholesterol was eluted with 3:2 ether–pentane solution. The ester was eluted with 10% acetone–ether, and toward the end, 20% acetone–ether. Fractions (20) of about 500 ml were collected, and appearance of the desired ester was monitored by tlc (4:1 ether–pentane on silica gel plates). A total of 74.2 g (75%) of ester was distributed in the fractions, which were separated into the first ten rich in (−)-(*S*)-I, and the second ten rich in diastereomer (+)-(*R*)-I. The residues from evaporation of the first half of the fractions were crystallized and recrystallized twice from pentane and gave (−)-(*S*)-I: 11.9 g (12%); mp 134–135.5°; $[\alpha]^{25}D$ −81.4° (*c* 4.53, chloroform). Rotation and melting point did not change with further recrystallization. *Anal.* Calcd for $C_{34}H_{53}O_2P$: C, 77.82; H, 10.18. Found: C, 78.02; H, 10.38.

The second 10 fractions were evaporated and the residue repeatedly recrystallized from pentane (six times), but could not be brought to constant melting point or rotation, the maximum rotation being $[\alpha]^{25}D$ +6.13° (*c* 2.33, chloroform).

Menthyl Methylphenylphosphinates [(−)-(*S*)-II and (−)-(*R*)-II].—Menthol (31.2 g, 0.195 mol) and pyridine (15.4 g, 0.195 mol) were dissolved in 450 ml of anhydrous ether. To this dry solution stirred under nitrogen was added dropwise 34.1 g (0.195 mol) of methylphenylphosphinic chloride[10] in 50 ml of ether. The resulting mixture (heavy precipitate) was stirred for 8 hr and shaken with 10% hydrochloric acid. The organic phase was washed, dried, and evaporated to give 48.3 g of an oil which was chromatographed on 710 g of silica gel. The unreacted menthol eluted with 15% ether–pentane, and the desired ester with 25% ether–pentane. The ester was collected in twenty-five 400-ml fractions, evaporation of which gave 34.8 g (61%) of ester. The progress of the separation was followed by tlc on silica gel plates (ether as eluent, phosphomolybdic acid as developer). The first fraction [(−)-(*R*)-II, 1.2 g, 2%] gave mp 89° and $[\alpha]^{25}D$ −15.4° (*c* 4.8, benzene) [lit.[5] mp 89°, $[\alpha]^{25}D$ −16.3° (*c* 1.3, benzene)]. The next 16 fractions contained mixtures of diastereomers. The last 8 fractions contained (−)-(*S*)-II: 5.7 g or 10%; mp 80°, $[\alpha]^{25}D$ −93.8° (*c* 1.45, benzene) [lit.[5] mp 79–80°, $[\alpha]^{25}D$ −94° (*c* 1.3, benzene)]. *Anal.* Calcd for $C_{17}H_{27}O_2P$: C, 69.36; H, 9.25. Found for (−)-(*R*)-II: C, 69.49; H, 8.99. Found for (−)-(*S*)-II: C, 69.52; H, 9.31.

Benzylmethylphenylphosphine Oxide [(+)-(*R*)-IV].—A Grignard reaction between benzylmagnesium chloride (6.3 g of benzyl chloride and 1.2 g of magnesium) and 2.62 g of cholesteryl methylphenylphosphinate [(−)-(*S*)-I, see above] in benzene at reflux for 8 hr was carried out, and quenched with aqueous ammonium chloride. The organic phase was washed, dried, and evaporated to give 5.05 g of residue which was chromatographed on 50 g of silica gel. Impurities were eluted with 10% acetone–ether, the phosphine oxide with acetone to give 0.97 g (84%) of material, recrystallization of which from acetone–ether gave mp 135–135.2°, $[\alpha]^{25}D$ +49.94° (*c* 1.64, methanol) [lit.[5] mp 134–135°, $[\alpha]^{25}D$ +50.9° (*c* 1–3, methanol), lit.[11] mp 135°].

***N*-(α-Phenylethyl) Methylphenylphosphinic Amides [(−)-(*SS*)-VI and (−)-(*SR*)-VI].**—To a solution of 1.21 g (0.01 mol) of (−)-(*S*)-α-phenylethylamine, $[\alpha]^{25}D$ −40.1° (neat),[8] in 5 ml of anhydrous ether under dry nitrogen was added 6.25 ml of a 1.6 *M* solution of *n*-butyllithium (0.01 mol) in hexane. A solution of 1.74 g (0.01 mol) of methylphenylphosphinic chloride[10] in 10 ml of ether was added to the mixture. The resulting mixture was stirred for 5 hr and shaken with water, and the organic phase was washed with water. The solid that separated (2.36 g) was collected, dissolved in dichloromethane, and chromatographed on 50 g of silica gel. The separation of the diastereomeric amides was followed by tlc on silica gel with 9:1 acetone–methanol as eluent and iodine as developer. Ten fractions (75 ml) were collected of 4.5:1 acetone–ether eluent. Fraction 4 on evaporation gave crystalline material, $[\alpha]^{25}D$ −16.1° (*c* 1.58, chloroform), and fraction 5, $[\alpha]^{25}D$ −16.2° (*c* 1.58, chloroform), combined wt 0.23 g. After recrystallization of this material from ether–pentane, it gave mp 117–119° [(−)-(*SR*)-VI]. *Anal.* Calcd for $C_{15}H_{18}NOP$: C, 69.49; H, 7.00. Found: C, 69.68; H, 7.02.

Fractions 6–10 exhibited rotations that increased from an initial $[\alpha]^{25}D$ −62.6° to a maximum of $[\alpha]^{25}D$ −64.6° (*c* 1.96, chloroform),

(8) (a) A. Ault, *J. Chem. Educ.*, **42**, 269 (1965); (b) W. Leithe, *Chem. Ber.*, **64**, 2827 (1931).

(9) E. Gil Av and B. Feibush, *Tetrahedron Lett.*, 3345 (1967), and earlier references.

(10) C. S. Gibson and J. D. A. Johnson, *J. Chem. Soc.*, 92 (1928).

(11) J. Meisenheimer, J. Casper, M. Horning, W Lauter, L. Lichtenstadt, and W. Samuel, *Justus Liebigs Ann. Chem.*, **449**, 213 (1926).

combined wt 0.6 g. After recrystallization, this material [(−)-(*SS*)-VI] from ether–pentane gave mp 133–134°. *Anal.* Found: C, 69.68; H, 6.93.

***N*-(α-Phenylethyl) Methylphenylphosphinic Amide [(−)-(*SS*)-VI] from Menthyl or Cholesteryl Methylphenylphosphinates [(−)-(*S*)-II and (−)-(*S*)-I].**—The procedure is illustrated as applied to the cholesteryl ester (−)-(*S*)-I. To a solution (4.12 g or 34 mmol) of (−)-(*S*)-α-phenylethylamine, $[\alpha]^{25}D$ −40.1° (neat),[3] in 20 ml of dry benzene was added 21.3 ml of a 1.6 *M* solution of *n*-butyllithium (34 mmol) in hexane with stirring under dry nitrogen. The mixture was stirred at reflux for 1 hr. A solution of 0.92 g (1.7 mmol) of (−)-(*S*)-I, $[\alpha]^{25}D$ −81.4°, *c* 4.53, chloroform (or 1.7 mmol of (−)-(*S*)-II, $[\alpha]^{25}D$ −94°, *c* 1.45, benzene) in 20 ml of dry benzene was added with stirring, and the mixture was held at reflux for 5 hr. The reaction mixture was shaken with 10% hydrochloric acid and dichloromethane. The organic layer was washed, dried, and evaporated to give 0.97 g of residue which was chromatographed on 25 g of silica gel. The first 4 fractions (75 ml each) were eluted with 1:1 ether–acetone, fractions 5–8 with pure acetone. The yellow oil from 5 and 6 was crystallized (nonfractionally) from ether–pentane to give 0.11 g (25%) of (−)-(*SS*)-VI, $[\alpha]^{25}D$ −63° (*c* 1.55, chloroform), mp 132–133.5°. An identical yield, melting point, and rotation were obtained from (−)-(*S*)-II. Examination of the crude amides from both preparations of (−)-(*SS*)-VI with tlc on silica gel plate, acetone–methanol, 9:1, showed the absence of other diastereomers. Control experiments with both diastereomers demonstrated that as little as 1–2% could have been detected.

***N*-Phenyl Methylphenylphosphinic Amide [(−)-(*S*)-III].**—Application of the above procedure to lithium anilide (10 mol excess) and either cholesteryl or menthyl methylphenylphosphinate [(−)-(*S*)-I or (−)-(*S*)-II] gave (−)-(*S*)-III. The yield after chromatography and nonfractional crystallization of (−)-(*S*)-III (acetone–pentane) from (−)-(*S*)-I was 35%, mp 161–163°, $[\alpha]^{25}D$ −26.2° (*c* 1.33, methanol). The yield after chromatography and nonfractional crystallization (acetone–pentane) from (−)-(*S*)-II was 38%, mp 161–163°, $[\alpha]^{25}D$ −26.1° (c 0.83, methanol). The literature[4] reported mp 164°, $[\alpha]^{25}D$ −25.8° (*c* 0.76, methanol).

***o*-Dodecyloxybromobenzene.**—A mixture of *o*-bromophenol (82.5 g), 250 ml of 95% ethanol, and 21 g of sodium hydroxide pellets was heated into solution, and 113.2 g of dodecyl bromide was added. After 24 hr at reflux, the product was isolated by extraction and distillation, wt 142 g (92%), bp 153° (0.14 mm). *Anal.* Calcd for $C_{18}H_{29}BrO$: C, 63.34; H, 8.56. Found: C, 63.47; H, 8.54.

***o*-Dodecyloxyphenylmethylphenylphosphine Oxide (VII).**—The Grignard reagent of *o*-dodecyloxybromobenzene was prepared by the "entrainment method"[12] from 34.1 g of bromide and 2.6 g of magnesium in 500 ml of dry ether. To this stirred mixture under nitrogen was added dropwise 17.4 g of methylphenylphosphinic chloride[10] in 200 ml of dry ether. The resulting viscous mixture was shaken with dilute hydrochloric acid, and the organic phase was washed with water, dried, evaporated, and distilled to give 19.6 g (49%) of VII as a viscous and slowly crystallizing oil, bp 188° (0.14 mm). *Anal.* Calcd for $C_{25}H_{37}O_2P$: C, 74.97; H, 9.31. Found: C, 75.01; H, 9.29.

Attempted Resolution by Glc.—A 0.25 in. (i.d.) × 10 ft column was packed with a 10% mixture by weight of diastereomerically pure cholesteryl methylphenylphosphinate [(−)-(*S*)-I] on Chromosorb W (80–100 mesh). About 15 g of mixture filled the column, which was cured in an oven at 170° for 90 min and at 155° for 3 hr. A small sample of pure (−)-(*S*)-I was found not to change its rotation when held at 165° for 12 hr. The chromatographic experiments were carried out on a Perkin-Elmer vapor fractometer, Model 154, at a column temperature of 144° with helium as a carrier. On this column, the following racemates had the indicated retention times, and the peaks were sharp: 2-octanol, 14 min; 2-phenylpropionitrile, 32 min; 3-methoxy-3-phenyl-2-butanone, 34 min; 2-methyl-1-phenyl-1-propanol, 28 min; 3-methoxy-2-methyl-3-phenyl-2-butanol, 44 min. In experiments that involved *o*-dodecyloxyphenylmethylphenylphosphine oxide (VII), 5% by weight of VII on Chromosorb W was employed in the same type of column and in the same machine and carrier gas. At 85°, 1-butanol, 2-butanol, and *tert*-butyl alcohol gave 6.3, 2.9, and 1.3 min retention times, respectively. At 105°, 1-octanol and 2-octanol gave 14.7 and 4.7 min retention time, respectively. At 87°, 1-butanol, 2-butanol, and 2-pentanol gave 2.7, 1.5, and 2.4 min retention times, respectively.

Registry No.—(−)-(*S*)-I, 20752-41-4; (−)-(*S*)-II, 16934-93-3; (−)-(*R*)-II, 26963-82-6; (−)-(*SR*)-VI, 20752-44-7; (−)-(*SS*)-VI, 20752-43-6; VII, 26910-10-1; *o*-dodecyloxybromobenzene, 26910-11-2.

(12) D. E. Pearson, D. Cowan, and J. D. Beckler, *J. Org. Chem.*, **24**, 504 (1959).

Carbon-14 Tracer Study of the Dehydrocyclization of *n*-Heptane

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The ^{14}C distribution in toluene from the dehydrocyclization of *n*-heptane-1-^{14}C and -4-^{14}C, both over the same chromia on "nonacidic" alumina preparation, is consistent with 80% or more of the aromatic being formed by direct six-carbon ring formation. Thus, chromia on "nonacidic" alumina can give results similar to other chromia and chromia–alumina. In general, a dehydrocyclization mechanism involving various size intermediates is not necessary even for the "nonacidic" catalyst.

The mechanism for the heterogeneous catalytic conversion of paraffins to aromatics, dehydrocyclization, has been widely studied.[1] Early workers, guided by aromatic product distributions and kinetics, supported a dehydrocyclization mechanism involving direct six-carbon ring formation. An early ^{14}C tracer study[2] also supported this mechanism.

Results of more recent ^{14}C tracer studies[3,4] were incompatible with this mechanism. To explain their ^{14}C distributions, Pines and Chen[4] proposed that cyclization to both six- and seven-membered-ring intermediates participate in the mechanism. The contribution of these intermediates varied with time on stream and catalyst. Such competition between various size ring intermediates would not allow the dehydrocyclization mechanism to have predictive value. On the other hand, Feighan and Davis[5] found that *n*-heptane-4-^{14}C

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(1) For a review of the literature, see (a) A. H. Steiner in "Catalysis," Vol. 4, P. H. Emmett, Ed., Reinhold, New York, N. Y., 1957, p 529; (b) H. Hansch, *Chem. Rev.*, **52**, 353 (1953); (c) H. Pines and C. T. Goetschel, *J. Org. Chem.*, **30**, 3530 (1965).

(2) R. W. Wheatcroft, Dissertation, University of California, 1949.

(3) J. J. Mitchell, *J. Amer. Chem. Soc.*, **80**, 5848 (1958).

(4) H. Pines and C. T. Chen, *J. Org. Chem.*, **26**, 1057 (1961).

(5) J. A. Feighan and B. H. Davis, *J. Catal.*, **4**, 594 (1965).

over a similar chromia–alumina catalyst gave a product with a tracer distribution consistent with direct six-carbon ring formation.

Contradictory results from different laboratories often are a result of the difficulty in preparing reproducible heterogeneous catalysts. We now report a study of the dehydrocyclization of *both* *n*-heptane-1-^{14}C and -4-^{14}C over the *same* preparation of chromia on "nonacidic" alumina in order to further clarify the mechanistic picture in this complex system.

Results and Discussion

The results for the dehydrocyclization of the two ^{14}C-labeled heptanes over the same chromia catalyst supported on "nonacidic" alumina at 500° are shown in Table I. The precentage of ^{14}C label in the methyl

TABLE I

METHYL ACTIVITY IN TOLUENE FROM DEHYDROCYCLIZATION OF *n*-HEPTANE-1-^{14}C AND *n*-HEPTANE-4-^{14}C

Sample	Time on stream, min	Liquid collected, cc	Conversion to toluene, mol % in liquid product	% methyl label of toluene
		n-Heptane-1-^{14}C		
1	45	0.4	49	43
2	97	1.0	41	39
3	137	0.8	37	40
		n-Heptane-4-^{14}C		
1	45	0.4	46	2.6
2	105	1.2	44	2.8
3	160	1.1	43	2.7
4	215	1.0	43	3.0

group of toluene is about 40% for *n*-heptane-1-^{14}C. The three samples collected at different time on stream show no variation in the label distribution. This is in contrast to the results of Pines and Chen[4] who found that the methyl-labeled toluene increased in the samples collected at increasing time on stream.

The first liquid sample in the present *n*-heptane-1-^{14}C run (0.4 ml, using 5 ml of catalyst) should correspond, at least qualitatively, to the first sample collected by Pines and Chen,[4] since it was taken at an earlier time on stream. (The first sample of Pines and Chen[4] calculates to be about 0.7 ml for 5 ml of catalyst.) Therefore, the difference in the amount of methyl label for the first sample of toluene from *n*-heptane-1-^{14}C for the present study and Pines and Chen[4] cannot be attributed to catalyst changes with time on stream.

The methyl label for toluene obtained from *n*-heptane-4-^{14}C is significantly higher than expected for only direct six-carbon ring formation (2.5–3.0% *vs.* predicted 0.0%). This methyl label is slightly greater than obtained by Feighan and Davis[5] in their study using *n*-heptane-4-^{14}C over chromia on "nonacidic" alumina (1.0–1.6% methyl label). Even so, the methyl activity is still much lower than would be expected for the nearly isotopic equivalency found by Pines and Chen[4] (and perhaps Mitchell[3]).

Mitchell[3] obtained toluene with about 25% ^{14}C in the methyl position from the dehydrocyclization of *n*-heptane-1-^{14}C over a chromia–alumina catalyst promoted with potassium and cerium ("nonacidic" catalyst). He proposed three reaction pathways which could explain the low methyl-labeled toluene: (a) the formation of a cycloheptane intermediate, (b) the formation of a bicycloheptene intermediate followed by opening of one ring to yield toluene, and (c) reversible isomerization between C_5- and C_6-ring structures.

Pines and Chen[4] found the predicted 50% methyl label in toluene from the dehydrocyclization of *n*-heptane-1-^{14}C over unsupported chromia and 40% methyl label in toluene using chromia supported on "acidic" alumina. But dehydrocyclization using chromia supported on "nonacidic" alumina initially yielded toluene with 17.5% (or less) ^{14}C in the methyl position; at later times on stream the methyl ^{14}C content has increased to 32%. An adsorbed cycloheptane intermediate that was able to "roll around" on the surface was proposed to give carbon equivalency at all positions; the adsorbed cycloheptane then underwent ring contraction to form a C_6 ring. Pines and Goetschel[1c] have obtained results for several reactants in addition to *n*-heptane that show that their chromia on "nonacidic" alumina gave much different results than either chromia or chromia on "acidic" alumina.

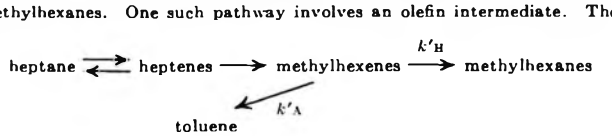
Feighan and Davis[5] obtained results with *n*-heptane-4-^{14}C which were in satisfactory agreement with C_6-ring formation. Contrary to Pines and Chen, a larger amount of isotope scrambling in the toluene was obtained over unsupported chromia than over chromia supported on either "acidic" or "nonacidic" alumina. For all three catalysts, the toluene product was predominately labeled at the position predicted for direct C_6-ring formation, the ring position meta to the methyl substituent.

The reason for the significant difference between results which support direct C_6-ring formation (this study, ref 2 and 5) and those in disagreement with this cyclization pathway[3,4] is not apparent. It is possible that the amount or location of the potassium "promotor" used to make the alumina "nonacidic" plays a more important role than previously suspected. Small differences in catalyst pretreatment may also cause large differences in the catalytic properties of potassium promoted catalysts. The amount of chromia on the support may be responsible for the different results.

This study cannot provide an answer to the mechanism responsible for the ^{14}C label at positions other than those predicted by direct C_6-ring formation. It is conceivable that this ^{14}C scrambling could occur through a cycloheptane intermediate. However, it is also possible to explain the ^{14}C scrambling by isomerization to a methylhexane carbon skeleton prior to or during cyclization.[6]

Only Feighan and Davis[5] have determined the ^{14}C ring distribution in toluene obtained from *n*-heptane dehydrocyclization. For *n*-heptane-4-^{14}C, the ^{14}C was

(6) Methylhexanes were not present in the liquid product in significant quantities. There are many isomerization mechanisms that could lead to methylhexanes. One such pathway involves an olefin intermediate. The



absence of methylhexanes can then be accounted for provided $k'_A > k'_H$ or by preferential conversion of methylhexanes. Our unpublished results show that both heptane and methylhexanes are converted at about the same rate when passed over the catalyst under similar conditions. It is known that olefins are aromatized more readily than paraffins,[1] but little is known about the relative rates k'_A and k'_H.

about equally distributed in all positions except the ring position meta to the methyl group. If we assume a similar ^{14}C distribution for the toluene obtained from *n*-heptane-4-^{14}C in the present study (*i.e.*, the ring positions, excluding the position meta to the methyl group, have the same activity as experimentally determined for the methyl position), we calculate that about 80% of the ^{14}C is in the position meta to the methyl group. For toluene from *n*-heptane-1-^{14}C, the methyl label was about 40%, also about 80% of that predicted by a direct C_6-ring formation mechanism.

The results of this study with *n*-heptane-4-^{14}C substantiate the earlier results of Feighan and Davis;[5] both support direct C_6-ring formation. Our tracer results suggest that the same amount of direct C_6-ring formation occurs over "nonacidic" chromia–alumina for *n*-heptane labeled either in the 1 or 4 position. More important, the results of the present study and those of Feighan and Davis[5] support a heptane dehydrocyclization mechanism of direct C_6-ring formation over a "nonacidic" chromia–alumina catalyst as well as over other chromia catalysts.

Experimental Section

Catalyst.—The "nonacidic" alumina was prepared by precipitation from potassium aluminate with CO_2.[7] The alumina was washed so that the potassium content was 0.1 wt % (based on weight after 600° calcination). The alumina was impregnated with chromic acid; the final catalyst contained 10.6 wt % Cr (15.6 wt % Cr_2O_3).

Hydrocarbons.—*n*-Heptane-4-^{14}C was prepared as shown in synthetic Scheme I.[8]

SCHEME I

$$HC^*O_2H \xrightarrow{EtOH} HC^*O_2C_2H_5 \xrightarrow{PrMgBr} C_3H_7C^*HOHC_3H_7$$

$$C_3H_7C^*HOHC_3H_7 \xrightarrow{HOAc} C_3H_7CHC_3H_7 \xrightarrow{400°} C_3H_7C^*H{=}CHC_2H_5$$
(OAc)

$$C_3H_7C^*H{=}CHC_2H_5 \xrightarrow[H_2]{PtO_2} C_3H_7C^*H_2C_3H_7$$

n-Heptane-1-^{14}C was prepared as shown in synthetic Scheme II. Sodium formate was purchased from Tracerlab. Sodium *n*-heptanoate-1-^{14}C was purchased from Nuclear-Chicago Corp.

Procedure.—The catalyst (5 ml, 4 g) was placed in an electrically heated Vycor glass continuous-flow unit and reduction

SCHEME II

$$C_6H_{13}C^*O_2H \xrightarrow{LiAlH_4} C_6H_{13}C^*H_2OH \xrightarrow{PBr_3} C_6H_{13}C^*H_2Br$$

$$C_6H_{13}C^*H_2Br \xrightarrow{Mg} C_6H_{13}C^*H_2MgBr \xrightarrow{H_2O} C_6H_{13}C^*H_3$$

effected *in situ* in flowing hydrogen (4 ml/min) for 3 hr. The labeled reactant was introduced by a motor-driven syringe pump (LHSV 0.3). Runs were effected at 500° and 1 atm. A detailed description of the apparatus has been reported earlier.[9]

The liquid products were diluted to about 10-cc volume with a 50:50 volume mixture of unlabeled *n*-heptane–toluene. This mixture was separated on a silica gel column using isopropyl alcohol as eluting agent. The first 0.5 ml of the toluene fraction eluting from the column was discarded.

The toluene was oxidized to benzoic acid using alkaline potassium permanganate. Details of the method are given in ref 5. The benzoic acid was burned to CO_2 by the van Slyke procedure and the CO_2, trapped in NaOH, was then collected as barium carbonate. The decarboxylation of benzoic acid was accomplished by heating at 260° in a CuO–quinoline mixture. Two, and for about half of the cuts three, combustions and decarboxylations were done on the benzoic acid. The percentages in the tables were calculated using an average of the $BaCO_3$ counts. Representative activities for the determinations are given in Table II.

TABLE II
REPRESENTATIVE DATA SHOWING THE REPRODUCIBILITY OF THE DECARBOXYLATION, BENZOIC ACID OXIDATION, AND $BaCO_3$ COUNTING PROCEDURES

	$BaCO_3$ sample[a]	Activity, counts/(min 100 mg of $BaCO_3$)
Sample 1, methyl carbon	1	16,719
(*n*-heptane-1-^{14}C run)	2	14,193
	3	14,178
Sample 1, benzoic acid carbons	1	4,733[b]
(*n*-heptane-1-^{14}C run)	2	5,191

[a] Three portions of the benzoic acid (from toluene oxidation) were decarboxylated; two portions of the benzoic acid were oxidized. [b] The activity for $BaCO_3$ from the total benzoic acid sample is less than that from methyl decarboxylations because the ^{14}C is diluted by six inactive carbons in the benzoic acid.

The ^{14}C activity of the $BaCO_3$ samples was determined by liquid scintillation. The sample was suspended in the scintillation solution (5 g of PPO and 0.3 g of POPOP per liter of toluene containing 4 wt % Cab-o-Sil).

Registry No.—*n*-Heptane-1-^{14}C, 26960-94-1; *n*-heptane-4-^{14}C, 26960-95-2.

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(9) B. H. Davis and P. B. Venuto, *J. Catal.*, **15**, 363 (1969).

Additions of Protonic Acids to 2,3-Dideuterionorbornene.[1] Evidence for the Existence of a Classical Norbornyl Cation

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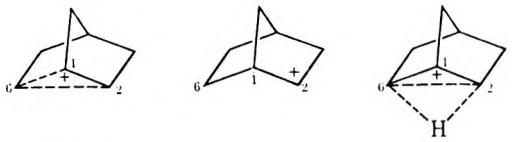
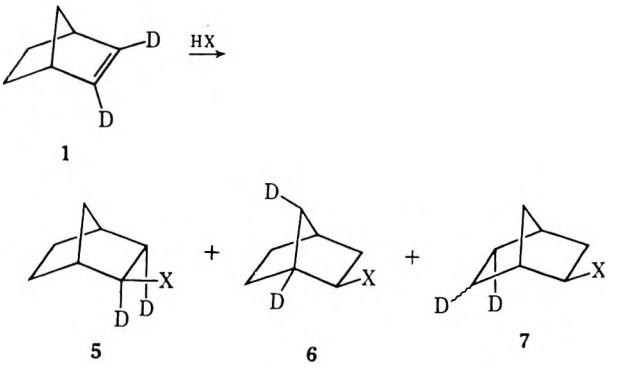
The synthesis of 2,3-dideuterionorbornene (1) and the additions of the protonic acids, hydrogen chloride, hydrogen bromide, hydrogen fluoride, formic acid, phenol, and methanol, to it gave only *exo*-norbornyl adducts. The additions of hydrogen chloride and hydrogen bromide gave greater than 50% of product resulting from an exo-cis addition. In the additions of formic acid, methanol, and hydrogen fluoride, the amounts of products resulting from exo-cis addition and Wagner–Meerwein rearrangement were essentially equal. A mechanistic interpretation of the data is presented, in which a classical norbornyl cation is formed in the course of addition of hydrogen chloride and hydrogen bromide to norbornene.

The electrophilic additions of protonic acids to norbornene usually proceed to give exo-substituted products,[4-8] *via* a positively charged intermediate, the norbornyl cation. Three different structures of the norbornyl cation in solution, a nonclassical bridged ion (**2**),[9] a localized classical ion (**3**),[10] and an edge-protonated nortricyclonium ion (**4**),[11,12] have been suggested.



2 **3** **4**

The deuterium labeled olefin, 2,3-dideuterionorbornene (**1**), was synthesized to facilitate the determination of the stereochemical courses of additions to this bicyclic system. Determination of the deuterium distribution in the product mixtures by analysis of the nmr spectra would be more accurate in the additions of protonic acids to **1** than in the additions of deuterionic acids to norbornene. The intermediate deuterium labeled norbornyl cation from the protonation of **1** suffers nucleophilic capture to give deuterium-labeled products. Capture at C-2 should yield **5**, the exo-cis addition product.[13] Capture at C-1 would yield **6**, resulting from a Wagner–Meerwein rearrangement of **3** or capture of **2** or **4** at C-1, and capture of the much less favored 6,2-hydride shift intermediate[12] would afford **7**.

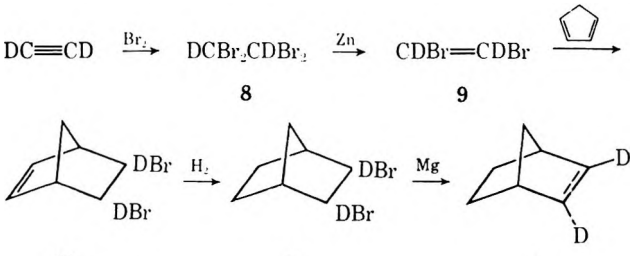


1

5 **6** **7**

Results

Synthesis of 1.—Dideuterioacetylene, generated from calcium carbide and deuterium oxide, was passed directly into molecular bromine to yield *sym*-tetrabromodideuterioethane (**8**). The debromination of **8** with zinc afforded a mixture of *cis*- and *trans*-1,2-dibromo-1,2-dideuterioethylene (**9**).[14] The Diels–Alder reaction of **9** and cyclopentadiene gave a mixture of *cis*- and *trans*-5,6-dibromo-5,6-dideuterionorbornene (**10**), which, when hydrogenated, yielded the corresponding 2,3-dibromo-2,3-dideuterionorbornanes (**11**).[14] Debromination of **11** with magnesium afforded **1**.[15] Mass spectral analysis of **1** showed it to be 95% d_2, 2% d_1, and 3% d_0 material. The signal at δ 5.93 ppm (vinyl hydrogen) was nearly absent in the nmr spectrum of **1**.



8 **9**

10 **11** **1**

Additions of HX to 1.—The additions of compounds of general formula HX (X = Cl, Br, F, OCHO, OCH_3, OC_6H_5) to **1** gave products **5**–**7**, the relative amounts of which were determined by analysis of the nmr spectrum of each product mixture. Corrections for the small amount of vinyl hydrogen present in **1** were incorporated to give the results summarized in Table I.

Deuterium chloride has been reported to add rapidly to norbornene at −78° in methylene chloride to yield 60% of product resulting from an exo-cis addition, 35% from a Wagner–Meerwein rearrangement, and 5%

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(3) Abstracted in part from the Ph.D. thesis of R. D. Hughes, University of Iowa, May 1970. National Defense Education Act Fellow, 1966–1969, Phillips Petroleum Fellow, 1969–1970.

(4) T. G. Traylor and A. W. Baker, *Tetrahedron Lett.*, No. 19, 14 (1959).

(5) L. Schmerling, J. P. Luvisi, and R. W. Welch, *J. Amer. Chem. Soc.*, **78**, 2819 (1956).

(6) H. A. Bruson and T. W. Riener, *ibid.*, **67**, 723 (1945).

(7) L. Schmerling, *ibid.*, **68**, 195 (1946).

(8) J. D. Roberts, E. R. Trumbull, Jr., W. Bennett, and R. Armstrong, *ibid.*, **72**, 3116 (1950).

(9) S. Winstein, *ibid.*, **87**, 376 (1965).

(10) H. C. Brown and M. H. Rei, *ibid.*, **90**, 6216 (1968).

(11) G. A. Olah, A. Commeyras, and C. Y. Lui, *ibid.*, **90**, 3882 (1968).

(12) G. A. Olah and A. M. White, *ibid.*, **91**, 3957 (1969).

(13) Exo attack on the trigonal C-2 in this system is generally accepted to be preferred over endo attack; see J. A. Berson, "Molecular Rearrangements," Part I, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, pp 130–133.

(14) N. A. Le Bel, P. D. Beirne, E. R. Karger, J. C. Powers, and P. M. Subramanian, *J. Amer. Chem. Soc.*, **85**, 3199 (1963).

(15) L. Schmerling, J. P. Luvisi, and R. W. Welch, *ibid.*, **78**, 2819 (1956).

TABLE I
PROTONIC ACID ADDITIONS TO 1

Acid (HX) and catalyst	Solvent	Temp, °C	Time, min	Product composition, %[a] 5	6	7
HCl	CH_2Cl_2	−78	5	56	42	~2
HCl	n-C_5H_{12}	−78	60	59	39	~2
HCl	$(C_2H_5)_2O$	27	190	65	27	8
HBr	CH_2Cl_2	−45	5.5	54	40	~5
HBr	H_2O	60	180	52	36	11
HOC_6H_5, BF_3	CH_2Cl_2	−22	240	47	39	14
HF	CH_2Cl_2	−78	5	22	24	54
HOCHO, BF_3	CH_2Cl_2	−22	60	47	46	7
$HOCH_3$, H^+	CH_3OH	Reflux	1290	38	42	20

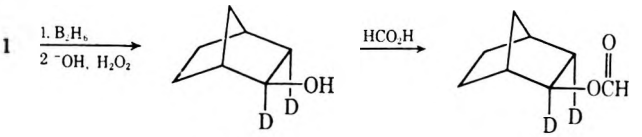
[a] Obtained from nmr spectra recorded with a Varian A-60 spectrometer as 20–30% solutions in $CDCl_3$ or C_6H_6 with tetramethylsilane as the internal standard. Product ratios were determined from the mean average of five tracings of the integral and were corrected for deuterium content as determined by mass spectra. These values are correct within ±2%, with the exception of the values 2 and 5% for 7 which were obtained by difference through normalization to 100% deuterium content.

from a 6,2-hydride shift.[16] Under similar conditions in chloroform, the reaction proceeds to completion in 2 min with 55% of the product resulting from exo–cis addition and 45% from a Wagner–Meerwein rearrangement.[17] The addition of hydrogen chloride to **1** was complete in 5 min at −78° in methylene chloride with **5**, **6**, and **7** (X = Cl) formed in the ratio of 56:42:2, respectively. Contrary to an earlier report, we were not able to detect a significant amount of 6,2-hydride shift product.[18] When the product mixture was placed back under the reaction conditions for an additional 50 min, the product ratio of 5:6:7 had only changed to 50:47:3. Apparently prolonged reaction times facilitated a small amount of solvolysis of the product chlorides and subsequently led to additional rearrangement. Less polar solvents such as pentane and ether were found to suppress rearrangement, and hence more **5** was found with these solvents. In all the additions of hydrogen chloride to **1**, only *exo*-norbornyl chloride was formed, to the exclusion of the endo isomer, as determined by vpc analysis.

The polar addition of anhydrous hydrogen bromide to **1** in methylene chloride at −45° was complete in 5.5 min with **5**, **6**, **7** (X = Br) produced in a ratio of 54:40:5, respectively. Deuteriobromic acid (48%) has been reported to add to norbornene to give 46% exo–cis addition and 51% rearrangement.[19] We carried out the addition of 48% hydrobromic acid to **1** and found the ratio of 5:6:7 (X = Br) to be 52:36:11, respectively. The products of these reactions undergo little or no change when subjected to the reaction conditions for prolonged times. No *endo*-norbornyl bromide was formed in any of the reactions, indicative of the absence of a radical reaction.[19]

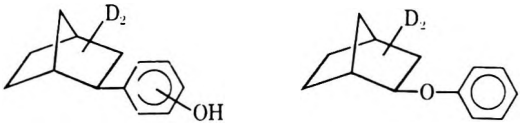
The addition of hydrogen fluoride to norbornene was reported to yield *exo*-norbornyl fluoride in low yields.[20] The reaction of hydrogen fluoride and **1** at −78° for 5 min in methylene chloride gave low yields of *exo*-norbornyl fluoride; the major product from the reaction was norbornene telomers. Analysis of the norbornyl fluoride product mixture showed a deuterium distribution of 22% at C-2 and 24% at C-1. This corresponds to a product mixture of **5**, **6**, and **7** (X = F) in a ratio of 22:24:54, respectively.

The boron trifluoride etherate catalyzed addition of formic acid to **1** proceeds to completion within 1 hr at −22° in methylene chloride. From careful integration of the appropriate signals in the nmr, it was determined that equimolar amounts (46%) of **5** and **6** (X = OCHO) and only 7% of **7** were formed. The uncatalyzed reaction required 48 hr at room temperature to proceed to completion with yields of **5**, **6**, **7** of 47, 42, and 11%, respectively. When an independently synthesized sample of *endo,endo*-2,3-dideuterio-*exo*-2-norbornyl formate (**13**) was placed in methylene chloride at −22° with formic acid and boron trifluoride, no rearrangement to **6** (X = OCHO) occurred. Thus, the product formates from the addition reaction must be stable to solvolysis under the reaction conditions.



12 13

The condensation of phenol with camphene at 0° is reported to give only isobornyl phenyl ether, when catalyzed with boron trifluoride etherate.[21] Under similar conditions **1** formed predominately C-alkylated phenols **14**, presumably the ortho and para isomers. The addition of phenol to **1** at −22° in methylene chloride with a boron trifluoride etherate catalyst was nearly com-



14 15

plete after 4 hr to yield the O-alkylated phenol **15** as the major product. The distribution of deuterium in the final product corresponded to a ratio of 47:39:14 for **5**, **6**, and **7** (X = OC_6H_5), respectively.

endo-Trimethylenenorbornene has been reported to undergo a sulfuric acid catalyzed reaction with methanol to give 15% of unrearranged addition product and 85% of product due to a Wagner–Meerwein rearrangement.[22] With deuteriomethanol the unrearranged addition product was determined to be the result of an exo–cis addition The sulfuric acid catalyzed addition of methanol to **1** in excess refluxing methanol yielded a product mixture in which 0.38 atoms of the deuterium were located at C-2, 0.42 atoms at C-1, and the remainder at the other positions. If one makes the reasonable assumption that no deuteride shifts have occurred,[23] this distribution of deuterium corresponds to a ratio of 38:42:20 for **5**, **6**, and **7** (X = OCH_3), respectively. Similar results were obtained when the reaction was

(16) H. C. Brown and K. T. Liu, *J. Amer. Chem. Soc.*, **89**, 3900 (1967).
(17) J. M. Brown and M. C. McIvor, *Chem. Commun.*, 238 (1969).
(18) J. K. Stille, F. M. Sonnenberg, and T. H. Kinstle, *J. Amer. Chem. Soc.*, **88**, 4922 (1966). The reported ratios of products resulting from exo–cis addition, Wagner–Meerwein rearrangement, and 6,2-hydride shift (50:12:38) were in error due to nmr instrumental errors in integration.
(19) H. Kwart and J. L. Nyce, *ibid.*, **86**, 2601 (1964).
(20) M. Hanack and W. Kaiser, *Justus Liebigs Ann. Chem.*, **657**, 12 (1962).
(21) W. F. Erman, *J. Amer. Chem. Soc.*, **86**, 2887 (1964).
(22) S. J. Cristol, L. K. Gaston, and D. W. Johnson, *Tetrahedron Lett.*, 185 (1963).
(23) A deuteride shift could occur only if the cation was long-lived enough for the unfavored 3,2-*endo*-hydride shift to take place. See ref 12.

carried out in methylene chloride with a fivefold excess of methanol. In all cases only exo products were formed.

Discussion

The preference of cis over trans addition of HX to norbornene has been estimated to be at least 10^2:1, but not more than 10^4:1, based on the limits of detectability of endo products.[24] No endo products were detected in any of the additions studied in this work. With hydrogen chloride and hydrogen bromide, exo–cis addition accounted for the majority of the total product.

The amount of rearrangement which occurs in additions to norbornene has been attributed to the ability of the electrophilic portion of the addend to stabilize the intermediate cation.[24] In the additions reported in this work the same stabilizing influence on the intermediate cation should be felt, regardless of the protonic reagent. Thus, the proportion of rearrangement in these additions must be governed by the difference in the nucleophilic character of X and the reaction conditions. In fact, the amount of rearrangement showed a dependence on the nature of the nucleophile in the order HF_2, CH_3OH, OCHO $\sim$ C_6H_5OH > Br >Cl. A significant dependence of the degree of rearrangement on the solvent (X = Cl, Br) or the reaction temperature for those cases tested (X = Br, OCHO) was not observed.

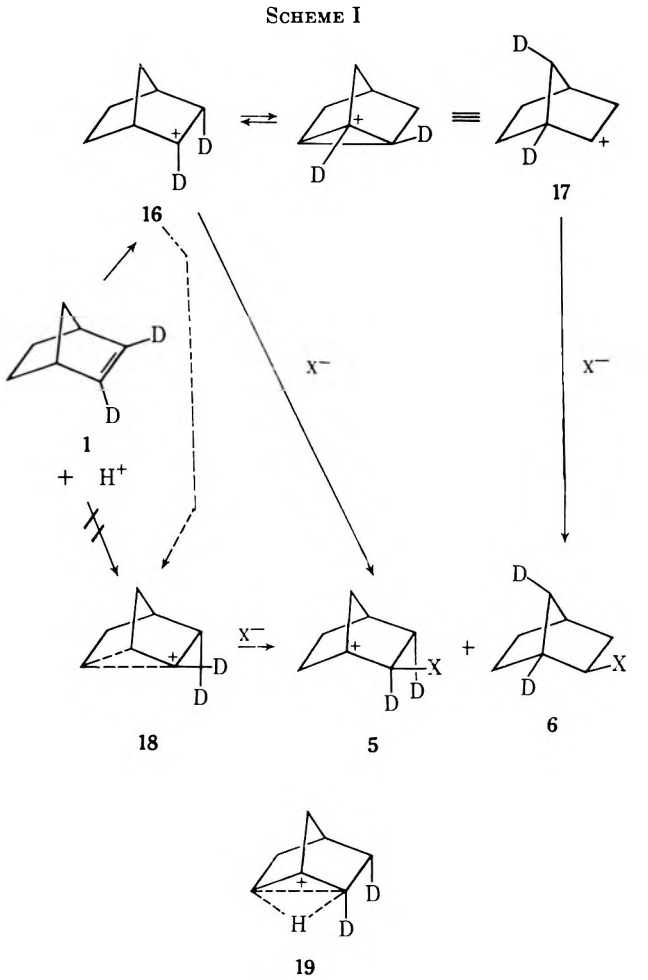
There are three possible intermediates which deserve consideration in the electrophilic additions to **1**: the classical norbornyl cation pair (**16** and **17**), the nonclassical norbornyl cation (**18**), and the nortricyclonium ion (**19**) (see Scheme I). Recent calculations suggest that under thermodynamically controlled conditions, **19** is more stable than either **16** or **17**.[25]

To invoke **19** as an intermediate in the additions to **1**, it must be concluded that the hydride shift which equilibrates positions C-1, C-2, and C-6 is extremely slow in comparison to the rate of capture by the nucleophile. This proton transfer would lead to the equivalence of C-1, C-2, and C-6 and hence, there should be equal probability of capture by X at these three sites. The amount of product formed *via* **19** in these additions could never, therefore, exceed that found for capture at C-6. Only when the protonic acid used was hydrogen fluoride was a significant amount of this product observed. In all other additions, and especially with hydrogen chloride and bromide, **19** cannot be an important intermediate in determining the product ratio.

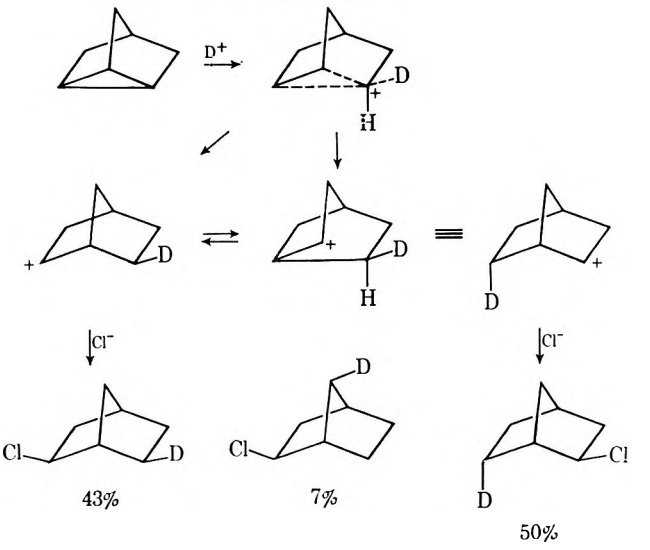
The addition of deuterium chloride to nortricyclene most certainly forms a protonated nortricyclonium ion as the initial intermediate[26,27] (Scheme II). This ion must rapidly and irreversibly leak to a classical or nonclassical norbornyl cation as no deuterium was found at positions C-1 or C-2 in the product mixture.[17] In the additions reported in this work, the product from capture of the cationic center at C-6 may best be accounted for by means of a competitive transannular hydride shift on the classical or nonclassical ions.

It is necessary to explain the 10–15% excess capture at C-2 over C-1 in the addition of hydrogen chloride and hydrogen bromide and the 8% excess in the addition of

SCHEME I



SCHEME II



phenol. In all other additions, the amount of capture at these two sites is essentially equal. Neglecting the relatively small amounts of 6,2-hydride shift product observed (capture at C-6), several explanations may be offered. (1) Ion **16** is the initially formed intermediate and either (a) 85–90% leaks irreversibly to **18** while the remainder undergoes capture by X before rearrangement, or (b) the excess attack at C-2 represents capture of **16** before it reaches equilibrium with **17**, *i.e.*, capture of the rapidly equilibrating classical ions in an unsymmetrical state (see Scheme I). (2) The reaction pro-

(24) T. G. Traylor, *Accounts Chem. Res.*, **2**, 152 (1969).
(25) G. Klopman, *J. Amer. Chem. Soc.*, **91**, 89 (1969).
(26) C. C. Lee and L. Gruber, *ibid.*, **90**, 3775 (1968).
(27) H. Fischer, H. Kollmar, H. O. Smith, and K. Miller, *Tetrahedron Lett.*, 5821 (1968).

ceeds by approximately 10–15% molecular (concerted or nearly concerted) addition of HX to 1 and about 85–90% through either (a) ion **18** in which capture occurs equally at C-1 and C-2 by X, or through (b) ion **16** which realizes complete equilibrium with **17** before capture by X.

Epoxidation, hydrogenation, and hydroboration, known concerted or molecular additions, add exo–cis to norbornene but add predominately endo–cis to 7,7-dimethylnorbornene.[28] The presence of 7,7-dimethyl substituents on norbornene, while successfully blocking the exo side to known molecular additions, has little or no effect upon blocking the additions of deuterium chloride and other ionic reagents from the exo side. It has been argued that electrophilic additions of protonic acids to 1 probably do not involve molecular addition. In light of this, explanations 2a and 2b are not likely.

On the basis of the results reported herein, it is not possible to distinguish between explanation 1a or 1b. Either pathway would successfully account for the relative proportions of attack at C-1 and C-2 by X. It would appear that only when X is chloride, bromide, or phenoxide is the rate of capture competitive with the rearrangement of **16** to **17** or leakage of **16** to **18**. It is important to point out that the results reported in Table I are not consistent with **18** as the sole product forming intermediate. Protonation must occur initially to give **16**, for if direct protonation to form **18** occurred, then an equal amount of product due to capture at C-1 and C-2 should always be observed.

Experimental Section[29]

2,3-Dideuterio-2,3-dibromonorbornene (11).—Hydrogenation of 83.2 g (0.328 mol) of 10[14] in ethyl acetate over platinum oxide under 50 psi of hydrogen yielded, after distillation, 76.8 g (91%) of clear liquid, bp 55–90° (0.5–0.05 mm) [lit.[30] undeuterated, bp 59.5–70° (0.8 mm)].

Debromination of 11.[15] Preparation of 1.—To 270 ml of anhydrous diethyl ether, 7.25 g (0.299 g-atom) of magnesium turnings, and a small crystal of iodine was added with stirring 50.0 g (0.197 mol) of 11 in 55 ml of anhydrous diethyl ether at such a rate so as to maintain a gentle reflux. Once all the solution had been added, the pot and contents were heated at the reflux temperature for an additional 2 hr. The reaction mixture was poured onto ice and extracted with ether. The ethereal extracts from this run, a second run using the same quantities, and a third run using one-half the quantities cited above were combined and dried. The ether was removed by distillation, and the residual liquid was distilled through a 30-cm zigzag column to afford 30.09 g (64%) of 1, bp 93.5–94° (lit.[31] undeuterated bp 96°), which solidified in the receiver.

Vpc analysis with a 15% SE-30 on Chromosorb W (20 ft by $^3/_8$ in.) column operated at 70° showed only norbornene was present. The signal at δ 5.92 (vinyl hydrogen) was absent in the nmr spectrum (CCl_4) of 1. Mass spectral analysis showed the sample to be composed of 95% d_2, 2% d_1, and 3% d_0 isomers.

Addition of Hydrogen Chloride to 1. Methylene Chloride Solvent.—To 4 ml of methylene chloride in the reaction flask of an automatic hydrochlorinator,[32] cooled to −78°, was added 0.486 g (0.005 mol) of 1 in 8 ml of methylene chloride. The reaction mixture was stirred vigorously under the atmosphere of anhydrous hydrogen chloride for 5 min. The stirring was then stopped and the reaction mixture poured immediately onto enough 7–10% sodium bicarbonate solution to neutralize all of the acid present and render the mixture weakly basic. The product was extracted with additional methylene chloride solution and the extracts were dried. Evaporation of the methylene chloride afforded 0.443 g (68%) of *exo*-norbornyl chloride.

Vpc analysis on a 5% Zonyl E-7 (40 ft by $^1/_4$ in.) column at 95° and a helium flow of 85 ml/min showed only *exo*-norbornyl chloride was present. This column was shown to separate *exo*- and *endo*-norbornyl chloride in an earlier experiment under similar conditions. From the nmr spectrum (C_6H_6) the amounts of exo–cis addition, Wagner–Meerwein rearrangement, and 6,2-hydride shift were determined. The relative integrals at δ 3.64 (C-2 H), 2.25 (C-1 H), 2.06 (C-4 H), and 0.99–1.87 ppm (remainder of H) were measured. Mass spectral analysis showed the material to be greater than 95% d_2 isomer.

Pentane Solvent.[33]—Dry hydrogen chloride gas was passed over a period of 1 hr through a solution of 0.908 g (0.0095 mol) of 1 in 10 ml of dry pentane cooled to −78°. The mixture was then allowed to warm to room temperature and stand overnight. Distillation afforded 0.858 g (69%) of *exo*-norbornyl chloride, bp 54–56° (18 mm) [lit.[34] undeuterated bp 75° (41 mm)]. The product was shown to be homogeneous by vpc analysis on the Zonyl E-7 column. Mass spectral analysis showed the material to be greater than 95% d_2 isomer. From the nmr spectrum (C_6H_6) the product ratios were determined (Table I).

Diethyl Ether Solvent.—The addition of hydrogen chloride to 1 was carried out by passing dry hydrogen chloride over a solution of 0.508 g (0.0052 mol) of 1 in 25 ml of dry diethyl ether for a period of 3 hr at room temperature. Removal of the solvent and excess reactants under reduced pressure and distillation of the residue afforded a small amount of clear liquid, bp 74–78° (40 mm) [lit.[34] undeuterated bp 75° (41 mm)]. The nmr spectrum (C_6H_6) of the material was recorded and the product distribution was determined (Table I). Mass spectral analysis showed the material to be greater than 95% d_2 isomer.

Addition of Hydrogen Bromide to 1.—To a flask attached to a reservoir containing anhydrous hydrogen bromide was added 5 ml of methylene chloride. The mixture was cooled at −45° (chlorobenzene slush bath) with stirring. To the cooled solution was added 0.552 g (0.0575 mol) of 1 in 3 ml of methylene chloride. The reaction was allowed to proceed for 5 min; then the stirring was stopped and the contents of the reaction flask were poured onto 75 ml of 10% sodium bicarbonate solution. The product was extracted with additional methylene chloride and dried. Evaporation of the methylene chloride left a clear liquid which was shown by vpc to be pure *exo*-norbornyl bromide. From the relative integral values of the nmr spectrum (C_6H_6) at δ 3.70 (C-2 H), 2.33 (C-1 H), and 0.54–2.25 ppm (remainder of H), the product ratio was determined (Table I). A sample of the product was placed back under the reaction conditions for an additional 75 min and then recovered and analyzed by nmr. No significant change in the spectrum or relative integral values was observed. Vpc analysis on the Zonyl E-7 column at 95° and a helium flow of 85 ml/min showed only exo product.

Addition of 48% Hydrobromic Acid to 1.[19]—To 3.3 g (0.0196 mol) of 48% hydrobromic acid was added 1.22 g (0.0127 mol) of 1, and the mixture was heated to 60° for 3 hr. The mixture was then cooled and the organic portion was separated. The aqueous layer was extracted with three portions of ether and the organic portions were combined. The organic phase was washed with water until neutral to litmus and was then dried. Distillation afforded 0.574 g (27%) of material, bp 68–70° (15 mm) [lit.[35] undeuterated bp 80° (28 mm)]. Vpc analysis with the Zonyl E-7 column showed only exo isomer was present. From the nmr spectrum (C_6H_6) of the sample the product ratio was determined (Table I).

Addition of Hydrogen Fluoride to 1.—To a polyethylene container cooled to −78° was added 10 ml of methylene chloride, and 1 ml of liquid hydrogen fluoride was condensed into it. A solution of 0.940 g (0.01 mol) of 1 in 5 ml of methylene chloride was added. The reaction mixture was stirred vigorously for 5 min at −78°, then quenched with enough 7–10% sodium bicarbonate solution to neutralize the excess acid present. The or-

(28) H. C. Brown and J. H. Kawakami, *J. Amer. Chem. Soc.*, **92**, 201 (1970).

(29) Nmr spectra were recorded with a Varian A-60 spectrometer (see Table I footnote). Vpc analyses were performed with the appropriate column on a Varian Associates Model 1520-C or Model 200 gas chromatograph. Mass spectra were obtained with a Hitachi RMU-6 mass spectrometer.

(30) N. A. LeBel, *ibid.*, **82**, 623 (1960).

(31) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 757.

(32) H. C. Brown and M. H. Rei, *J. Org. Chem.*, **31**, 1090 (1966).

(33) F. M. Sonnenberg, Ph.D. Thesis, University of Iowa, 1966, p 86.

(34) J. D. Roberts and W. Bennett, *J. Amer. Chem. Soc.*, **76**, 4623 (1954).

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ganic portion was collected and dried. Evaporation of the solvent and sublimation of the residue afforded 0.171 g (15%) of *exo*-norbornyl fluoride. Norbornene telomers (0.291 g) were also isolated. The *exo*-norbornyl fluoride obtained was further purified by preparative vpc on the 15% SE-30 column at 70° with a helium flow rate of 85 ml/min. The nmr spectrum of the purified material was virtually identical with that of an authentic sample of *exo*-norbornyl fluoride.[20] The product ratio was determined from the nmr spectrum ($CDCl_3$) (Table I). The relative integrals at δ 4.55 (C-2 H, J_{HF} = 56.5 Hz), 2.05–2.62 (C-1 and C-4 H), and 0.67–2.05 (remainder of H) were measured. Mass spectral analysis showed the material to be greater than 95% d_2 isomer.

Addition of Formic Acid to 1. Boron Trifluoride Catalyzed Addition.—To a solution of 2 ml (0.054 mol) of formic acid, 1 ml of boron trifluoride etherate, and 50 ml of methylene chloride at −22° (tetrachloroethylene slush bath) was added 0.832 g (0.0087 mol) of 1 in 4 ml of methylene chloride. The reaction mixture was stirred at −22° for 60 min and then poured onto enough 7–10% sodium bicarbonate solution to neutralize all of the acid present. The organic portion was collected and dried; the solvent was removed to yield 0.818 g (66%) of clear liquid. Vpc analysis with a 20% SE-30 (5 ft by 1/4 in.) column at 125° and a helium flow of 70 ml/min showed the product to be *exo*-norbornyl formate. A sample of a mixture of *exo*- and *endo*-norbornyl formates could be separated on this column under these conditions. The nmr spectrum ($CDCl_3$) of the formate product was recorded and the amounts of exo–cis addition, Wagner–Meerwein rearrangement, and 6,2-hydride shift were determined (Table I). The relative integrals at δ 7.96 (HCO_2), 3.70 (C-2 H), 2.14–2.47 (C-1 and C-4 H), and 0.83–2.00 (remainder of H) were measured.

Uncatalyzed Addition.—To 4.12 g (0.089 mol) of formic acid at ambient temperature was added 0.681 g (0.007 mol) of 1. The reaction mixture was stirred for 48 hr and then poured onto dilute sodium bicarbonate solution. Work-up in the usual manner, followed by distillation, afforded 0.50 g (50%), bp 74–75° (20 mm) [lit.[36] undeuterated bp 79–80° (25 mm)], of *exo*-norbornyl formate. The nmr spectrum ($CDCl_3$) of the product was recorded and the product distribution was determined (Table I). Vpc analysis as described above showed only *exo*-formate was present.

***endo,endo*-2,3-Dideuterio-*exo*-2-norbornanol (12).**—The hydroboration of 1 was carried out exactly as described[37] with 1.995 g (0.021 mol) of 1. After work-up and sublimation, 1.97 g (84%) of 12 was obtained. The nmr spectrum ($CDCl_3$) was similar to that of *exo*-norbornanol, except the resonance at δ 3.75 ppm (hydrogen attached to carbon bearing the alcohol group) was nearly absent in the spectrum of 12. The integral ratio of the spectrum of 12 was consistent with the presence of two atoms of deuterium per molecule.

***endo,endo*-2,3-Dideuterio-*exo*-2-norbornyl Formate (13).**—A mixture of 0.45 g (0.004 mol) of 12 and 3 ml of formic acid was stirred for 10 hr at room temperature. The reaction mixture was quenched with dilute sodium bicarbonate solution and then the product was isolated in the usual manner. Flash distillation afforded 0.355 g (60%) of material, bp >100° (20 mm). The nmr spectrum of the product was identical with that of *exo*-norbornyl formate, except the signal at δ 4.70 ppm (hydrogen attached to the carbon bearing the formate group) was absent. The integral ratio was consistent with two atoms of deuterium per molecule.

A sample of this material was placed under the reaction conditions described for the boron trifluoride etherate catalyzed addition of formic acid to 1 for a period of 62 min. The material was recovered and its nmr spectrum ($CDCl_3$) was essentially identical with that of 13, with no signal at δ 4.70 ppm.

Addition of Phenol to 1.—To 1.210 g (0.0126 mol) of 1, 1.246 g (0.0132 mol) of phenol, and 25 ml of methylene chloride, cooled to −22°, was added 0.25 ml of boron trifluoride etherate. After 4 hr the mixture was quenched with 10% sodium hydroxide solution. The aqueous portion was extracted several times with methylene chloride and the extract was dried. Evaporation of the methylene chloride and distillation of the residual liquid afforded 0.891 g (41%) of material, bp 78–80° (0.3 mm). Vpc analysis on the 15% SE-30 column showed only one component. The nmr spectrum ($CDCl_3$) of the product was consistent with that expected for *exo*-norbornyl phenoxide. The relative integrals at δ 6.61–7.50 (OC_6H_5), 4.10 (C-2 H), 2.10–2.99 (C-1 and C-4 H), and 0.83–2.00 ppm (remainder of H) were measured and the product ratio was determined (Table I).

Anal. Calcd for $C_{13}H_{14}D_2O$: C, 82.06; H and D, 9.53. Found: C, 82.07; H and D, 9.60.

Addition of Methanol to 1.—To a mixture of 20 ml of methanol and 1.18 ml of sulfuric acid at the reflux temperature was added 1.445 g (0.015 mol) of 1 in 3.6 ml of methanol. The mixture was heated at the reflux temperature for 21.5 hr and then poured onto enough sodium bicarbonate solution to neutralize the acid present. The product was extracted with ether, and distillation of the dried ether extracts afforded 1.033 g (56%), bp 84° (85 mm) [lit.[38] undeuterated bp 56–62° (30 mm)], of *exo*-norbornyl methoxide. Vpc analysis on a 20% SE-30 (5 ft by 1/4 in.) on Chromosorb W column at 125° with a helium flow rate of 60 ml/min showed only exo isomer was present. The exo and endo isomers could be separated by this column under these conditions. From the nmr spectrum ($CDCl_3$) the product ratio was determined (Table I) by measurement of the relative integrals at δ 3.17 (C-2 H and OCH_3), 2.00–2.30 (C-1 and C-4 H), and 0.75–1.80 ppm (remainder of H).

Registry No.—1, 13317-75-4; 15, 26854-01-3; hydrogen chloride, 7647-01-0; hydrogen bromide, 10035-10-6; hydrogen fluoride, 7664-39-3; formic acid, 64-18-6; phenol, 108-95-2; methanol, 67-56-1.

Acknowledgment.—The authors wish to acknowledge the National Science Foundation for financial assistance to the University of Iowa for the purchase of the Hitachi RMU-6 mass spectrometer.

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The Stereochemistry of Addition of Methanol to Hexafluoro-2-butyne and Trifluoromethylacetylene

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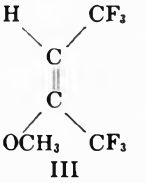
The stereochemistry of the products from the methoxide ion and the triethylamine-catalyzed addition of methanol to hexafluoro-2-butyne and to trifluoromethylacetylene have been determined. In all cases the addition is predominantly trans and is consistent with previously proposed mechanisms for nucleophilic additions to activated triple bonds. A small amount of *trans*-1,1,1,2,4,4,4-heptafluoro-2-butene was formed in the triethylamine-catalyzed addition to hexafluoro-2-butyne and a small amount of the geminal addition product of methanol to trifluoromethylacetylene was formed in the methoxide-catalyzed addition.

That the stereochemistry of nucleophilic additions to activated triple bonds is related to the nature of the activating groups is illustrated by the fact that the tertiary amine catalyzed addition of methanol to ethyl propiolate is 68% cis addition, whereas the similar addition of methanol to dimethyl acetylenedicarboxylate is 90% trans addition.[2] Although the stereochemistry of nucleophilic additions to various activated triple bonds has been reported,[3-14] little attention has been directed to the stereochemical course of additions to trifluoromethyl activated triple bonds.[15-21] The stereochemistry of these additions is of particular interest since in contrast to carbonyl, carboxylate, and cyanide activated triple bonds, the activation here should be largely inductive in nature. The sodium alkoxide catalyzed addition of alcohols to trifluoromethylacetylene and to hexafluoro-2-butyne has been studied,[15,16] but there are no reports on the stereochemistry of the products.

We have found that the sodium methoxide catalyzed addition of methanol to trifluoromethylacetylene (R_1 = H; R_2 = $-CF_3$) and both the sodium methoxide and the triethylamine catalyzed additions of methanol to hexafluoro-2-butyne (R_1 = R_2 = $-CF_3$) are predominantly trans additions (>97%) yielding I and II, respectively. Triethylamine failed to catalyze the addition of methanol to trifluoromethylacetylene, even at elevated temperature, and no detectable addition to either hexafluoro-2-butyne or trifluoromethylacetylene took place in the absence of catalyst. The cis isomer (III) was not isomerized under the reaction conditions, indicating that the trans isomer obtained in the reaction is the kinetic product.

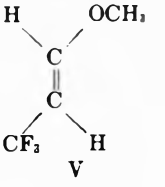


III

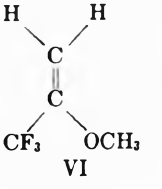
The stereochemistry of the reaction can be accounted for by assuming that it goes in accord with the mechanism proposed by Truce[4] and Miller[5] to account for the invariably trans addition which is observed in nucleophilic additions of thiols to acetylenes. Truce proposed that the approach of the negatively charged anion to the triple bond pushes an electron pair to the opposite side of the reaction intermediate where it is protonated (presumably by either protonated base molecules or by molecules of the addend), accounting for the observed trans addition.

The reaction products were analyzed by gas–liquid chromatography. In addition to the trans isomer, small amounts of the cis isomer III and of the HF addition product IV were isolated from the triethylamine-catalyzed addition of methanol to hexafluoro-2-butyne. Cullen and Dawson[18] also obtained IV from the reaction of hexafluoro-2-butyne, trimethylamine, and water in 27% yield. These authors proposed the reactions shown in Scheme I as one possible mechanism. Only the cis and trans isomers, II and III, were formed when sodium methoxide rather than triethylamine was the catalyst.

The *trans*-1-methoxy-3,3,3-trifluoropropene (the result of cis addition) (V) and the *gem*-trifluoromethyl-



V



VI

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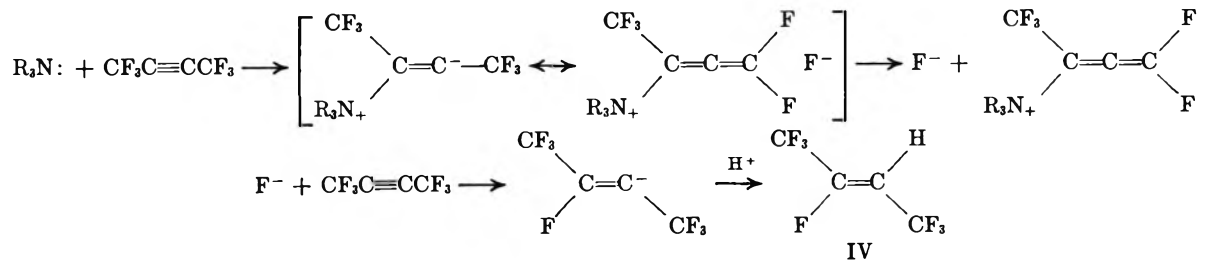
SCHEME I



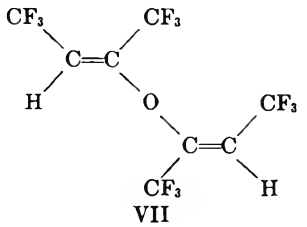
IV

TABLE I

NMR DATA FOR COMPOUNDS I, II, III, V, AND VI

	H^1 nmr			F^{19} nmr		
Compd	Group	Shift, δ	J, Hz	Group	Shift, ppm	J, Hz
I	CH_3O	3.70 (s)		$CF_3>C=$	+58.0 (d)	8.2
	$CF_3>C=$ H	4.58 (m), a quartet of doublets	8.2 7			
	$=C<^{OCH_3}_{H}$	6.21 (d)	7			
II	CH_3O	3.90 (s)		$CF_3>C=$ H	+57.8 (d)	8
	$=C<_{H}$	5.66 (q)	8	$=C<^{OCH_3}_{CF_3}$	+71.0 (s)	
III	CH_3O	3.66 (s)		$CH_3>C=$ H	+54.5 (m), a quartet of doublets	11 8
	$=C<^{H}$	5.04 (q)	8	$=C<^{CF_3}_{OCH_3}$	+68.9 (q)	11
V	CH_3O	3.56 (s)		$CF_3>C=$	+60.4 (m), a doublet of doublets	6.3 2.0
	$CF_3>C=$ H	4.88 (m), a quartet of doublets	6.3 13			
	$=C<^{H}_{OCH_3}$	6.03 (m), a quartet of doublets	2 13			
VI	CH_3O	3.58 (s)		$CF_3>C=$	+73.5 (d)	1.8
	$=C<^{H}$	4.28 (m), a quartet of doublets	1.8 3.5			
	$=C<^{H}$	4.72 (d)	3.5			

methoxyethene (VI) were formed in small amounts (1.8 and 1.5%, respectively) in the sodium methoxide catalyzed addition to trifluoromethylacetylene. Assignments of stereochemistry and of structure are based primarily on nmr spectroscopy. The stereochemical assignments are based on ones made by Cullen and Dawson[18] for the analogous compound VII. The nmr data are summarized in Table I.



VII

Experimental Section

All reactions were carried out by use of a vacuum line. The hexafluoro-2-butyne was obtained from Peninsular ChemResearch, Inc., Gainesville, Fla.

The proton nmr spectra were determined on a Varian HA-100 spectrometer, using tetramethylsilane as an internal standard. The fluorine nmr spectra were determined on a Varian HA-100-MHz spectrometer, using $CFCl_3$ as an internal standard. All positive values given for F^{19} nmr are upfield from $CFCl_3$. A Beckman IR5A was used to obtain infrared spectra. All infrared bands are given in reciprocal centimeters (cm^{-1}). Gas chromatographic analysis was carried out using a Varian-Aerograph Model 90-P equipped with a 12-ft copper column (0.25 in.) packed with 10% QF-1 on 60–70 Chromosorb W. Mass spectra were obtained from a RMU-6E Hitachi mass spectrometer.

Hexafluoro-2-butyne, Methanol, and Triethylamine.—Hexafluoro-2-butyne (1.62 g, 10 mmol) and 10 mmol (0.32 g) of absolute methanol were condensed into a 500-ml reaction vessel and allowed to come to room temperature. After 2 days, infrared showed no reaction had occurred. Triethylamine (0.101 g, 1 mmol) was then condensed into the vessel. After 24 hr, a strong absorption at 1695 cm^{-1} was found. A crude separation was accomplished by passing the volatile components through a −78° (acetone–Dry Ice) slush bath and a −196° (liquid nitrogen) bath. No unreacted butyne was found in either trap. Three components were isolated by gas chromatography of the material which condensed in the −78° trap.

The first peak was identified as *trans*-1,1,1,2,4,4,4-heptafluoro-2-butene (IV): ir (vapor) 1722 (C=C), 1404 (CF), 1309 (CF) 1272 (CF), 1220 (CF), 1192 (CF), 862 ($C=C<^{H}$), 735 (CF); mass spectrum (70 eV) *m/e* (relative intensity) 182 (11), 163 (34), 113 (100), 69 (25). This agreed closely with the data obtained by Cullen and Dawson.[18] The second peak was identified as *trans*-1,1,1,4,4,4-hexafluoro-2-methoxy-2-butene (II): ir (vapor) 2940 (CH), 1695 (C=C), 1469 (CH_3), 1399 (CH_3), 1300 (CF), 1272 (CF), 1212 (CF), 1170 (CF), 1100 (CO), 866 ($C=C<^{H}$);

mass spectrum (70 eV) *m/e* (relative intensity) 194 (48), 175 (20), 110 (19), 91 (100), 69 (33). *Anal.* Calcd for $C_5H_4F_6O$: C, 30.94; H, 2.08. Found: C, 30.62; H, 2.07. The third peak was identified as *cis*-1,1,1,4,4,4-hexafluoro-2-methoxy-2-butene (III): ir (vapor) 1680 (C=C), 1466 (CH_3), 1400 (CH_3), 1320 (CF), 1269 (CF), 1181 (CF), 1125 (CO), 914 ($C=C<^{H}$); mass spectrum (70 eV) *m/e* (rel intensity) 194 (48), 175 (14), 110 (19), 91 (100), 69 (36).

Hexafluoro-2-butyne, Methanol, and Sodium Methoxide.—Hexafluoro-2-butyne (1.30 g, 8 mmol) and 8 mmol (0.256 g) of absolute methanol were condensed into a 500-ml reaction vessel containing *ca.* 0.8 mmol (42.9 mg) of sodium methoxide and the resulting solution was allowed to stand (room temperature) for 10 hr. The infrared showed a strong absorption at 1695 cm^{-1} and showed that no butyne was present. The procedure described above was used to isolate the components from the reaction mixture. Two major peaks accounting for 98.6% of the material present were collected by glc and identified as *trans*-1,1,1,4,4,4-hexafluoro-2-methoxy-2-butene (II), 97.8%, and *cis*-1,1,1,4,4,4-hexafluoro-2-methoxy-2-butene (III), 2.2%. No peak corresponding to *trans*-1,1,1,2,4,4,4-heptafluoro-2-butene (IV) appeared.

Attempted Isomerization of *cis*-1,1,1,4,4,4,Hexafluoro-2-methoxy-2-butene (III) with Triethylamine.—*cis*-1,1,1,4,4,4-Hexafluoro-2-methoxy-2-butene (0.0305 g, 0.157 mmol) was sealed in an nmr tube with 0.015 mmol (0.0015 g) of triethylamine and 0.75 mmol of tetramethylsilane. The nmr taken immediately after the sample tube had reached room temperature and the nmr taken after 3 days at room temperature were identical with the spectrum of the *cis*-vinyl ether (III). Then 0.015 mmol (4.8×10^{-4} g) of absolute methanol was condensed into the nmr tube containing the cis compound and the triethylamine. After 3 days, the nmr spectrum showed only the cis compound III present.

Trifluoromethylacetylene, Methanol, and Triethylamine.—Trifluoromethylacetylene (0.376 g, 4 mmol) and 4 mmol (0.128 g) of absolute methanol were condensed into a 500-ml reaction vessel and allowed to come to room temperature. After 20 hr, infrared analysis showed no reaction. Triethylamine (0.04 g, 0.4 mmol) was then condensed into the reaction vessel. After 7 hr, no reaction could be detected, so another 0.4 mmol (0.04 g) of triethylamine was added. After 39 hr, the reaction mixture had turned brown, but no carbon–carbon double bond could be found in the ir. Unreacted $CF_3C{\equiv}CH$ (0.229 g, 2.44 mmol) was recovered from the reaction.

Trifluoromethylacetylene, Methanol, and Sodium Methoxide.—Trifluoromethylacetylene (0.780 g, 8.3 mmol) and 8 mmol (0.256 g) of absolute methanol were condensed into a 1-l. reaction vessel with 1.6 mmol (0.0534 g) of sodium methoxide and allowed to come to room temperature. After 3 hr, an absorbance at 1690 cm^{-1} was observed in the ir. After 45 hr of reaction, the mixture was separated *via* slush baths. The material from a −98° trap [CH_3OH, N_2(liquid)] was separated *via* glc. Separation was carried out at room temperature. The material isolated from the liquid N_2 trap was unreacted $CF_3C{\equiv}CH$ (44.5%). Three major peaks were collected by glc of the contents of the −98° trap. The first peak collected was identified as *gem*-trifluoromethylmethoxyethene (VI): ir (vapor) 2941 (CH_3), 1667 ($C=C<^{H}_{H}$), 1399 ($C=C<^{H}_{H}$), 1370 (CH_3), 1277 (CO), 1205 (CF), 1177 (CF), 1156 (CF), 843 ($C=C<^{H}_{H}$); mass spectrum (70 eV) *m/e* (rel intensity) 126 (100), 107 (8.5), 95 (20), 91 (17), 76 (14), 69 (35), 57 (33), 43 (31), 42 (32). The second peak corresponded to *trans*-1-methoxy-3,3,3-trifluoropropene (V): ir (vapor) 2933 (CH_3), 1672 ($_{H}>C=C<^{H}$), 1454 (CH_3), 1351 ($_{H}>C=C<^{H}$), 1242 (CF), 1178 (CF), 1123 (CF), 953 ($_{H}>C=C<^{H}$); mass spectrum (70 eV) *m/e* (rel intensity) 126 (100), 111 (6), 107 (19), 95 (42), 91 (33), 77 (34), 76 (18), 69 (38), 57 (18), 37.5 (0.5), 31 (92). The third peak corresponded to *cis*-1-methoxy-3,3,3-trifluoropropene (I): ir (vapor) 2933 (CH_3), 1692 ($^{H}>C=C<^{H}$), 1464 (CH_3), 1280 (CF), 1203 (CF), 1148 (CF), 718 ($_{H}>C=C<_{H}$); mass spectrum (70 eV) *m/e* (rel intensity) 126 (100), 111 (9), 107 (39), 95 (44), 91 (54), 77 (47), 76 (26), 69 (51), 59 (25), 51 (15), 37.5 (0.5), 31 (57). *Anal.* Calcd for $C_4H_5F_3O$: C, 38.11; H, 4.00. Found: C, 38.38; H, 4.40.

Registry No.—I, 26885-67-6; II, 400-21-5; III, 26885-69-8; IV, 17157-69-6; V, 26885-71-2; VI, 26885-72-3; methanol, 67-56-1; hexafluoro-2-butyne, 692-50-2; trifluoromethylacetylene, 661-54-1.

Acknowledgments.—The authors wish to express their thanks to Dr. J. M. Shreeve and coworkers for the F^{19} nmr spectra and help on vacuum line techniques. Thanks also go to J. A. Johnson and S. McCarron for the mass spectra and H^1 nmr spectra.

The Synthesis of Fluorine-Containing Heterocyclic Nitramines[1]

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Received June 25, 1970

Trifluoroacetaldehyde reacted readily with ammonia to give 2,4,6-tris(trifluoromethyl)hexahydro-*s*-triazine (**1d**), which on nitrosation gave the 1,3,5-trinitroso derivative **1e**. 2,4,6-Trimethyl-1,3,5-trinitrosohexahydro-*s*-triazine (**1f**) could not be converted to the trinitro compound; the fluorine-containing trinitroso compound underwent this conversion successfully, although a displacement rather than an oxidation reaction was indicated. 2,2-Diaminohexafluoropropane condensed with formaldehyde and methylenedinitramine to give a mixture of 2,2-bis(trifluoromethyl)-5-nitrohexahydro-*s*-triazine (**2b**) and 2,2-bis(trifluoromethyl)-5,7-dinitro-1,3,5,7-tetraazacyclooctane (**3c**). Several *N*-nitroso and *N*-nitro derivatives of these two ring systems were prepared.

Saturated cyclic polyamines with rings composed of alternating carbon and nitrogen atoms, as in Chart I, tend to be unstable. Solutions of formaldehyde and ammonia contain hexahydro-*s*-triazine (**1a**), but it cannot be isolated from solution and probably is in equilibrium with open-chain forms and with ammonia and formaldehyde.[3,4] Reported derivatives of **1a** always have been stabilized by structural features such as the condensed tricyclic system in hexamethylenetetramine, the electronegative groups in RDX (1,3,5-trinitrohexahydro-*s*-triazine (**1b**), or the C-substituted alkyl groups in 2,4,6-trimethylhexahydro-*s*-triazine (**1c**); the cyclic

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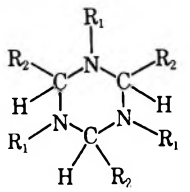
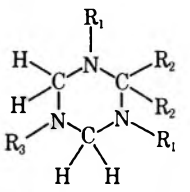
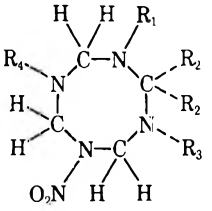
CHART I



1a, $R_1 = R_2 = H$
b, $R_1 = NO_2$; $R_2 = H$
c, $R_1 = H$; $R_2 = CH_3$
d, $R_1 = H$; $R_2 = CF_3$
e, $R_1 = NO$; $R_2 = CF_3$
f, $R_1 = NO$; $R_2 = CH_3$
g, $R_1 = NO$; $R_2 = H$
h, $R_1 = NO_2$; $R_2 = H$
i, $R_1 = NO_2$; $R_2 = CF_3$



2a, $R_1 = NO_2$; $R_2 = H$; $R_3 = CH_3$
b, $R_1 = H$; $R_2 = CF_3$; $R_3 = NO_2$
c, $R_1 = NO$; $R_2 = CF_3$; $R_3 = NO_2$
d, $R_1 = R_3 = NO_2$; $R_2 = CF_3$



3a, $R_1 = R_3 = R_4 = NO_2$; $R_2 = H$
b, $R_1 = NO_2$; $R_2 = H$; $R_3 = R_4 = CH_3$
c, $R_1 = R_3 = H$; $R_2 = CF_3$; $R_4 = NO_2$
d, $R_1 = NO$; $R_2 = CF_3$; $R_3 = H$; $R_4 = NO_2$
e, $R_1 = R_3 = NO$; $R_2 = CF_3$; $R_4 = NO_2$
f, $R_1 = R_4 = NO_2$; $R_2 = CF_3$; $R_3 = H$

structure of **1c**, "aldehyde–ammonia," has been questioned in the past but has been firmly established by more modern methods such as X-ray[5,6] and infrared[7] spectroscopy. A reaction product of chloral and ammonia is also believed to be cyclic. The eight-membered ring system of Chart I is known only in compounds stabilized by nitration or nitrosation of the nitrogen atoms. Two possible routes leading to analogs of RDX and HMX [1,3,5,7-tetranitro-1,3,5,7-tetraazacyclooctane (**3a**)] are (1) reaction of an aldehyde with an amine to give a cyclic, symmetrically substituted poly(secondary)amine, followed by N-nitration, and (2) condensation of a nitramine with an aldehyde and an amine to give a cyclic polyamine already partially stabilized by the nitramine function. This paper reports the synthesis of new compounds based on the hexahydro-*s*-triazine and 1,3,5,7-tetraazacyclooctane ring systems which are obtained by these two routes.

Trifluoroacetaldehyde reacted readily with ammonia even at −50°. As is the case with hexafluoroacetone, the initial adduct subsequently loses the elements of water rather than of ammonia (spontaneously in the case of trifluoroacetaldehyde); however, where hexafluoroacetone gives the monomeric imine, $(CF_3)_2C{=}NH$,[8] trifluoroacetaldehyde gave the trimer, 2,4,6-tris(trifluoromethyl)hexahydro-*s*-triazine (**1d**). The compound was a stable, easily subliming solid.

Treatment of **1d** with dinitrogen tetroxide gave the trinitroso compound, **1e**, in 58% yield; the corresponding nonfluorinated compound, **1f**, was obtained only in a much lower yield (14%) under somewhat milder conditions by nitrosation of commercial "aldehyde–ammonia." The fluorinated *N*-nitroso compound was the more stable of the two but did decompose at 25° over several days' time.

Oxidation of the C-unsubstituted trinitroso compound **1a** to RDX is well established.[4] In contrast, the *C*-methyl compound **1f** failed under all conditions to give a product which could be characterized as the trinitramine **1h**; however, the tris(trifluoromethyl)nitroso compound **1e** was successfully converted to the trinitramine **1i** in 80% yield by treatment with a mixture of 100% nitric acid and trifluoroacetic anhydride. Although this reaction is ostensibly an oxidation, it does not seem to be so in fact, as other oxidizing agents were without effect, even peroxytrifluoroacetic acid, which is a very powerful and specific reagent for the nitrosamine–nitramine oxidation. In such a highly acid medium, a displacement of the nitrosonium ion by the nitronium ion, in an electrophilic attack at the nitrogen atom, seems plausible. The fluorinated trinitramine was also prepared by direct nitration of the hexahydrotriazine **1d**, but the resulting material was less easily purified than that made from the nitroso precursor. When pure, the trinitramine **1i** seemed to be indefinitely stable.

Methylamine condenses with methylenedinitramine (MEDINA) and formaldehyde to give derivatives of the hexahydro-*s*-triazine[9] and 1,3,5,7-tetraazacyclooctane[10] systems, specifically **2a** and **3b**. We investigated the condensation of alkylamines with MEDINA and trifluoroacetaldehyde, and with trifluoroethylidenedinitramine[11] and formaldehyde, in anticipation that a fluorine-containing cyclic compound would be formed in which the *N*-alkyl group might be converted into a nitro group by oxidative nitration. However, in spite of extensive investigation of reaction conditions, no cyclic condensation products were obtained from either of these two systems. A third possibility was the reaction of a fluorinated *gem*-diamine with MEDINA and formaldehyde, and this route proved to be successful.

Two attempts to prepare a fluorinated *gem*-diamine containing a single trifluoromethyl group were unsuccessful. The reduction of trifluoroacetamidine, $CF_3C{=}NH(NH_2)$, to 1,1-diamino-2,2,2-trifluoroethane failed, and hydrolysis of $CF_3CH(NHCHO)_2$ to $CF_3CH(NH_2{\cdot}HCl)_2$ gave only ammonia and unidentified fluorine-containing substances. The presence of a second trifluoromethyl group, however, stabilizes the *gem*-diamine structure, and $(CF_3)_2C(NH_2)_2$ is accessible by the method of Krespan.[8] By analogy with the reaction of methylamine, condensation of the fluorinated diamine with MEDINA and formaldehyde would be expected to produce 2,2-bis(trifluoromethyl)-5-nitrohexahydro-*s*-triazine (**2b**) and 2,2-bis(trifluoromethyl)-5,7-dinitro-1,3,5,7-tetraazacyclooctane (**3c**). The condensation proceeded smoothly at 25°, and both of the anticipated products **2b** and **3c** were obtained. These were sep-

(5) N. F. Moerman, *Z. Krist.*, **98**, 447 (1938).
(6) E. W. Lund, *Acta Chem. Scand.*, **12**, 1768 (1958).
(7) A. Novak, *Spectrochim. Acta*, **16**, 1001 (1960).
(8) W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **30**, 1398 (1965).
(9) F. Chapman, P. G. Owston, and D. Woodcock, *J. Chem. Soc.*, 1638 (1949).
(10) W. J. Chute, D. C. Downing, A. F. McKay, G. S. Myers, and G. F. Wright, *Can. J. Res., Sect. B*, **27**, 218 (1949).
(11) J. A. Krimmel, J. J. Schmidt-Collerus, J. A. Young, G. E. Bohner, and D. N. Gray, *J. Org. Chem.*, **36**, 350 (1971).

arated from unidentified side products by fractional extraction with $CF_2ClCFCl_2$ (Freon 113) and were identified by elemental analyses and infrared spectra.

Nitrosation of the hexahydrotriazine derivative **2b** with dinitrogen tetroxide in acetic acid gave a 60% yield of a material whose ir spectrum indicated the absence of N–H and the presence of N=O bonds, presumably the structure **2c**. The material decomposed slowly at room temperature. Nitration of **2b** gave a 70% yield of the stable trinitramine **2d**.

The tetraazacyclooctane ring proved to be less tractable, and neither nitrosation nor nitration gave stable products capable of characterization. Nitrosation of the dinitramino compound **3c** with sodium nitrite and hydrochloric acid, or with nitrosonium fluoroborate, was ineffective. The progressively stronger nitrosating systems of sodium nitrite in acetic anhydride[12] and dinitrogen tetroxide with sodium acetate[13] gave materials which seemed to be, respectively, a dinitromononitroso and a dinitrodinitroso compound, according to their ir spectra, as shown by **3d** and **3e**. Both compounds decomposed slowly on standing, **3e** being somewhat more stable than **3d**. The nitrosoamine groups could not be oxidized to nitramine groups; 100% nitric acid or hydrogen peroxide in acetic acid had no effect, hydrogen peroxide in trifluoroacetic acid led to decomposition, and peroxytrifluoroacetic acid removed both nitroso groups, re-forming **3c**.

Although the stability of cyclic nitramines increases with increasing symmetry, the reactivity of the two nitrogen atoms adjacent to the carbon bearing the trifluoromethyl groups is decreased by both steric and electronic effects, and attempts to obtain a fully nitrated compound with four nitramino groups were unsuccessful, either *via* the nitrosamines described above or by direct nitration of **3c**. Nitration of **3c** with 100% nitric acid in trifluoroacetic anhydride gave a product in good yield whose infrared spectrum indicated that a third nitro group had been introduced (**3f**); however, the material was quite unstable and could not be adequately purified. It precipitated during the nitration reaction, and attempts to circumvent this difficulty by reaction at higher temperatures or in an inert medium failed.

Experimental Section

Infrared absorptions are given, where applicable, for the N–H stretch and N–O (asymmetric) stretch. The N=O (symmetric) stretch cannot be assigned unequivocally since it appears in the same general region as the C–F stretch. Spectra were taken as split mulls on a Beckman IR-8.

1,3,5-Trinitroso-2,4,6-trimethylhexahydro-*s*-triazine (1f).—A stirred solution of 40 g (0.22 mol) of technical acetaldehyde–ammonia (Eastman) in 175 ml of dry chloroform was cooled to −20° and nitrogen oxide fumes were passed through for 2 hr. The nitrogen oxides, a mixture of N_2O_3 and N_2O_4, were generated by adding concentrated nitric acid to powdered arsenic sesquioxide and warming as needed to produce a steady gas flow. A precipitate formed as the reaction proceeded. The mixture was poured into water, the chloroform layer removed, and the aqueous layer extracted with additional chloroform. The chloroform layers were combined, washed with water, dried, and concentrated almost to dryness. The precipitate formed by addition of 20 ml of absolute ethanol was filtered and dried: weight 6.5 g (14% yield); mp (after recrystallization from absolute ethanol) 163° (lit.[14] 161°); infrared NH, none, N=O (asymmetric) 1488 cm^{-1}.

Anal. Calcd for $C_6H_{12}N_6O_3$: C, 33.3; H, 5.6; N, 38.9. Found: C, 34.0; H, 6.0; N, 39.4.

2,4,6-Tris(trifluoromethyl)hexahydro-*s*-triazine (1d).—Anhydrous trifluoroacetaldehyde was made by dehydrating the commercial hydrated form (Peninsular ChemResearch) with phosphorus pentoxide and polyphosphoric acid. The anhydrous aldehyde, 66 g (0.68 mol), was added as a gas below the surface of a solution of liquid ammonia, 30 g (1.8 mol), in 140 ml of ether, stirred at −50°. After a short reflux (Dry Ice condenser), the mixture was warmed and the excess ammonia and solvent removed by distillation, heating to a pot temperature of 70°. Benzene (200 ml) was added and the water present removed azeotropically. After removal of the benzene, the semicrystalline residue was filtered, dried, and purified by vacuum sublimation at 40° and recrystallization from cyclohexane and petroleum ether: yield 24 g (36% of theory); mp 83–84°; infrared NH, 3315, 3340 cm^{-1}; N=O none.

Anal. Calcd for $C_6H_6F_9N_3$: C, 24.8; H, 2.1; F, 58.7; N, 14.4; mol wt, 291. Found: C, 25.1; H, 2.3; F, 59.0; N, 14.2; mol wt, 301 (ebullioscopic in benzene).

On standing for several days, the filtrate from the crude product developed more crystalline material. Each subsequent filtrate likewise crystallized in part, so that the eventual yield probably approaches 50% of theory.

1,3,5-Trinitroso-2,4,6-tris(trifluoromethyl)hexahydro-*s*-triazine (1e).—To a suspension of 24 g of powdered, freshly fused sodium acetate in 100 ml of glacial acetic acid, cooled to 10°, was added 20 g of liquid dinitrogen tetroxide. With stirring, 9.5 g (0.033 mol) of 2,4,6-tris(trifluoromethyl)hexahydro-*s*-triazine was added in small portions during a period of 1 hr. After another 1.5 hr at 5–10°, the mixture was poured on ice. The precipitated product, after drying, was recrystallized from petroleum ether to give 4.7 g, mp 45–46°. Additional material obtained from the mother liquors brought the yield to 58% of theory.

Anal. Calcd for $C_6H_3F_9N_6O_3$: C, 19.1; H, 0.1; F, 45.2; N, 22.2. Found: C, 18.4; H, 1.5; F, 42.3; N, 20.2.

Although these analytical data are not in good agreement with theory, the absence of N–H absorption in the infrared as well as the facile conversion of this compound to the trinitro derivative are good evidence that it is the desired trinitrosohexahydro-*s*-triazine.

1,3,5-Trinitro-2,4,6-tris(trifluoromethyl)hexahydro-*s*-triazine (1i).—To a nitrating mixture prepared by adding 80 g of absolute nitric acid to 80 g of trifluoroacetic anhydride below 10°, 7.5 g of **1e** was added in small portions over 1 hr at 0–5°. The reaction was stirred while warming to room temperature (4 hr) and then was drowned in ice and water. The crude product was filtered, washed with cold water, dried *in vacuo*, and recrystallized from cyclohexane to give 5.7 g (67%) of material: mp 117–118°; infrared NH, none, N=O (asymmetric) 1625 cm^{-1}.

Anal. Calcd for $C_6H_3F_9N_6O_6$: C, 16.9; H, 0.7; F, 40.1; N, 19.7. Found: C, 17.1; H, 0.8; F, 40.0; N, 19.5.

2,2-Bis(trifluoromethyl)-5-nitrohexahydro-*s*-triazine (2b) and 2,2-Bis(trifluoromethyl)-5,7-dinitro-1,3,5,7-tetraazacyclooctane (3c).—In an open beaker, 65 g (0.48 mol) of MEDINA and 82 g (0.96 mol) of 35% formaldehyde were stirred at 10–15° for 0.5 hr, and 87 g (0.48 mol) of 2,2-diaminohexafluoropropane was then added during a period of 20 min. The mixture was stirred at 10–15° for 1 hr and then for several hours while warming to room temperature, until the two liquid phases which formed could no longer be intimately mixed because of solidification. The contained water was allowed to evaporate at room temperature and the residue was ground and dried *in vacuo* for 16 hr at 25–30° and then extracted continuously with Freon 113. In the first stages of the extraction, before the appearance of crystals (1–3 hr, depending on the efficiency of the extraction), the extract contained mainly **2b**, which was considerably more soluble in Freon 113 than **3c**. Removal of any crystals formed, followed by slight concentration and chilling, gave **2b**. Further extraction of the crude product with Freon 113 gave mainly **3c**, which was only slightly soluble in Freon 113 at room temperature. Pure samples of the two compounds were obtained by repeated fractional extraction and/or recrystallization from Freon 113, using melting points and infrared spectra as criteria of purity. The triazine derivative **2b** melted at 88° and showed complex absorptions at 3300–3400 (NH) and 1450–1510 cm^{-1} (NO); the tetraazacyclooctane derivative **3c** melted at 127–128° and showed sharp absorption bands at 3390, 3360 (NH), and 1530 cm^{-1} (NO). Reaction in the quantities cited gave 5 g of **2b** and 31 g of **3c**, representing conversions of 4 and 19%, respectively, based on 2,2-

(12) E. H. White, *J. Amer. Chem. Soc.*, **77**, 6008 (1955).
(13) W. M. Jones and J. M. Denham, *ibid.*, **86**, 944 (1964).
(14) M. Delepine. *Bull. Soc. Chim. Fr.*, **19**, 15 (1898).

diaminohexafluoropropane, plus additional impure material. The extraction residue showed no infrared indication of NNO_2 or CF groups.

Anal. Calcd for $C_5H_6H_6N_4O_2$ (**2b**): C, 22.4; H, 2.3; F, 42.5; N, 20.9; mol wt, 268. Found: C, 22.6; H, 2.1; F, 36.1; N, 21.0; mol wt, 275 (ebullioscopic in benzene). Calcd for $C_6H_8F_6N_6O_4$ (**3c**): C, 21.2; H, 2.4; F, 33.3; N, 24.6; mol wt, 342. Found: C, 21.1; H, 2.5; F, 28.5; N, 24.1; mol wt, 351 (ebullioscopic in benzene).

Nitrosation of 2b.—To a mixture of 5 g of dinitrogen tetroxide, 6.5 g of freshly fused sodium acetate, and 20 ml of acetic acid was added, in small portions, 1.5 g (0.006 mol) of **2b**. After stirring for 1 hr at 10–20° and 0.5 hr at 20–25°, the mixture was poured on ice. The product was filtered, washed, dried, and recrystallized from petroleum ether to give 1.1 g (60% yield) of alleged **2c**, mp 96–97°.

2,2-Bis(trifluoromethyl)-1,3,5-trinitrohexahydro-*s*-triazine (2d).—**2b** (4 g, 0.015 mol) was added in small portions to a stirred mixture of 7.3 g of 100% nitric acid and 24 g of trifluoroacetic anhydride during a period of 0.5 hr and stirred for an additional 3 hr, all operations being carried out at 5–10°. The precipitated solid was filtered, washed, dried, and recrystallized to give 3.7 g of **2d**: mp 108°, or 70% of theory; infrared NH, none, NO (asymmetric) 1560, 1600, 1620 cm^{-1}.

Anal. Calcd for $C_5H_4F_6N_6O_6$: C, 16.8; H, 1.1; F, 31.8; N, 23.5. Found: C, 16.9; H, 1.1; F, 30.6; N, 22.7.

Attempted Nitrosation and Nitration of 3c.—To a stirred solution of 5 g (0.015 mol) of **3c** in 25 ml of acetic acid and 75 ml of acetic anhydride was added slowly 20 g (0.35 mol) of sodium nitrite at 0–5°. After the mixture was stirred for 2 hr, it was poured into 250 ml of ice and water. The solid was filtered, washed, dried, and recrystallized from ethylene dichloride to give 4.3 g of presumed **3d** (79% yield): mp 156–157°; infrared NH, 3390, NO (asymmetric), 1525 (sh), 1535, 1560 cm^{-1}.

Nitrosation of **3c** as in the preparation of **2c** gave a 76% yield of presumed **3e**: mp 151°, infrared NH, none, NO (asymmetric) 1535, 1555 (sh), 1560, 1580 cm^{-1}.

The compound **3c** was nitrated as in the preparation of **2d**. The crude product, obtained in approximately 75% yield, melted at 50–75°. Recrystallization of a small sample from benzene raised this figure to 120–123°, but attempted recrystallization of the main product resulted in progressive deterioration, as indicated by a lowered melting point and the appearance of many new peaks in the infrared spectrum. The recrystallized product after standing 2 weeks at room temperature melted at 105–106°: infrared NH, 3350, NO 1530–1560, 1600 cm^{-1}.

Registry No.—**1d**, 26960-86-1; **1e**, 26960-87-2; **1f**, 27074-73-3; **1i**, 26960-88-3; **2b**, 26960-89-4; **2c**, 26960-90-7; **2d**, 27006-03-7; **3c**, 26960-91-8; **3d**, 26960-92-9; **3e**, 26960-93-0.

Notes

The Synthesis of Fluorine-Containing Aliphatic *gem*-Dinitramines[1]

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As part of an extensive program on fluorine-containing *N*-nitro and *C*-nitro compounds, the preparation of a partially fluorinated aliphatic dinitramine related to MEDINA, $CH_2(NHNO_2)_2$, was of interest. This paper describes the synthesis of trifluoromethyl-MEDINA, $CF_3CH(NHNO_2)_2$, and its nonfluorinated analog, methyl-MEDINA, $CH_3CH(NHNO_2)_2$.

MEDINA has best been made[2,3] by condensing formamide with an aldehyde to form an alkylidenebisamide, nitrating the bisamide to an alkylidenebis(*N*-nitroamide), and hydrolyzing the nitramide to the free nitramine, as shown in Scheme I.

This general route was followed in the synthesis of trifluoromethyl-MEDINA and methyl-MEDINA, but variations in properties due to the trifluoromethyl and methyl groups often necessitated considerable modification of reaction conditions. Although the reactions of substituted aldehydes with acetamide and formamide have previously been studied by several workers,[4-8]

SCHEME I

$$\mathrm{RCHO} + \mathrm{R'CONH_2} \longrightarrow \underset{\mathbf{1}}{\mathrm{RCH(NHCOR')_2}}$$

$$\mathbf{1} + \mathrm{HNO_3}\text{–}(\mathrm{CF_3CO})_2\mathrm{O} \longrightarrow \underset{\mathbf{2}}{\mathrm{RCH[N(NO_2)COR']_2}}$$

$$\mathbf{2} + \mathrm{H_2O} \longrightarrow \mathrm{RCH(NHNO_2)_2} + \mathrm{R'COOH}$$

neither of the bisformamides **1** (R = CH_3, CF_3) has been reported, and no aldehyde other than formaldehyde has been successfully converted to a *gem*-dinitramine.

Bis(formamido)methane, bis(acetamido)methane, and bis(trifluoroacetamido)methane were made by the method of Sauer,[2] utilizing a high temperature reaction of hexamethylenetetramine and the appropriate amide. 1,1-Bis(acetamido)ethane was prepared by the method of Noyes and Forman,[9] but all published techniques for bisamide formation proved unsuccessful in the case of 1,1-bis(formamido)ethane. This compound was prepared by a method similar to that used for bisurethans,[10] the aldehyde and amide being reacted in aqueous solution for brief periods at 25–40° in the presence of hydrochloric acid. 1,1-Bis(formamido)-2,2,2-trifluoroethane and 1,1-bis(acetamido)-2,2,2-trifluoroethane were made by sealed tube reactions at 130°, using anhydrous trifluoroacetaldehyde and the amide. Attempts to prepare a bisamide from propionaldehyde were unsuccessful. A sealed tube reaction of hexa-

(1) This work was supported by Detachment 4, Eglin Field, U. S. Air Force.

(2) C. W. Sauer, U. S. Patent 2,713,594 (1955).

(3) C. W. Sauer, U. S. Patent 2,856,429 (1958).

(4) G. Pulvermacher, *Ber.*, **25**, 304 (1892).

(5) V. von Richter, *ibid.*, **5**, 477 (1872).

(6) A. Reich, *Monatsh. Chem.*, **25**, 933 (1904).

(7) K. Bulow, *Ber.*, **26**, 1973 (1893).

(8) A. Roth, *Justus Liebigs Ann. Chem.*, **154**, 72 (1870).

(9) W. A. Noyes and D. B. Forman, *J. Amer. Chem. Soc.*, **55**, 3493 (1933).

(10) W. M. Kraft and R. M. Herbst, *J. Org. Chem.*, **10**, 485 (1945).

fluoroacetone and formamide gave only a 1:1 adduct which dissociated on heating and reverted to free amide and ketone.

MEDINA was prepared from bis(acetamido)methane following the procedure of Brian and Lamberton,[11] but none of the other three bisacetamides 1 (R = CH_3, CF_3, R′ = CH_3; R = CH_3, R′ = CF_3) could be nitrated using either a nitric acid–acetic anhydride or a nitric acid–trifluoroacetic anhydride system. Nitrosyl chloride and dinitrogen pentoxide, both reported to be excellent nitrating agents in anhydrous solvents,[12] also failed to give the desired nitramides. Failure to nitrate 1,1-bis(acetamido)ethane has been reported previously.[11] Sauer[3] succeeded in obtaining good yields of bis(nitroformamides) by the use of 98% nitric acid in either acetic or trifluoroacetic anhydride, and the latter technique was found to be satisfactory with only slight modification for nitration of both 1,1-bis(formamido)-ethane and 1,1-bis(formamido)-2,2,2-trifluoroethane. No nitramides were obtained when acetic anhydride was employed.

The three sets of compounds, bisformamides, bis(*n*-nitroformamide)s, and dinitramines, constitute a series in which the character of the nitrogen atom is markedly influenced by the atom or group (R = CH_3, H, CF_3) attached to the central carbon atom. This influence was reflected to the greatest extent in the properties of the nitramides. Bis(*N*-nitroformamido)-methane was a fairly stable compound when pure and dry and presented no great difficulty either in isolation from the nitration step or in hydrolysis to the nitramine. 1,1-Bis(*N*-nitroformamido)ethane was quite insoluble in water and fairly stable when dry but was very sensitive to strong acids and decomposed rapidly when left in contact with formic acid. On the other hand, 1,1-bis(*N*-nitroformamido)-2,2,2-trifluoroethane appeared to be rather soluble in water and was unstable at room temperature, although it was much more resistant to decomposition by acids. Consequently, the desired hydrolysis to the substituted nitramines suffered from simultaneous decomposition of the nitramides, hydrolytic in one case and thermal in the other, resulting in lower and more erratic yields of methyl-MEDINA and trifluoromethyl-MEDINA than that of MEDINA itself.

Trifluoromethyl-MEDINA is strongly hydrogen bonded. For the N=O asymmetric stretch in infrared spectra taken on split mulls, MEDINA showed a singlet at 1580 cm^{-1} and methyl-MEDINA showed a main peak at 1581 with a shoulder at 1568 cm^{-1}, while trifluoromethyl-MEDINA showed a doublet at 1688 and 1722 cm^{-1} which reverted to a singlet at 1621 cm^{-1} when the spectrum was taken of a carbon tetrachloride solution. The NH stretch of trifluoromethyl-MEDINA was a broad band at 2950–3250 cm^{-1} in the mull sample but a sharp singlet at 3380 cm^{-1} in the solution.

Experimental Section

1,1-Bis(formamido)-2,2,2-trifluoroethane.—In a high vacuum system, 25 g (0.26 mol) of anhydrous trifluoroacetaldehyde was transferred into a heavy-walled Pyrex tube containing 25 g (0.55 mol) of formamide. The tube was sealed and heated at 120° for 8 hr, cooled to −80°, broken, and reheated until the completely crystalline mass had melted. The contents were poured out and allowed to crystallize. After recrystallization from acetonitrile, the yield of material melting at 193° was 16.2 g or 74% of theory, assuming that 2 mol of aldehyde is necessary to form 1 mol of bisamide plus 1 mol of trifluoroacetaldehyde hydrate. Attempts to prepare trifluoroethylidenebisformamide from the aldehyde hydrate rather than the free aldehyde were completely unsuccessful. Infrared absorptions (split mull, Beckman IR-8) showed NH, 3100, 3280, N=O (asymmetric), none, C=O 1690 cm^{-1}.

Anal. Calcd for $C_4H_6F_3N_2O_2$: C, 28.2; H, 3.0; F, 33.5; N, 16.5. Found: C, 28.4; H, 3.5; F, 34.6; N, 17.3.

1,1-Bis(acetamido)-2,2,2-trifluoroethane.—Reaction of 11.5 g (0.12 mol) of trifluoroacetaldehyde and 11.8 g (0.20 mol) of acetamide for 15 hr at 140°, removal of excess amide by vacuum distillation, and crystallization of the solidified residue from acetonitrile gave 4.1 g (34% of theory) of product: mp 265°; infrared NH, 3115, 3290, NO (asymmetric), none, CO 1678 cm^{-1}.

Anal. Calcd for $C_6H_9F_3N_2O_2$: C, 36.4, H, 4.6; N, 14.1. Found: C, 37.0; H, 4.8; N, 15.7.

1,1-Bis(*N*-nitroformamido)-2,2,2-trifluoroethane.—1,1-Bis(formamido)-2,2,2-trifluoroethane (5 g, 0.03 mol) was dissolved in 20 g of trifluoroacetic anhydride and 17 g of 100% nitric acid was added slowly with stirring at 5°. After aging for 4 hr at 5 ± 3°, the reaction mixture was poured slowly with vigorous stirring into 100 g of finely crushed ice. The resulting white gummy solid was washed with ice water by decantation, transferred immediately to a small flask, and subjected to high vacuum (<10 μ) while kept in an ice bath. After about 5 hr, the granular dry, white residue was recrystallized from methylene chloride to give 4.0 g of product. After standing 17 days in a refrigerator at 5°, the material showed a change in melting point from an initial figure of 56° to 35–45°. Because of the instability of the material no elemental analysis was attempted. Infrared showed NH, none, N=O (asym) 1611, 1637, C=O, 1739, 1761 cm^{-1}.

1,1-Dinitramino-2,2,2-trifluoroethane (Trifluoromethyl-MEDINA).—The crude gummy white solid obtained from nitration of 5 g (0.03 mol) of trifluoroethylidenebisformamide was left at room temperature for 1 week, and the partially crystalline residue evaporated under vacuum. After two recrystallizations from chloroform, 1.2 g of product, mp 81°, was obtained for an overall yield, based on bisamide, of 20%. Infrared showed NH, 2950–3250, N=O (asym) 1688, 1722, C=O, none.

Anal. Calcd for $C_2H_3F_3N_4O_4$: C, 11.8; H, 1.5; F, 27.9; N, 27.5. Found: C, 11.9; H, 1.6; F, 25.3; N, 28.1.

1,1-Bis(formamido)ethane.—Formamide (60 g, 1.33 mol) was dissolved in 15 ml of water containing 1.5 ml of concentrated hydrochloric acid, and 30 g (0.68 mol) of monomeric acetaldehyde was added in one portion. The reaction mixture was allowed to stand for 3 hr, during which time the temperature rose to 41° and then subsided. After vacuum distillation, by which 25 g of formamide was recovered, the viscous residue was washed out of the flask with a hot solution of 20 ml of isopropyl alcohol and 60 ml of acetonitrile. The crude product which separated on cooling was recrystallized by dissolving it in the minimum amount of boiling isopropyl alcohol, adding 3 vol of hot acetonitrile, and cooling. The yield of product, mp 119°, was 27 g or 62% based on unrecovered formamide.

Anal. Calcd for $C_4H_8N_2O_2$: C, 41.4; H, 6.9; N, 24.1. Found: C, 41.5; H, 7.2; N, 24.3.

1,1-Bis(*N*-nitroformamido)ethane.—1,1-Bis(formamido)ethane (3.7 g, 0.03 mol) was added in several portions to a stirred mixture of 18 g of 100% nitric acid and 18 g of trifluoroacetic anhydride at 10°. After aging for 2.5 hr, the reaction mixture was added slowly to 200 g of crushed ice, with rapid stirring. After about 5 min a finely divided, almost colorless solid appeared which was filtered and washed once with ice water. The yield of product so obtained averaged about 1.7 g (26% of theory), but yields as high as 60% were sometimes obtained using much larger quantities of trifluoroacetic anhydride. If necessary, the product was recrystallized from a mixture of ethylene dichloride, and ligroin: mp (then) 71°; infrared NH, none, N=O (asym) 1566, 1600, C=O, 1732, 1740 cm^{-1}.

1,1-Dinitraminoethane (Methyl-MEDINA).—To 2.0 g (10 mol) of ethylidenebis(nitroformamide) ten drops of water was added with stirring and the resulting paste allowed to stand at room temperature. After 1 hr the mixture had completely liquefied and the temperature had risen to about 35°. After an additional hour the liquid was filtered, cooled in an ice bath, and filtered again to give 0.5 g (33%) of product, mp 115°. This hydrolysis gave very inconsistent results and the figure cited is the maximum

(11) R. C. Brian and A. H. Lamberton, *J. Chem. Soc.*, 1633 (1949).
(12) C. C. Price and C. A. Sears, *J. Amer. Chem. Soc.*, **75**, 3276 (1953).

yield obtained. Infrared showed NH, 3110–3220, N=O (asym), 1568 (sh), 1581, C=O, none.

Registry No.—1,1-Bis(formamido)-2,2,2-trifluoroethane, 26958-24-7; 1,1-bis(acetamido)-2,2,2-trifluoroethane, 27039-91-4; 1,1-bis(*N*-nitroformamido)-2,2,2-trifluoroethane, 26958-25-8; 1,1-dinitramino-2,2,2-trifluoroethane, 26958-26-9; 1,1-bis(formamido)ethane, 20602-52-2; 1,1-bis(*N*-nitroformamido)ethane, 26958-28-1; 1,1-dinitraminoethane, 26958-29-2.

Reactions of Dodecabromopentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane with Sodium Methoxide

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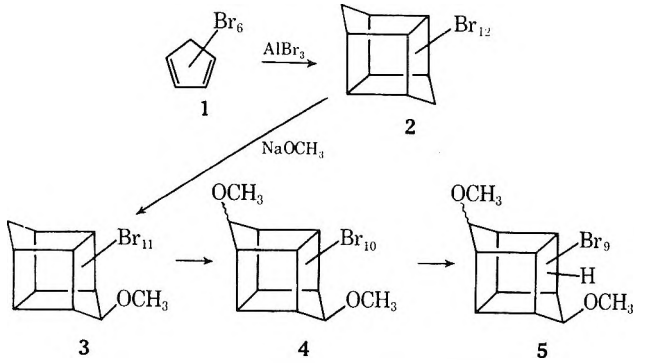
Received December 29, 1969

Hexabromocyclopentadiene (**1**) is dimerized by aluminum tribromide in refluxing bromine to give dodecabromopentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane (**2**).[2] Examination of molecular models leads to the prediction that **2** would be very inert toward nucleophilic attack. The compound has a small cluster of carbon atoms at its center and a large protective outer armor of bromine atoms. Back-side attack at any carbon atom of **2** appears to be impossible. Nevertheless, bromocarbon **2** reacts with sodium methoxide in tetrahydrofuran to give a series of cage compounds.

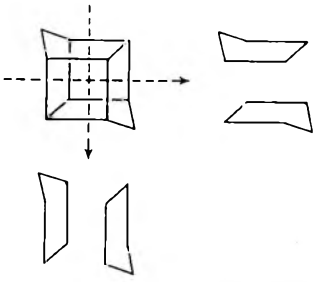
Kinetic control by slow addition of sodium methoxide and patient tlc analysis revealed initial formation of a monomethoxy derivative **3**, which was converted to a dimethoxy derivative **4**. Most of the starting material **2** and compound **3** disappeared before a third product **5** appeared along with several open cage products which had double bond adsorption in their infrared spectra. Compound **4** was prepared in 70–80% yield by following the reaction by tlc and quenching at a maximum concentration of **4**.



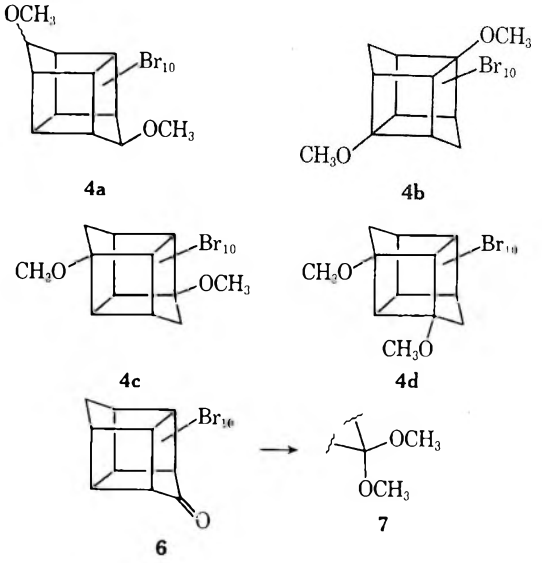
The structures of **3**, **4**, and **5** are assigned on the basis of their nmr, mass spectra, and relative reaction rates.

Nmr spectra of mixtures of **3** and **4** exhibit two poorly resolved lines at δ 3.97 in DMSO-d_6 with a separation of 0.009 ppm. Thus the environment of the single methyl of **3** is very similar to the environment of the two methyls of **4**. Although **5** appears pure by mass spectral analysis, its nmr can only be explained as a mixture. No attempt has been made for an assignment of various isomer ratios of **5** to the nmr spectrum, since the structure is tentative.

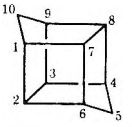
The normal fragmentation pattern observed in mass spectra of bishomocubane compounds is cleavage to two five-carbon rings by the two routes illustrated below.[3]



The most intense ion in the mass spectrum of **4** is *m/e* 407 from $C_5Br_4OCH_3^+$. An important feature is the lack of any C_5 fragments from **4** with two OCH_3 groups. Thus the methoxy groups must not be placed on the same five-carbon ring. Compounds **4a–d** satisfy the mass spectrum and the symmetry requirement necessary to give a single line nmr. An alternate structure is the dimethyl ketal **7**, which is readily prepared from ketone **6**, but **7** has ir, nmr, and mass spectra which are quite different from the spectra of **4**.



The structure of **3** is based primarily on its conversion to **4** and on its mass spectrum. Structure **4a** is assigned to **4** on the basis of the reaction rate data. A monomethoxy derivative is formed which reacts with methoxide at about the same rate as bromocarbon **2**. Further reaction with methoxide is slower than formation of the first two products. If reaction occurs first at C-10 the activity at C-5 would not be altered, and the product would readily react at C-5 to form **4**. After forma-



(1) To whom inquiries should be addressed: Textile Department, Clemson University, Clemson, S. C. 29631.

(2) C. W. Roberts and M. B. Chenoweth, U. S. Patent 3,212,973 (1965).

(3) W. L. Dilling and M. L. Dilling, *Tetrahedron*, **23**, 1225 (1967).

tion of **4** all of the remaining carbons are quite different from C-5 and C-10. A difference in rate would be expected and is observed.

If reaction occurs first at C-1, the second OCH_3 might become attached to C-6, C-9, or C-4. If C-1 and C-4 are substituted, further reaction at C-6 or C-9 would be expected to give trimethoxy products just as fast as dimethoxy products are formed. This is not observed. Similar arguments can be developed against initial attack at any carbon other than C-5 or C-10.

Compound **4** is most likely a mixture of cis and trans isomers. Separation of the two isomers by the isolation methods used and nmr resolution of the different methyls is unlikely. Conformation of the structures of **3** and **4** requires cleavage of the ethers to form ketones. If the methoxyls are on the bridgehead carbons, alcohols will be formed. At this time a satisfactory cleavage procedure has not been found.

Compound **5** exhibits mass spectral peaks at *m/e* 407 and 329 from fragments $C_5Br_4OCH_3$ and $C_5HBr_3OCH_3$. If the third reaction step had been introduction of a third OCH_3, a peak at *m/e* 359 from $C_5Br_3(OCH_3)_2$ would be expected, but it is not present in the mass spectrum. The hydrogen atom is presumably introduced during aqueous work-up of the reaction. Attempts to separate the isomers of **5** by tlc and recrystallization were unsuccessful.

The mechanism of the displacement reaction is speculative at this point. As discussed previously, backside attack on the bridgehead carbons is impossible and similar attack on the bridge carbons appears to be hindered by the bromine atoms. Formation of a carbonium ion at the bridgehead carbons is unlikely since they cannot become planar, and formation of carbonium ions at bridge carbons has not been observed with perhalogenated bishomocubyl compounds except under extreme conditions.[4] If the reaction occurs through a carbonium ion at C-5, dimethyl ketal **7** would be expected to form faster than **4**. Ketal **7** is not a major product.[5]

Experimental Section

Infrared spectra were obtained with Beckman IR-9 and Perkin-Elmer 137 spectrometers. The mass spectra were obtained on a CEC-21-110B (Direct Probe) instrument. Nuclear magnetic resonance spectra were obtained on Varian A60 and HA100 spectrometers. Thin layer chromatogaphy (tlc) plates were prepared from silica gel G containing 0.04% of Rhodamine 6G.

Hexabromocyclopentadiene (**1**) was prepared by the method of Straus[7] or by a modification of West's[8] procedure. Recrystallization from hexane or methanol yielded a product melting at 86.5–88°.

Dodecabromopentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane (**2**).—The procedure previously described[2] was modified as follows. Hexabromocyclopentadiene (473 g, 0.88 mol), 2500 g (800 ml) of anhydrous bromine, and 105 g (0.39 mol) of aluminum bromide were mixed at 25° and heated at reflux under anhydrous conditions for 72 hr. After decomposing the aluminum bromide with water, the bromine was steam distilled off. The granular residue was collected and washed with water and hexane to give 454 g (96%), mp 330–340° dec. Recrystallization with charcoal decolorization from ethylene dibromide, toluene, or *m*-xylene gave 440 g (93%) of **2**, mp 340° dec, mass spectrum P^+ at *m/e* 1068 (Br^{79}).

5,10-Dimethoxydecabromopentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane (**4**).—Bromocarbon **2** (19.7 g, 0.018 mol) was dissolved in 300 ml of tetrahydrofuran, and sodium methoxide (3 g, 0.055 mol) was added. The mixture was stirred at room temperature under nitrogen and followed by periodic tlc analysis of the liquid phase. An additional 3 g of sodium methoxide was added after 17 hr. After 89 hr ice was added slowly until the base dissolved. Water was added dropwise with stirring at a rate which gave a granular precipitate. The product was collected by suction filtration, washed with water, and dried under vacuum at 65° (20 mm) to yield 15.7 g of **4** (84% crude) as an off-white solid. Tlc analysis indicated a purity of 95% or better. Recrystallization from boiling toluene gave 12.5 g of white crystals which slowly decomposed above 230° without melting: ir OCH_3 at 2958, 2852, 1446, and 1263 cm^{-1}, no double bond absorption; nmr (DMSO-d_6) single line δ 4.00; nmr (benzene-d_6) single line δ 3.74; mass spectrum P^+ at *m/e* 972 with ten bromine atoms, most intense peak at *m/e* 407 from $C_5Br_4OCH_3^+$, no peaks from C_5 fragments bearing two methoxy groups were observed.

Anal. Calcd for $C_{12}H_6Br_{10}O_2$: mol wt, 981.3; C, 14.69; H, 0.62; Br, 81.44. Found: C, 15.0; H, 0.63; Br, 81.3.

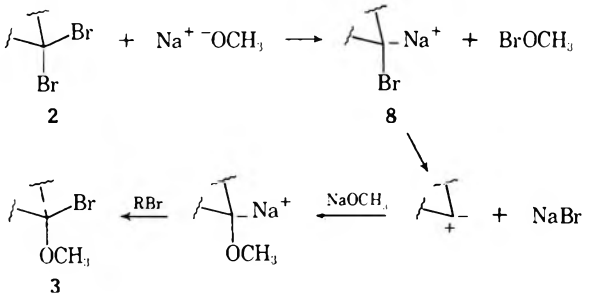
5-Methoxyundecabromopentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane (**3**).—Following the procedure above, the reaction was stopped when a small amount of starting material **2** and a moderate amount of **3** were present. A sample of **3** was collected by tlc for a mass spectrum: P^+ at *m/e* 1020 with 11 bromine atoms (weak); $P^+ - Br$ at *m/e* 941 with ten bromines is strong (insufficient material was collected for an infrared spectrum). An nmr spectrum of the product mixture from a similar run with only **2**, **3**, and **4** present had two poorly resolved lines at δ 3.97 in DMSO-d_6 with a separation of 0.009 ppm and a ratio of 1.4:1. The ir spectrum of this mixture did not have double bond adsorption.

Dimethoxynonabromopentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane (**5**).—Following the procedure above the reaction was stopped when **2**, **3**, and **4** had disappeared. The crude product was eluted from a silica gel column with hexane–benzene. The first fraction gave only one spot on tlc. Recrystallization from hexane–chloroform gave white crystals which decomposed without melting above 260°: nmr ($CDCl_3$) major δ 3.83 and 4.01, minor δ 3.9, 4.0, and 4.5, ratios uncertain from overlap of signals; ir (KBr) OCH_3 at 2960, 2860, 1449, and 1280 cm^{-1}, no double bond absorption; mass spectrum P^+ at *m/e* 894 (weak), $P^+ - Br$ at 815 (strong), fragments at 407 and 392.

Anal. Calcd for $C_{12}H_7Br_9O_2$: mol wt, 902.3; Br, 79.70. Found: Br, 79.4.

5,5-Dimethoxydecabromopentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane (**7**) was prepared from the methyl hemiketal[9] of ketone **6** in 70–90% yields by reaction with diazomethane in ether[4] or by reaction with powdered sodium hydroxide and dimethyl sulfate in ether. Recrystallization from hexane–chloroform gave white crystals which decomposed above 260° without melting: ir (OCH_3) at 2949, 2841, 1459, 1443, 1435, and 1229 cm^{-1}; nmr ($CDCl_3$) one line at δ 3.64.

Anal. Calcd for $C_{12}H_6Br_{10}O_2$: mol wt, 981.3; C, 14.69; H, 0.62; Br, 81.44. Found: C, 14.7; H, 0.53; Br, 81.2.



(4) G. W. Griffin and A. K. Price, *J. Org. Chem.*, **29**, 3192 (1964); W. L. Dilling, Ph.D. Thesis, Purdue University, 1962.

(5) A possible reaction of bromocarbon **2** is displacement on bromine to form a carbanion **8**. Dr. K. Scherer (personal communication) has proposed the following mechanism to account for the formation of **3** and **4**. This mechanism is consistent with the observed rate data and the expected carbanion stabilities based on analogous chlorocage carbanions.[6] Compound **5** could be formed similarly by protonation of bridgehead carbanions.

(6) G. A. Ungefug, Ph.D. Thesis, University of California, Berkeley, Calif., 1968.

(7) F. Straus, L. Kollek, and W. Heyn, *Ber.*, **63b**, 1868 (1930).

(8) P. T. Kwitowski and R. West, *J. Amer. Chem. Soc.*, **88**, 4541 (1966); **90**, 4697 (1968).

(9) R. G. Pews and C. W. Roberts, *J. Org. Chem.*, **34**, 2029 (1969).

CAUTION: Prolonged skin contact with ketone 6 and its derivatives may be fatal.

Registry No.—2, 5144-46-7; 3, 26932-22-9; 4, 26932-23-0; 5, 26913-18-8; 7, 26932-24-1.

Acknowledgments—The authors are grateful to L. Shadoff for the mass spectral data, to R. Nyquist for the infrared spectra, to J. Heeschen and T. Evans for the nmr data, and to L. Swim and P. North for the elemental analyses.

Synthesis and Certain Reactions of 1-Aryl-4-(2-quinolyl)-1,3-butanediones, a New Class of β-Diketones[1]

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Received June 3, 1970

In connection with the synthesis of potential new antimalarial agents, a series of 1-aryl-4-(2-quinolyl)-1,3-butanediones (**4**) were required as key intermediates. In spite of their seemingly simple array of functionality, β-diketones of type **4** have not been reported. Moreover, their preparation *via* standard Claisen condensations of a 2-quinolineacetic acid ester with substituted acetophenones appeared to hold little promise of success, owing to the probability that the basic reagents commonly employed in such reactions would preferentially abstract one of the highly acidic methylene hydrogens of the ester.

We now wish to describe a general method for the preparation of this new class of β-diketones as exemplified by the synthesis of five such compounds from readily available starting materials (see Scheme I). The present sequence involved metalation of quinaldine (**1**) with *n*-butyllithium in tetrahydrofuran–hexane at room temperature to afford lithio derivative **2**, which was then acylated with ethyl acetate to give 2-acetonylquinoline (**3**).[3] Completion of the β-dicarbonyl side chain was then accomplished by selective aroylation at the methyl position of **3** using the appropriate aromatic ester and excess sodium hydride in refluxing 1,2-dimethoxyethane as the condensing agent (see Table I). The rather unusual tendency for ketone **3** to undergo preferential aroylation at the less acidic methyl site may be due to the fact that the azomethine function imparts

SCHEME I

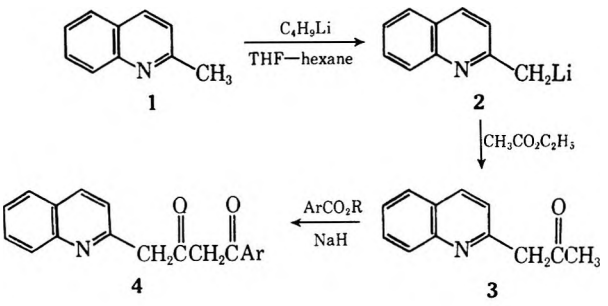


TABLE I[a]

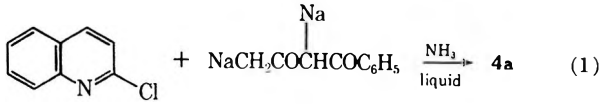
AROYLATIONS OF 2-ACETONYLQUINOLINE (**3**) TO PRODUCE β-DIKETONES **4**

β-Diketone Ar	No.	Reaction period, hr	Yield, %	Mp, °C
C_6H_5	**4a**	24	56	138–139 5[b]
C_6H_4Cl-*p*	**4b**	12	62	158–160[c]
3,4-$C_6H_3(Cl)_2$	**4c**	4	64	186–188[c]
p-$C_6H_4OCH_3$	**4d**	22	45	145–147[c]
3,4,5-$C_6H_2(OCH_3)_3$	**4e**	24	30	158–160[c]

[a] Satisfactory analytical data (±0.3 for C, H, N, and when present Cl) were found for all compounds: Ed. [b] Recrystallized from methanol. [c] Recrystallized from 95% ethanol.

to **3** chemical characteristics similar to those of a β-diketone. Consequently, these condensations may then proceed by one of the possible mechanistic pathways recently proposed to account for the conversion of β-diketones to 1,3,5-triketones under similar reaction conditions.[4] Incidentally, alkali amides, which have also been used to effect terminal aroylations of β-diketones,[5] were found to be much less satisfactory than sodium hydride for the conversion of **3** to **4a**.

Structural assignments for new β-diketones **4a–e** were confirmed by analyses (Table I), spectral data, and, in the case of **4a**, independent synthesis from 2-chloroquinoline and disodiobenzoylacetone (eq 1).[6] The nmr



(1)

spectra of **4a–e** (Table II), which had multiple peaks in the vinyl proton region, were consistent with the presence of several enolic forms for each of these compounds in solution. Comparison of the integrated intensity of the methylene proton absorption to that of the aromatic resonance in the spectrum of **4a** indicated the total enol content of this ketone to be approximately 75% in $CDCl_3$.

In order to test the feasibility of utilizing the β-dicarbonyl function of the above ketones for the construction of a second heterocyclic moiety, we examined the cyclization of several of these compounds with hydrazine and urea. Treatment of β-diketones **4a–c** and **4e** with the

* To whom correspondence should be addressed.

(1) (a) This is Contribution No. 807 from the Army Research Program on Malaria and was supported by Contract No. DA-49-193-MD-3024 from the U. S. Army Research and Development Command. (b) Presented before the Medicinal Chemistry Division of the American Chemical Society, New York, N. Y., Sept 1969.

(2) Abstracted from the Ph.D. Dissertation of T. P. M., Virginia Polytechnic Institute, Oct 1969.

(3) This procedure utilizing commercial *n*-butyllithium and ethyl acetate for the synthesis of **3** was found to be much more satisfactory than the method of M. J. Weiss and C. R. Hauser [*J. Amer. Chem. Soc.*, **71**, 2023 (1949)], in which alkali amides and acetic anhydride are employed as the metalating and acylating agents, respectively. It also gives a comparable yield and is less tedious than the procedure of N. N. Goldberg and R. Levine [*ibid.*, **74**, 5217 (1952)], which involves the preparation of phenyllithium as the metalating agent.

(4) See M. L. Miles, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **30**, 1007 (1965).

(5) R. J. Light and C. R. Hauser, *ibid.*, **25**, 538 (1960).

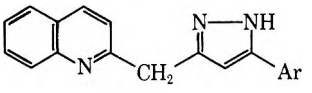
(6) The possibility of utilizing 1,3-dialkali salts of other β-diketones in a one-step route to quinolyl β-diketones of type **4** did not pass unnoticed. However, numerous unsuccessful attempts to increase the low yield of **4a** obtained in the above reaction forced us to abandon this approach.

TABLE II
NMR DATA FOR β-DIKETONES 4 AND 3-QUINALDYLPYRAZOLES 5

Compd	Types of hydrogen, δ values (multiplicities) ArH	Vinyl	Methylene	Other
4a[a]	7.9 (m)	6.66 (s), 6.24 (s) 5.72 (s), 5.44 (s)	4.38 (s), 4.36 (s)	16.76 (s),[c] 14.76 (s)[c]
4b[a]	7.87 (m)	6.66 (s), 6.24 (s) 5.78 (s), 5.48 (s)	4.3 (s), 4.44 (s)	16.76 (s),[c] 14.82 (s)[c]
4c[a]	7.49 (m)	6.45 (s), 6.21 (s) 5.92 (s), 5.47 (s)	4.42 (s), 4.3 (s)	16.7 (s),[c] 15.82 (s)[c]
4d[b]	8.32 (m)	6.68 (s), 6.08 (s) 5.88 (s)	4.64 (s), 4.46 (s)	14.9 (s),[c] 4.26 (s)[d]
4e[b]	8.34 (m)	6.95 (s), 6.2 (s) 5.94 (s)	4.76 (s), 4.58 (s)	15.56 (s),[c] 14.12 (s)[c] 4.3 (s),[d] 4.2 (s)[d]
5a[b]	8.23 (m)		4.72 (s)	13.88 (s),[e] 7.0 (s)[f]
5b[b]	7.67 (m)		4.3 (s)	13.16 (s),[e] 6.44 (s)[f]
5d[b]	7.42 (m)		4.3 (s)	12.8 (s),[e] 6.44 (s)[f] 3.8 (s),[d] 3.69 (s)[d]

[a] $CDCl_3$ was used as the nmr solvent. [b] DMSO-d_6 was used as the nmr solvent. [c] Enolic NH or OH. [d] CH_3O. [e] Pyrazole NH. [f] Pyrazole CH.

former reagent in refluxing ethanol resulted in their smooth conversion to 3-quinaldylpyrazoles **5a–d**, the



5a, Ar = C_6H_5
b, Ar = *p*-C_6H_4Cl
c, Ar = 3,4-$C_6H_3(Cl)_2$
d, Ar = 3,4,5-$C_6H_2(OCH_3)_3$

analyses (Table III) and nmr spectra (Table II) of

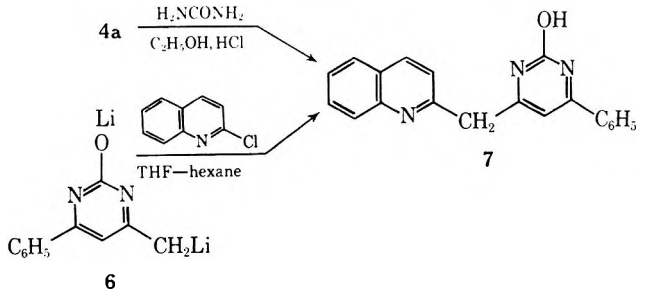
TABLE III[a]
CYCLIZATIONS OF β-DIKETONES 4 TO 3-QUINALDYLPYRAZOLES 5

β-Diketone	Pyrazole	Yield, %	Mp, °C	Recrystn solvent
4a	5a	59	168.5–170	Acetone–heptane
4b	5b	90	175–179	Ethanol–water
4c	5c	59	166–168	Benzene
4e	5d	72	165–167	Benzene

[a] Satisfactory analytical data (±0.25 for C, H, and N) were found for all compounds: Ed.

which were in accord with the proposed structures. Acid-catalyzed cyclization of diketone **4a** with urea afforded 6-quinaldylpyrimidinol **7**, which was also prepared independently, albeit in low yield, by allowing 2-chloroquinoline to react with dilithio derivative **6**[7] (see Scheme II).

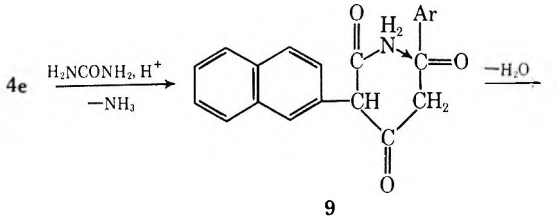
SCHEME II



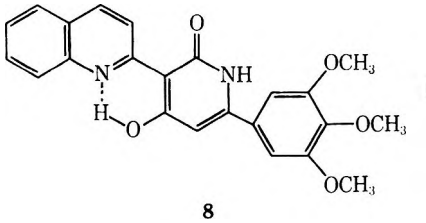
6 7

In contrast to **4a**, β-diketone **4e** was not transformed into the expected quinaldylpyrimidinol on treatment with urea. Instead a single product, to which we have assigned pyridone structure **8**,[8] was isolated. This formulation was based on the molecular formula, $C_{23}H_{20}N_2O_5$, derived from mass spectral analyses. In addition, the ir spectrum (KBr), which had principal bands at 3400 and 1650–1580 cm^{-1}, was also compatible with the assigned structure. The nmr spectrum of **8** (CF_3COOH) had singlets at 4.14 (9 H), 7.14 (1 H), and 7.26 ppm (2 H), attributable to methoxy protons, the C-5 proton of pyridone ring, and the two equivalent protons of the trimethoxyphenyl residue, respectively. In addition, there was a multiplet centered at 8.16 (4 H), which was assigned to the benzenoid protons of the quinoline nucleus, and an AB group at 9.04 ppm (2 H), which was attributed to the C-3 and C-4 protons of the quinoline ring.

It is conceivable that transformation of β-diketone **4e** into pyridone **8** by urea may involve initial formation of carbamoyl derivative **9**, which then undergoes cyclization to afford **8** (eq 2). Although attempts to further define the course of this reaction by isolation of possible acyclic intermediates such as **9** were unsuccessful, carbamoylation at an active methylene position by urea, or



9



8 (2)

(7) J. F. Wolfe and T. P. Murray, *Chem. Commun.*, 336 (1970).

(8) For convenience we have chosen the above structural representation, although other tautomers are possible. An intramolecularly hydrogen-bonded structure such as **8** would have the carbonyl group of the pyridone ring fixed in such a position to cause deshielding of the C-3 hydrogen of the quinoline nucleus, thereby accounting for the downfield position of this proton in the nmr spectrum of **8**. The alternative 2-hydroxy-4(1)-pyridone tautomer could assume a similar hydrogen-bonded configuration with the C-4 carbonyl function of the pyridone ring exerting a similar deshielding effect.

a urea derivative, is not without precedent.[9] However, reactions of this type appear to have been limited previously to β-dicarbonyl compounds which are sterically prohibited from undergoing cyclization to form pyrimidine or pyridone derivatives.[9c]

Experimental Section[10]

Preparation of 2-Acetonylquinoline (3).—To a stirred solution of 14.32 g (0.10 mol) of quinaldine (1) in 100 ml of dry tetrahydrofuran (THF) at 25° under nitrogen, was added 70 ml (0.11 mol) of a 1.6 *M* solution of *n*-butyllithium in hexane. The resulting dark red solution of lithio derivative 2 was stirred for 10 min before addition of 13.2 g (0.015 mol) of ethyl acetate as a 50% v/v solution in dry THF. After 1 hr the reaction mixture was quenched with 75 ml of water and the original organic layer combined with an ethereal extract (100 ml) of the aqueous layer. The extracts were dried (Na_2SO_4), the solvent removed, and the resulting oil distilled to afford 8.2 g (44%) of 2-acetonylquinoline (3), bp 140–145° (4.0 mm) [lit.[3] bp 145–147° (2.5 mm)]. The distillate, which solidified on standing, was recrystallized from hexane to give the desired ketone as yellow needles, mp 73–75° (lit.[3] mp 76–77°).

Aroylations of 3 by Means of Sodium Hydride to Form β-Diketones 4a–e.—The aroylation of 3 with methyl benzoate is described in detail. Other aroylations were conducted in a similar manner and the results of these reactions are summarized in Table I.

In a 2-l., three-necked flask equipped with a pressure-equalizing addition funnel, a mechanical stirrer, and a reflux condenser, connected at its upper end through a cold trap (Dry Ice–acetone) to a Precision Scientific wet-test meter filled with water, were placed 1000 ml of 1,2-dimethoxyethane (DME) and 2.6 mol of sodium hydride dispersion. A solution of methyl benzoate (54.4 g, 0.4 mol) and 3 (46.4 g, 0.26 mol) in 250 ml of DME was placed in the addition funnel. The system was purged with dry nitrogen, then closed to the atmosphere. The solvent in the reaction flask was heated to reflux, and when thermal equilibrium had been established, an initial reading was taken on the gas meter. The solution of ester and ketone was then added over a period of 20 min, and the resulting suspension was refluxed until hydrogen evolution had ceased.[11] The solvent was removed under reduced pressure, and the remaining pasty residue was cooled to 0°. Addition of ether (250 ml) was followed by the cautious addition of 150 ml of water. The sodio salt of the product, which separated between the layers, was collected and stirred with 500 ml of water, then acidified (pH 6) with dilute HCl. The resulting solid was collected by filtration, washed with 5% aqueous $NaHCO_3$, and crystallized from methanol to give 41.0 g of 1-phenyl-4-(2-quinolyl)-1,3-butanedione (4a).

The nmr spectra of β-diketones 4a–c (Table II) were consistent with the assigned structures. Each of the ir spectra had several strong bands in the 1670–1550 cm^{-1} region. The mass spectra of 4a–d had molecular ion peaks at *m/e* 289, 324, 358, and 319, respectively.

Benzoylation of 3 by Means of Sodium Amide.—To a stirred solution of sodium amide,[12] prepared from 0.375 g-atom of sodium in 300 ml of anhydrous liquid ammonia, was added a solution of 2.32 g (0.0125 mol) of 3 in 10 ml of dry ether. The resulting deep red solution was allowed to stir for 30 min before a solution of 2.72 g (0.02 mol) of methyl benzoate in 10 ml of ether was added. After 1 hr the reaction mixture was neutralized with 10 g of solid NH_4Cl and the ammonia was removed on a steam bath as an equal volume of ether was added. Water (100 ml) was added, the resulting layers were separated, and the aqueous layer was extracted with two 100-ml portions of ether. The original ethereal layer and extracts were combined, dried (Na_2SO_4), and concentrated to yield a red oil which slowly crystallized. Recrystallization of this crude product from methanol afforded 0.5 g (14%) of β-diketone 4a.

Independent Synthesis of 4a from 2-Chloroquinoline and Disodiobenzoylacetone.—To a stirred suspension of 0.025 mol of disodiobenzoylacetone[13] in 300 ml of liquid ammonia was added 4.07 g (0.025 mol) of 2-chloroquinoline as a 20% w/v solution in dry ether. The reaction mixture was stirred for 2.5 hr, quenched with excess solid NH_4Cl, and processed as in the reaction of 3 with methyl benzoate and sodium amide. The semisolid crude product thus obtained was crystallized from 95% ethanol to give 1.19 g (17%) of diketone 4a, mp 138–140°, which was identical in all respects with a sample of 4a prepared from ketone 3.

Cyclization of β-Diketones 4a–c and 4e with Hydrazine to Form Pyrazoles 5a–d.—A 0.01-mol sample of the appropriate β-diketone was treated with hydrazine [3.80 g (0.10 mol) of an 85% aqueous solution] in 40 ml of refluxing ethanol for 2 hr. Removal of the ethanol under reduced pressure and recrystallization of the resulting solid gave the respective pyrazole.

Yields and analytical data for these products are given in Table III. Principle nmr absorptions for 5a, 5b, and 5d are listed in Table II. All pyrazoles had major ir bands at 3350–3300 (NH) and 1620–1550 cm^{-1}. The mass spectrum of 5a had a molecular ion peak at *m/e* 285.

Cyclization of β-Diketone 4a with Urea to Form 2-Hydroxy-4-phenyl-6-quinaldylpyrimidine (7).—To a hot, stirred solution of 2.89 g (0.01 mol) of 4a in 75 ml of absolute ethanol were added urea (3.60 g, 0.06 mol) and concentrated HCl (1 ml, 0.01 mol). After refluxing for 17 hr, the mixture was cooled and the resulting solid filtered, washed with ether, and recrystallized from 95% ethanol to give 1.81 g (59%) of 7: mp 265–267° (sealed tube); ir (KBr) 3400–3180, 1700–1640, and 1545 cm^{-1}; nmr (CF_3CO_2H) δ 9.08 (m, 12, aromatic) and 5.70 ppm (s, 2, CH_2); mass spectrum, molecular ion peak at *m/e* 313, with abundant fragment peaks at *m/e* 128 and 77.

Anal. Calcd for $C_{20}H_{15}N_3O$: C, 76.65; H, 4.82; N, 13.41. Found: C, 76.77; H, 4.61; N, 13.55.

Independent Synthesis of 7 Using Dilithio Derivative 6.—To a stirred solution of 4.62 g (0.025 mol) of 2-hydroxy-4-methyl-6-phenylpyrimidine[14] in 250 ml of dry THF at 0° under nitrogen was added dropwise, 35 ml (0.56 mol) of a 1.6 *M* solution of *n*-butyllithium in hexane. The soluble, red pyrimidine dianion 6 was stirred for 30 min, and 4.07 g (0.025 mol) of 2-chloroquinoline, in 10 ml of dry THF was then added dropwise. The reaction mixture was allowed to stir for 1.5 hr before being quenched with 100 ml of water. The THF–hexane was removed on a rotary evaporator and the resulting solution was acidified with 10 ml of concentrated HCl. The precipitate which formed was filtered, washed with dilute aqueous NH_4OH, dried, and recrystallized from 95% ethanol to give 0.6 g (7%) of 7, mp 263–265° (sealed tube). The ir spectrum of this product was identical with that of a sample of 7 prepared by urea cyclization of β-diketone 4a.

Urea Cyclization of β-Diketone 4e to Form Pyridone 8.—To a stirred solution of 3.79 g (0.01 mol) of 4e in absolute ethanol (80 ml) was added 1 ml of concentrated HCl and 3.60 g (0.06 mol) of urea. The mixture was allowed to reflux for 48 hr before being cooled to precipitate the crude product, which was collected by filtration and crystallized from ethanol to afford 3.0 g (75%) of 3-(2-quinolyl)-4-hydroxy-6-(3,4,5-trimethoxyphenyl)-2(1)-pyridone (8): mp 286–288° (sealed tube); mass spectrum (50 eV), molecular ion peak at *m/e* 404.

Anal. Calcd for $C_{23}H_{20}N_2O_5$: C, 68.25; H, 4.98; N, 6.94. Found: C, 68.53; H, 5.18; N, 6.71.

Several attempts to isolate possible acyclic intermediates by decreasing both reaction time and the molar quantity of urea afforded only unreacted β-diketone 4e and pyridone 8.[15]

(9) For examples, see (a) H. C. Scarborough, *J. Org. Chem.*, **26**, 2579 (1961); (b) H. C. Scarborough, *ibid.*, **26**, 3717 (1961); (c) H. C. Scarborough and W. A. Gould, *ibid.*, **26**, 3720 (1961).

(10) Infrared spectra were taken on a Beckman IR-5A infrared spectrophotometer. Nmr spectra were determined on an A-60 spectrometer with tetramethylsilane as internal standard. Mass spectra were obtained on a Perkin-Elmer Hitachi RMU-6E mass spectrometer at 50 eV. The sodium hydride used was an approximately 50% dispersion in mineral oil, obtained from Metal Hydrides, Inc. *n*-Butyllithium, as a 1.6 *M* solution in hexane, was obtained from Foote Mineral Co. 1,2-Dimethoxyethane and tetrahydrofuran were distilled from sodium ribbon immediately before use.

(11) A total of 3 mol equiv of hydrogen was evolved in this and subsequent aroylations of ketone 3.

(12) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. React.*, **8**, 122 (1954).

(13) K. G. Hampton, R. J. Light, and C. R. Hauser, *J. Org. Chem.*, **30**, 1413 (1965).

(14) C. R. Hauser and R. M. Manyik, *ibid.*, **18**, 588 (1953).

(15) We wish to thank Mr. J. C. Greene for carrying out these experiments.

Registry No.—**4a**, 26958-30-5; **4b**, 26958-31-6; **4c**, 26958-32-7; **4d**, 26958-33-8; **4e**, 27039-92-5; **5a**, 26958-34-9; **5b**, 26958-35-0; **5c**, 27006-05-9; **5d**, 26958-36-1; **7**, 26958-37-2; **8**, 26958-38-3.

Viologen Radical from Di(4-pyridyl) Ketone Methiodides in Hydroxide[1]

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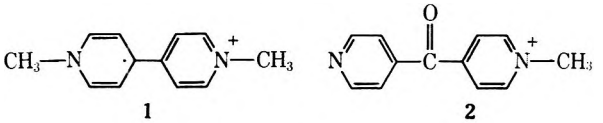
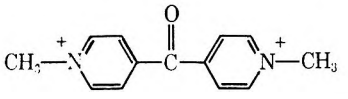
Received August 10, 1970

The stability of pyridinyl radical cations has made them subject to intense investigations.[3-8] Kosower and Cotter reported an interesting formation of dimethylviologen radical **1** from 4-cyanopyridinium methiodide and sodium dithionite, presumably *via* dimerization of the neutral 4-cyanopyridinyl radical intermediate.[6] We report here on the unusual formation of the same viologen radical from di(4-pyridyl) ketone mono- and dimethiodides (**2** and **3**) in aqueous hydroxide solution.



1

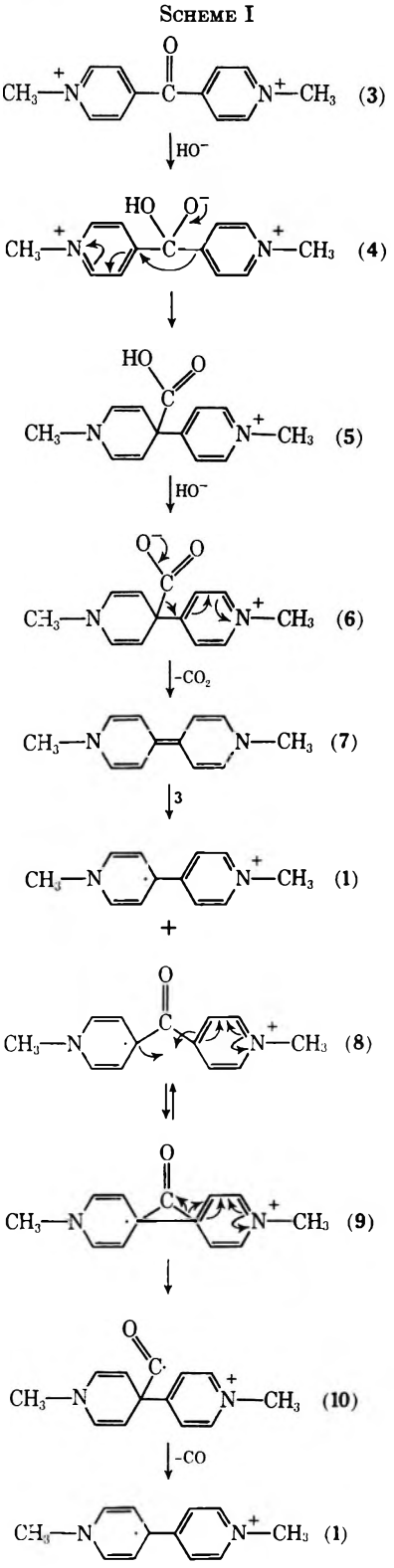
2



3

When 1 *M* NaOH solutions, thoroughly degassed by numerous freeze–thaw cycles, were mixed under vacuum with crystals of either **2** or **3**, the resulting mixture turned deep blue immediately and remained so indefinitely (months). As the color developed, the near-uv–visible absorption showed a parallel increase in the two structured bands characteristic[6] of **1**, namely, in the visible at λ_{max} (ϵ) 560 (7450), 602 (10,400), 660 (5500), and 730 nm [1650l./(mol cm)] and in the uv at 367 (12,300), 384 (22,300), and 395 nm [34,200 l./(mol cm)]. The blue solutions gave strong esr signals whose presence or absence paralleled that of the color. Examination of high-resolution esr spectra clearly indicated that the blue paramagnetic species formed from both **2** and **3** was dimethylviologen cation radical.[6,9,10] The experimental splitting constants for **1** in water, which differ only slightly from those in ethanol,[9] are 1.33 and 1.59 Oe for the ring protons, 3.99 Oe for the methyl hydrogens, and 4.25 Oe for the nitrogens; a spectrum simulated by computer,[11] with Lorentzian line shape and with a line width of 140 mOe, verified the constants. Radical **1** was generated in a similar manner in nondeaerated samples. Eventually, after months in open sample tubes or much more rapidly upon oxygenation, the blue alkaline solutions turned pale yellow or reddish brown, depending on concentration, and lost their para-

SCHEME I



(1) Taken in part from work done by C. L. T. in partial fulfillment of the Ph.D. requirements at The George Washington University.

(2) To whom correspondence should be directed at The George Washington University.

(3) P. Borger and A. San Pietro, *Arch. Biochem. Biophys.*, **120**, 279 (1967).

(4) P. Borger, C. C. Black, and A. San Pietro, *Biochemistry*, **6**, 80 (1967).

(5) O. Rogne, *Biochem. Pharmacol.*, **16**, 1853 (1967).

(6) E. M. Kosower and J. L. Cotter, *J. Amer. Chem. Soc.*, **86**, 5524 (1964).

(7) E. M. Kosower and E. J. Poziomek, *ibid.*, **86**, 5515 (1964).

(8) E. M. Kosower and I. Schwager, *ibid.*, **86**, 5528 (1964).

(9) C. S. Johnson and H. S. Gutowsky, *J. Chem. Phys.*, **39**, 58 (1963).

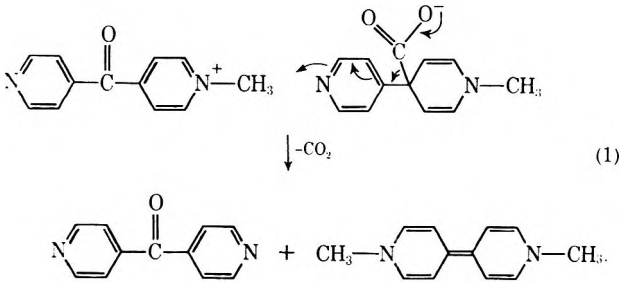
(10) A. H. Corwin, R. R. Arellano, and A. B. Chivvis, *Biochim. Biophys. Acta*, **162**, 533 (1968).

(11) Modifications to a program by A. Inzaghi and L. Mongini, European Atomic Energy Commission-Euratom, Report EUR-4064e.

magnetism. Preparative scale solutions of either **2** or **3** purposely decolorized with CO_2-free oxygen produced copious amounts of carbon dioxide upon acidification. An approximate gravimetric evaluation indicated 30 mol % CO_2 yield with respect to original dimethiodide. Furthermore, carbon monoxide was detected with the I_2O_5 test for both **2** and **3**. The liberated iodine in the case of **3** was determined both colorimetrically and by titration to be about 12 mol %. These observations were useful in the formulation of a reaction mechanism. When the base concentration was lower than ~0.1 *M*, no blue color developed. On the other hand, when the base concentration was very high (~10 *M*), the methiodides were no longer soluble and only a very weak blue color developed.

Unlike those of its methiodides, sodium hydroxide solutions of the parent dipyridyl ketone remained colorless and diamagnetic under similar conditions.[12]

A plausible mechanism for viologen radical formation from **3** is shown in Scheme I. Although the hydroxide ion could abstract protons from the methyl groups activated by the pyridinium nitrogens, it seems to attack preferentially the carbonyl group, followed by a 1,2 "push–pull" migration of a 4-pyridinium group to generate cation **5**. One can easily visualize proton abstraction from **5** and subsequent facile decarboxylation of zwitterion **6** with formation of the powerful reducing agent[10,13,14] *N,N'*-dimethyldihydro-4,4'-bipyridyl (**7**), which is rapidly oxidized by dimethiodide **3** to viologen radical **1**. It is known that such molecules as **7**, which have also been called "alkali-metal analogs," are capable of generating viologen radicals in reaction even with common solvents.[13,14] We found that radical cation **8** formed by metal reduction of **3** has a long lifetime in degassed acetonitrile.[15] Apparently, however, in aqueous hydroxide it undergoes rapid decarbonylation *via* **9** and **10**, as shown in Scheme I, with ultimate formation of another viologen radical. It is conceivable that radical **8** leads reversibly to **9** with slow leakage over an energy barrier to **10**. Presence of both carbon monoxide and carbonate among products together with viologen-radical yields of roughly 50 mol %[16] tends to confirm the postulated mechanism. A reaction path for viologen-radical formation from monomethiodide **2** requires decarboxylation, decarbonylation, and either fission at the carbonyl site with subsequent coupling of *N*-methylpyridine moieties or acquisition of a second methyl group at the nonmethylated nitrogen. This latter alternative can be visualized as shown in eq 1. However, this possibility should be considered only tentative, since further analytical work may be necessary to substantiate such a mechanism.



(12) F. L. Minn, C. L. Trichilo, C. R. Hurt, and N. Filipescu, *J. Amer. Chem. Soc.*, **92**, 3600 (1970). Preparation and identification of the methiodides **2** and **3** were also given in this article.

(13) E. Müller and K. A. Bruhn, *Ber.*, **86**, 1122 (1953).

(14) E. Weitz and A. Nelken, *Justus Liebigs Ann. Chem.*, **425**, 187 (1921).

(15) N. Filipescu, F. E. Geiger, C. L. Trichilo, and F. L. Minn, *J. Phys. Chem.*, in press.

(16) The conversion of the methiodides to viologen radical was evaluated spectroscopically in degassed samples of known concentrations from maximum absorbance at 395 and 602 nm.

Registry No.—**1**, 26985-31-9; **2**, 26988-47-6; **3**, 26988-48-7.

Acknowledgment.—We thank Professor E. M. Kosower for helpful suggestions and the Atomic Energy Commission for partial support on Contract AT-(40-1)-3797.

A Stereoselective Synthesis of *trans*-Isobornylcyclohexanol

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Received July 13, 1970

The long-recognized value of sandalwood oil as a perfume essential to the formulation of a variety of fine soap fragrances has prompted us to consider syntheses for other materials reputed to possess sandalwood-like odors. The curious discovery that a mixture of terpene cyclohexanols, formed by catalytic reduction of the condensation products of camphene and guiacol or camphene and phenol, provides a sandalwood odor first appeared about 20 years ago.[1] Although there has been some use of this material in perfumery, it was some years before Demole[2] isolated and synthesized the one material responsible for the sandalwood-like odor, *trans*-3-(*exo*-5-isocamphyl)cyclohexanol. Meanwhile, Russian workers reported[3] that the somewhat simpler system, *trans*-3-isobornylcyclohexanol (**7**), also possessed a "strong sandalwood" odor.

The reported odor properties for trans isomer **7** seemed to mark it as a unique member in a family of similar compounds. Each of the 2- and 4-isobornylcyclohexanols, prepared by others,[4] and 4-bornylcyclohexanol, prepared in these laboratories,[5] were characterized as almost odorless. Furthermore, the *cis*-3-isobornylcyclohexanol (**8**) was claimed to possess a cedar note. Because of what appeared to be very unique and strict structural requirements for the sandalwood odor, we wished to validate this observation through independent synthesis.

(1) J. R. Byers, Jr., *Amer. Perfumer*, **49**, 483 (1947); German Patent 834,593 (1952); *Chem. Abstr.*, **47**, 5446*i* (1953).

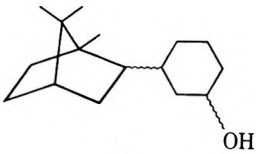
(2) E. Demole, *Helv. Chim. Acta*, **47**, 319, 1766 (1964).

(3) (a) L. A. Kheifits and I. S. Aul'chenko, "Synthese der Reichstoffeaus Terpenphenolen," Preprint from conference held at Geneva, Nov 17, 1966. (b) L. A. Kheifits and I. S. Aul'chenko, *Biol. Aktiv. Soedin*, 166 (1968); *Chem. Abstr*, **71**, 102026 (1969). (c) NOTE ADDED IN PROOF.—I. S. Aul'chenko and L. A. Kheifits. *Amer. Perfum., Cosmet.*, **85**, 37 (July 1970).

(4) L. A. Kheifits, G. I. Moldovanskaya, A. V. Kokhmanskii, and V. N. Belov, *Zh. Obshch. Khim.*, **33**, 1676 (1963); *Chem. Abstr.*, **59**, 12845*e* (1963); G. I. Moldovanskaya, L. A. Kheifits, A. V. Kokhmanskii, and V. N. Belov, *Zh. Obshch. Khim.*, **33**, 3392 (1963); *Chem. Abstr.*, **60**, 5555*h* (1964).

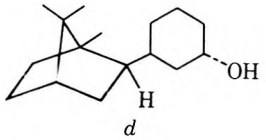
(5) W. F. Erman, unpublished observations.

Synthetic schemes directed toward terpene cyclohexanols have been several in number.[2-9] As those which allow the preparation of pure materials are particularly limited, it was our intent to develop a scheme (Scheme I) which possessed stereoselectivity. There are theoretically 16 diastereomers of the bicyclo[2.2.1]-heptylcyclohexanol I. By starting with optically pure

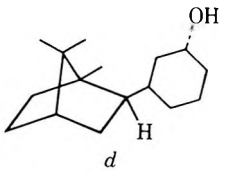


I

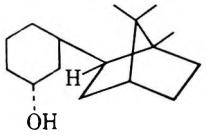
d-camphor, it is possible by this procedure to isolate stereoselectively the two diastereomeric cyclohexanols **7a** and **7b**. However, in our work we began with *dl*-camphor and obtained principally the four diastereomeric alcohols **7a–d**.



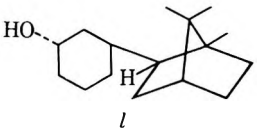
d
7a



d
7b



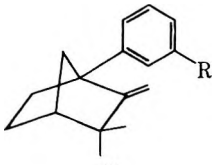
l
7c



l
7d

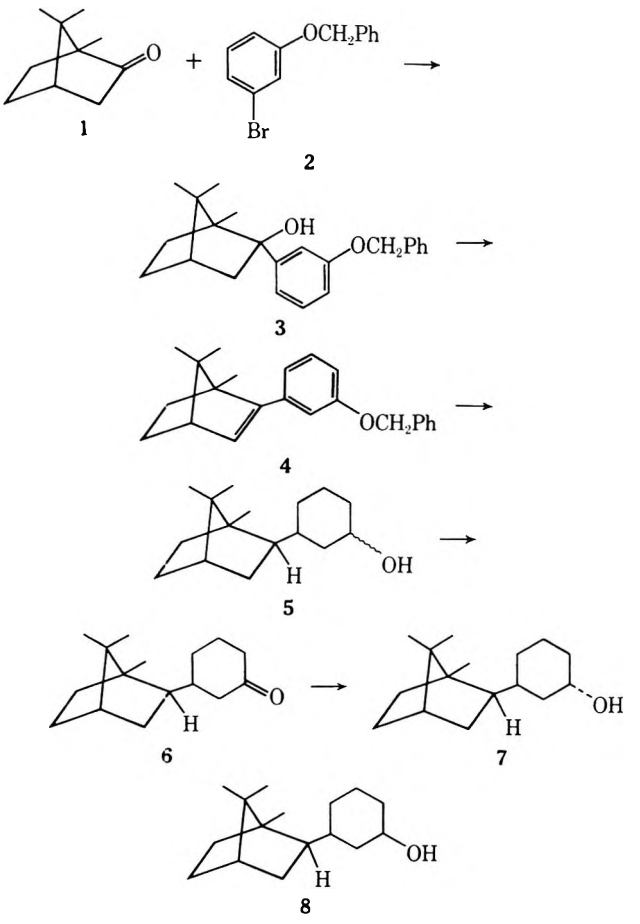
The required carbon framework was created through the interaction of camphor (**1**) and the Grignard of bromo ether **2**. Alcohol **3**, obtained in modest yield, was contaminated with several by-products including substantial amounts of benzyl phenyl ether. As the oily alcohol **3** resisted distillation, rigorous purification was not possible. Spectral data, however, corroborated assignment of structure **3** to the major product from the Grignard reaction.

Prior dehydration studies on model systems had revealed that while boron trifluoride etherate was a satisfactory catalyst for dehydrating 2 and 4 isomers,[6,7] it was not suitable for structure type **3**. The 3-substituted isomers were, in fact, prone to rearrangement under these conditions and afforded substantial amount of 1-arylcamphene **9**. Thionyl chloride proved to be a useful substitute for boron trifluoride, and olefin **4** could be smoothly generated using this reagent. This material could subsequently be fully saturated using fresh W-6 Raney nickel.[10]

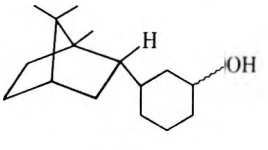


9

SCHEME I



The product mixture obtained on reduction was usually complex and could be only partially separated by careful column chromatography. In addition to 60–80% of the expected alcohol mixture **5**, several hydrocarbons, aromatics, and carbonyl-containing materials were also isolated. The ratio of cis alcohol **8** to trans alcohol **7** varied between *ca.* 6:4 and 7:3. While the various by-products described above could be minimized through slight experimental modifications, other alcoholic impurities, believed to be bornyl mixture **10** (10–15%), were carried through the remainder of the sequence.



10

Since chromatographic efforts to isolate the pure trans isomer from this mixture proved inefficient, we chose to examine an alternate, more selective synthetic route. The use of iridium compounds as reduction transfer catalysts has been reported to be a very effective method for generating high purity axial alcohols. Following published reports,[11] we found a strong pref-

(6) W. F. Erman and T. J. Flautt, *J. Org. Chem.*, **27**, 1526 (1962).
(7) W. F. Erman, *J. Amer. Chem. Soc.*, **86**, 2887 (1964).
(8) I. S. Aul'chenko and L. A. Kheifits, *J. Org. Chem. USSR*, **2**, 2015 (1966).
(9) L. A. Kheifits, I. S. Aul'chenko, and G. M. Shchegoleva, *ibid.*, **2**, 2019 (1966).
(10) A. A. Pavlic and H. Adkins, *J. Amer. Chem. Soc.*, **68**, 1471 (1946).
(11) (a) Y. M. Y. Haddad, H. B. Henbest, J. Husbands, and T. R. B. Mitchell, *Proc. Chem. Soc.*, 361 (1964). (b) We thank Professor Eliel for communicating this procedure to us prior to its publication.

erence for the formation of trans isomer **7** on reduction of ketone **6**. Gas chromatographic examination demonstrated the presence of trans isomer **7** (80–90%) mainly contaminated with a material tentatively identified as *trans*-bornyl isomer **10** (axial OH). Further purification of alcohol **7** was possible through careful glpc. Less than 5% cis isomer **8** was detected in the reduction mixture.

The purest samples of *cis*- or *trans*-isobornylcyclohexanol (**7**, **8**) or of mixture **5** exhibited rather weak odors. Although trans isomer **7** possessed a sandalwood note, it did not compare well in intensity with *trans*-3-(*exo*-5-isocamphyl)cyclohexanol.[12]

Experimental Section[13]

3-Benzyloxyphenylborneol (3).—The procedure of Erman and Flautt[6] was employed. A solution of 17.6 g (0.07 mol) of 3-benzyloxy-1-bromobenzene (**2**)[14] in 16 ml of tetrahydrofuran (Fisher Certified) was added dropwise over 0.5 hr to 1.87 g (0.08 g-atom) of magnesium (20 mesh).[13b] The resulting mixture was refluxed for 2 hr, cooled slightly, and treated over 1 hr with a solution of 10.3 g (0.07 mol) of camphor in 16 ml of tetrahydrofuran. The reaction was refluxed for 2 hr, cooled to 0–5°, and decomposed cautiously with 17 ml of a saturated aqueous solution of sodium sulfate over 15 min. The resulting ether layer was decanted and the residual salts were washed well with several portions of ether. The combined organic layers were washed once with saturated aqueous sodium sulfate solution and dried ($MgSO_4$). Solvent removal afforded 31 g of oil which was subjected to distillation. Starting materials, predominantly camphor, were removed first, bp 90–110° (bath) (0.35 mm), followed by 5.7 g of benzyl phenyl ether, bp 85–95° (0.35 mm), mp 35.5–37.5°. Recrystallization (CH_3OH) gave pure ether: mp 39–40°; ir (CCl_4) 6.31, 8.12, 9.75 μ (lit.[15] mp 39–40°). Distillation up to 165° (0.5 mm) gave only a small amount of additional crude ether, mp 33–35°.

The residual 10 g (44%) of material could not be induced to crystallize and was used directly for the next reaction. The material exhibited spectral properties consistent with the expected product **3**: ir (film) 2.81, 2.88, 3.26, 3.29, 6.21, 6.30, 7.91, 10.3, 11.6, 12.7, 13.5, 14.3 μ; nmr (CCl_4) τ 2.50–3.40 (complex, 2, aromatic), 5.02 (s, 2, OCH_2), 8.80 (s, 3, C_1 CH_3), 9.15, 9.18 (2 s, 6, C_7 CH_3's).

3-Benzyloxyphenylbornylene (4).—A solution of 4.6 g (0.014 mol) of crude borneol **3** in 50 ml of anhydrous pyridine cooled to −5 to −10° was treated over 5 min with 28 ml of a 1:1 mixture of thionyl chloride and anhydrous pyridine.[13b] The reaction was stirred at −5° for an additional 10 min and was poured into *ca.* 100 ml of cold pentane. The pentane solution was treated cautiously with ice chips and the resulting layers separated. Several pentane extracts were combined and washed with two portions of 3% aqueous hydrochloric acid, followed by brine until neutral. The pentane extract was dried ($MgSO_4$) and the solvent removed. As distillation could not be effected [up to 170° (bath) (0.4 mm)], the crude was purified by passage through 150 ml of Florisil. Monitoring by infrared analysis indicated that 2.6 g (59%) of essentially pure bornylene **4** was eluted with hexane and 2% ether in hexane. Material purified by glpc (SE-30, 225°) exhibited the following properties: $n^{25.5}D$ 1.5745; ir (film) 3.26, 3.30, 6.18, 6.24, 6.33, 8.30, 9.52, 9.75, 12.8, 13.6, 14.3 μ; nmr (CCl_4) τ 2.65–3.60 (complex, 9, aromatic), 4.19 (d, 1, J = 4 Hz, C=CH), 5.11 (s, 2, OCH_2), 7.75 (t, 1, J = 3 Hz, C_4 H), 9.00 (s, 3, C_1 CH_3), 9.18, 9.25 (2 s, 6, C_7 CH_3's).

Anal. Calcd for $C_{23}H_{26}O$: C, 86.74; H, 8.23. Found: C, 86.75; H, 8.15.

Further elution (5% ether in hexane through 100% ether) afforded 1.1 g of additional, semicrystalline material. Repeated recrystallization from ethanol afforded 3,3′-dibenzyloxybiphenyl: mp 120–121°; ir ($CHCl_3$) 3.26, 3.32, 6.23, 6.33, 9.71, 11.6, 14.3 μ; nmr ($CDCl_3$) τ 2.2–3.17 (complex, 18, aromatic), 4.91 (s, 4, OCH_2); mass spectrum m/e 366.

Anal. Calcd for $C_{26}H_{22}O_2$: C, 85.21; H, 6.05. Found: C, 85.25; H, 6.0.

***cis*-3-Isobornylcyclohexanol (8).**—A solution of 3.5 g (0.01 mol) of bornylene **4** in 30 ml of absolute ethanol was hydrogenated for 20 hr at 112° and 2400 psi of hydrogen over *ca.* 3 g (wet with ethanol) of freshly prepared Raney nickel catalyst.[10] The catalyst was removed by filtration and the solvent was removed at reduced pressure. A 1.51-g portion of the residual 1.95 g (83%) of oil was chromatographed on 150 g of Woelm neutral alumina (activity grade I). Fraction monitoring by infrared analysis indicated several hydrocarbons, aromatics, and carbonyl-containing materials eluted prior to the desired cyclohexanols. Several 2–5% ethyl acetate in ether fractions which contained predominantly trans isomer **7** and the cis isomer **8** were collected. Although the first fractions were enriched in **7** and the latter in isomer **8**, the majority of the fractions were poorly resolved. Further elution afforded mixtures of cyclohexanols and incompletely reduced phenolic products.

In latter experiments we found it possible to obtain satisfactory purity by carrying out the reduction at 130° for 36 hr. The resultant cyclohexanol mixture **5** was obtained in 70–80% yield by direct distillation at 115–130° (0.03 mm). The mixture usually contained 60–70% isomer **8** and 30–40% isomer **7** by gas chromatographic analysis. Further purification of the cis isomer **8** by gas chromatography (FFAP, 200°) gave material exhibiting the following properties: $n^{22}D$ 1.5086 (lit.[3] $n^{20}D$ 1.5088); ir (film) 3.00, 7.19, 9.52, 10.4 μ; nmr ($CDCl_3$) τ 6.55 (m, 1, CHOH), 7.15 (s, 1, OH), 9.00–9.30 (complex, CH_3's). The 3,5-dinitrobenzoate derivative exhibited mp 152° (lit.[3] mp 157–159°).

3-Isobornylcyclohexanone (6).—A solution of 4.24 g (0.02 mol) of cyclohexanol mixture **5** in 40 ml of acetone, cooled to 5°, was treated with 5 ml of Jones reagent[16] over 15 min. The reaction was stirred an additional 5 min at 5°, and the excess oxidizing agent was decomposed by the dropwise addition of isopropyl alcohol. The mixture was poured into brine and the organic material was isolated with ether. The combined extracts were washed with saturated aqueous sodium bicarbonate and brine until neutral. Removal of the dried ($MgSO_4$) solvent afforded 4.47 g of crude product which was distilled to afford 3.86 g (29%) of light yellow product, bp 103–115° (0.05 mm). Further purification by redistillation, bp 105° (0.05 mm), and gas chromatography (SE-30, 200°) gave ketone **6**: $n^{25.5}D$ 1.5033; ir (film) 5.81, 7.19, 7.59, 8.11 μ; nmr ($CDCl_3$) τ 9.20 (CH_3).

Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 82.1; H, 11.2.

The semicarbazone was recrystallized from ethanol as a microcrystalline powder, mp 219–220°.

Anal. Calcd for $C_{17}H_{29}N_3O$: C, 70.06; H, 10.03; N, 14.42. Found: C, 70.2; H, 10.2; N, 14.35.

***trans*-3-Isobornylcyclohexanol (7).**—The procedure of Henbest *et al.*,[11a] was employed. A solution of 0.52 g (2.2 mmol) of isobornylcyclohexanone **6**, 40 mg (0.12 mmol) of chloroiridic acid (Alpha), 0.55 ml of trimethyl phosphite, and 1.0 ml of water in 7 ml of isopropyl alcohol was refluxed for 100 hr.[13b] Isolation (ether)[13f] afforded 0.7 g of crude product which was distilled to

(12) We want to thank Dr. E. Demole for a sample of *trans*-3-(*exo*-5-isocamphyl)cyclohexanol.

(13) (a) The prefix *dl* is omitted from the names of racemic substances. (b) The apparatus described by W. S. Johnson and W. P. Schneider [*Org. Syn.*, **30**, 18 (1950)] was used to maintain a nitrogen atmosphere. (c) Infrared spectra were determined on a Perkin-Elmer Model 237 spectrophotometer; nmr spectra were determined with a Varian Model HA-100 spectrometer by R. Reavill and associates of these laboratories [chemical shifts measured relative to tetramethylsilane (τ 10)]; gas–liquid partition chromatography was accomplished with an Aerograph Model 202B using a flow rate of 100 cc/min on 5 ft × 0.25 in. columns packed with 20% FFAP on 60–80 Chromosorb P or 20% SE-30 on 60–80 Chromosorb W at the temperature indicated unless otherwise specified. (d) Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. (e) Anhydrous pyridine was obtained by distillation from barium oxide. (f) The isolation procedure consisted of thorough extraction with the specified solvent, washing the combined extracts with brine solution, and drying over anhydrous magnesium sulfate. The solvent was removed from the filtered extracts under reduced pressure on a hot water bath. (g) Melting points are corrected.

(14) Benzyloxy-1-bromobenzene (**2**), mp 55–57°, was prepared according to Y. Wu, W. A. Gould, W. G. Lobeck, Jr., H. R. Roth, and R. F. Feldkamp, *J. Med. Pharm. Chem.*, **5**, 752 (1962), in quantitative yield. Pure material, mp 58–59°, could be obtained in 90% yield by recrystallization from methanol.

(15) E. Vowinkel, *Chem. Ber.*, **99**, 1479 (1966); *Chem. Abstr.*, **65**, 2159*d* (1966).

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

give 0.5 g (95%) of colorless, viscous oil, bp 120–130° (bath) (0.1 mm). Gas chromatographic examination utilizing a 20 ft × 1/8 in. column packed with 10% FFAP on Aeropak 30, 80–100, indicated less than 5% of the cis isomer **8**. The major product impurity (~10–15%) has been tentatively identified as bornyl isomer **10** (trans). The trans isomer **7** on further purification (FFAP, 200°) exhibited the following properties: $n^{20}D$ 1.5115 (lit.[3] $n^{20}D$ 1.5112); ir (film) 2.98, 7.19, 10.3 μ; nmr ($CDCl_3$) τ 6.05 (m, 1, CHOH), 7.33 (s, 1, OH), 9.10–9.40 (complex, CH_3's).

Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.4; H, 12.0.

The 3,5-dinitrobenzoate derivative after several crystallizations exhibited mp 101–103° (lit.[3] 107–108°). Iridium tetrachloride[11b] could be used in place of chloroiridic acid with comparable results.

Registry No.—**4**, 26988-38-5; 3,3′-dibenzyloxybiphenyl, 26988-39-6; **6**, 26988-40-9; **6** semicarbazone, 24739-52-4; **7**, 24739-41-1.

Acknowledgments.—The technical assistance of Mr. Kerry M. Fitzpatrick on part of this work is gratefully acknowledged.

5,6-Dibromoacenaphth[5,6-*cd*]-1,2-oxathiole 2,2-Dioxide. A Potential Sulfene Precursor

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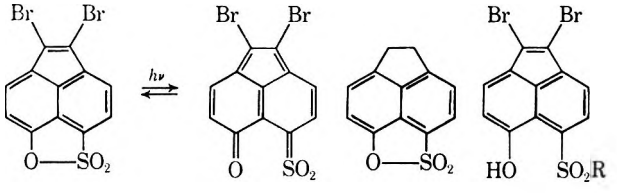
Received August 13, 1970

The evidence for a sulfene intermediate generated through photochemical processes is limited.[1-4] We report the synthesis of 5,6-dibromoacenaphth[5,6-*cd*]-1,2-oxathiole 2,2-dioxide (**1**) and adduce evidence that implicates the ketosulfene intermediate (**2**) in photochemical reactions.



1 **2** **3** **4**, R = OCH_3; **5**, N; **6**, OH

Acenaphthene sultone (**3**),[5,6] was treated with 4 equiv of NBS, and the product was isolated in the usual manner.[7] After recrystallization from acetonitrile, a 62% yield of bright red needles of **1**, mp >300°, was obtained. An ethereal solution of **1** when treated with excess pyrrolidine instantly produced an intense purple solution. Evaporation of the ether gave a purple solid that upon heating to 85° (1 mm) in an Abderhalden changed to a deep red solid. Preparative tlc of the substance yielded compound **5**, mp 180–181°. The rapid reaction of **1** with pyrrolidine compared to the slow reaction of **3** with pyrrolidine[8] suggests the existence of ring strain in the ground state of **1**. The purple color is undoubtedly due to the formation of the anion of **5** because the color can be reversibly generated by repeated acid and base treatment of **5**.[9]

A 200-mg sample of **1** was irradiated in 500 ml of absolute methanol using the standard Hanovia 450-W immersion apparatus, Pyrex filter, and continuous nitrogen purge, and maintaining a temperature of 18–20°. A portion of the original reaction mixture was set aside in an opaque container. Periodic analysis of the irradiation reaction by tlc showed that compound **1** disappeared within 30 min. The control mixture maintained in the dark showed no change during the same interval. Removal of the methanol from the irradiated mixture by vacuum rotary evaporation produced 170 mg of deep red **4** that after crystallizing from hexane had mp 107–108°.

A methanolic solution of **1** was allowed to stand undisturbed for 2 weeks in an opaque container. Vacuum rotary evaporation of this solution left a brown residue whose aqueous solution was acidic to Hydrion paper[10] and formed a precipitate upon treatment with $BaCl_2$ solution. Although the brown residue was not further characterized, its properties reflect those to be associated with **6**.

Reaction of **1** with methanolic sodium methoxide followed by neutralization with acid produced a deep red compound whose physical and chemical properties were identical with those of compound **4**. The Sn2 ring-opening process of sultones is well documented.[11,12] Thus, this ground-state reaction verifies the structure of **4**.

The differences between ground-state and excited-state solvolysis reactions of **1** are obvious. Although a variety of reactive species in the excited state can be envisioned, we currently favor the ketosulfene **2** as a reactive intermediate derived from an excited singlet-state process. Intermediate **2** is structurally analogous to the proposed diketene intermediates derived from the excited-state chemistry of pyracyloquinone.[13,14]

Additional corroborative evidence for our proposal is a comparison of the irradiation reaction of **1** with acrylonitrile to the irradiation of 1,2-dibromoacenaphthylene in acrylonitrile. No acrylonitrile polymer was found when 20 mg of **1** was irradiated in 5 ml of acrylonitrile through Pyrex during an 8-hr interval. Under similar conditions 1,2-dibromoacenaphthylene causes

(1) J. F. King, P. de Mayo, E. Morkved, A. B. M. A. Sattar, and A. Stoessel, *Can. J. Chem.*, **41**, 100 (1963).

(2) J. F. King and T. Durst, *ibid.*, **44**, 1859 (1966).

(3) R. J. Mulder, A. M. van Leusen, and J. Strating, *Tetrahedron Lett.*, 3057 (1967).

(4) J. L. Charlton and P. de Mayo, *Can. J. Chem.*, **46**, 55 (1968).

(5) The rigorous *Chemical Abstracts* name for **3** is 5,6-dihydroacenaphth-[5,6-*cd*]-1,2-oxathiole 2,2-dioxide.

(6) M. T. Bogert and R. B. Concklin, *Collect. Czech. Chem. Commun.*, **5**, 187 (1933).

(7) This procedure is similar to that for the synthesis of 1,2-dibromoacenaphthylene: B. M. Trost and D. R. Britelli, *J. Org. Chem.*, **32**, 2620 (1967).

(8) Compound **3** was quantitatively recovered after standing for 1 hr admixed with an ethereal solution of excess pyrrolidine.

(9) This result is in accord with the observations[1] made by de Mayo and coworkers upon structurally similar compounds.

(10) Under similar conditions de Mayo and coworkers[1] found "acidic" products resulting from reaction of their sultones.

(11) A. Mustafa, *Chem. Rev.*, **54**, 195 (1954).

(12) O. R. Zaborsky and E. T. Kaiser, *J. Amer. Chem. Soc.*, **92**, 860 (1970).

(13) B. Trost, *ibid.*, **91**, 918 (1969).

(14) F. M. Beringer, R. E. K. Winter, and J. A. Castellano, *Tetrahedron Lett.*, 6183 (1968).

extensive polymerization of acrylonitrile.[15] If 1 forms an excited triplet state, its efficiency for initiating polymerization of acrylonitrile is extremely low.

Experimental Section

General.—Melting points were taken on a Fisher-Johns hot stage and are uncorrected. Ultraviolet and visible spectra were recorded on Beckman DU-2 and DBG spectrophotometers. Infrared spectra were determined on a Perkin-Elmer Model 337 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Model T-60 spectrometer in hertz (Hz) with reference to internal tetramethylsilane. Elemental analyses were determined by Galbraith Laboratories.

Sodium Acenaphthene-5-sulfonate.—To a mixture of 460 g (3.0 mol) of acenaphthene and 2 l. of methylene chloride in a three-necked flask, equipped with overhead stirrer, thermometer, and addition funnel was added dropwise with stirring and ice cooling 349.5 g (3.0 mol, 198 ml) of chlorosulfonic acid. The addition rate was adjusted to maintain the reaction temperature at 0–5°. When the addition was complete, 500 ml of petroleum ether was added, the mixture was filtered, and the white precipitate was washed with 250 ml of petroleum ether. The white solid was dissolved in water, neutralized with solid sodium carbonate, and treated with 600 ml of saturated sodium chloride solution. The mixture was cooled in a refrigerator overnight and the resulting white solid was collected by vacuum filtration. The solid was washed with 250 ml of saturated sodium chloride solution and dried at 110° for 24 hr: yield 465 g (1.82 mol) (62%); mp >300°;[16] ir (KBr) 3000 (C–H) (w), 2900 (m), SO_2 1185 (s), aromatic C–H 1221 (m), 1110 (m), 1100 (m), 1052 (m), 1028 (m), 835 cm^{-1} (m).

Sodium 6-Nitroacenaphthene-5-sulfonate.—To a suspension of 465 g (1.82 mol) of pulverized sodium acenaphthene-5-sulfonate and 1 l. of glacial acetic acid, contained in a three-necked flask, fitted with overhead stirrer, thermometer, and addition funnel, was added dropwise, 240 ml of red fuming nitric acid, while maintaining the reaction temperature at 15–16°. After the addition was complete, some material remained suspended, and the mixture was stirred at 0–10° for 15 min. The mixture was poured onto 2 l. of crushed ice and filtered, and the filtrate treated with approximately 30 l. of saturated sodium chloride solution until precipitation was complete. The resulting yellow solid was filtered, dissolved in 500 ml of hot water, precipitated hot with excess saturated sodium chloride solution, and collected by vacuum filtration: yield 285 g (0.95 mol) (54%); mp >300°;[16] ir (KBr) 2920 (C–H) (w), SO_2 1200 (s), NO_2 1510 (s), 1310 (s), 1112 (aromatic C–H) (w), 1040 (w), 1025 (w), 825 cm^{-1} (w).

6-Aminoacenaphthene-5-sulfonic Acid.—A solution of 15 g (54 mmol) of sodium 6-nitroacenaphthene-5-sulfonate in 150 ml of water, contained in a 250-ml erlenmeyer flask, was treated with approximately 0.1 g of palladium on charcoal, and 2.5 g (66 mmol) of powdered sodium borohydride was added portionwise, at room temperature, over a period of 1 hr. The mixture which was originally yellow turned dark brown and was filtered to remove the palladium/charcoal; the filtrate was acidified with concentrated hydrochloric acid. The light tan solid was recovered by suction filtration; yield 4.5 g (17 mmol) (31%); mp >300°;[16] ir (KBr) 2930 (C–H) (m), H_3N 2630 (w), 1175 (SO_2) (s), 1115 (aromatic C–H) (w), 1055 (m), 1025 (m), 827 cm^{-1} (m).

Acenaphthene-5,6-sultone.—To a mixture of 10 ml of concentrated hydrochloric acid, 10 ml of ice, and 2.5 g (10 mmol) of 6-aminoacenaphthene-5-sulfonic acid, in a 125-ml erlenmeyer flask, was added dropwise, with stirring and ice cooling, a solution of 0.69 g (10 mmol) of sodium nitrite in 10 ml of water. When the addition was complete, the mixture was allowed to stand for 10 min and was then filtered. The filtrate was treated with enough sulfamic acid to destroy the excess nitrous acid. The solution was heated to boiling until evolution of nitrogen ceased, and the crude sultone precipitated from the hot solution. After cooling, the white solid was recovered by vacuum filtration, washed with 25 ml of water, and recrystallized from 5 ml of 95% ethanol: yield 0.07 g (0.3 mmol) (3%); mp 176.0–176.5° (lit.[6] mp 173°); ir (KBr) 3070 (C–H) (w), 2920 (w), SO_2 1185 (s), 1208 (aromatic C–H) (m), 1092 (m), 1070 (w), 1035 (w), 834 cm^{-1} (m); nmr δ ($CDCl_3$) 3.57 (s, 4, $ArCH_2$), 7.02 (d, 1, J = 7.0 Hz), 7.35 (d, 1, J = 7.0), 7.55 (d, 1, J = 7.8), 7.92 ppm (d, 1, J = 7.8); uv (CH_3OH) 320 nm (ϵ 4500), 242 (27,000), 215 (19,500).

1,2-Dibromoacenaphthylene-5,6-sultone.—A solution of 0.3 g (1.29 mmol) of acenaphthene-5,6-sultone in 25 ml of carbon tetrachloride was heated to reflux for 15 min, and 0.92 g (5.2 mmol) of freshly recrystallized *N*-bromosuccinimide and approximately 50 mg of dibenzoyl peroxide were added to the hot solution. The mixture was refluxed for 4.5 hr, cooled in an ice bath, and filtered. The solvent was removed from the filtrate by rotary evaporation. The residue was crystallized from 5 ml of chloroform, and recrystallized from 8 ml of acetonitrile; yield 0.31 g (0.81 mmol) (62%); mp >300°; ir (KBr) 3050 (C–H) (w), C=C 1630 (m), SO_2 1190 (s), 1222 (aromatic C–H) (m), 1125 (m), 1040 (w), 1010 (w), 832 cm^{-1} (m); nmr δ ($CDCl_3$) 6.94 (d, 1, J = 7.8 Hz), 7.64 (d, 1, J = 7.8) 7.78 (d, 1, J = 7.0), 7.98 ppm (d, 1, J = 7.0); uv (C_6H_{12}) 450 nm (ϵ 1140), 370 (8520), 363 (8470), 354 (11,600), 347 (10,500), 335 (13,200), 235 (33,000). *Anal.* Calcd for $C_{12}H_4Br_2SO_3$: C, 37.14; H, 1.04; Br, 41.19; S, 8.26. Found: C, 37.27; H, 1.01; Br, 41.31; S, 8.15.

Control Reaction. 1,2-Dibromoacenaphthylene-5,6-sultone in Moist Ether.—A solution of 5.48 mg (14 μmol) of 1,2-dibromoacenaphthylene-5,6-sultone in 75 ml of moist ether was allowed to stand in the dark, and the progress of the reaction was followed through visible–ultraviolet spectroscopy. During a 2-day period, a peak at 338 nm slowly diminished in intensity while a peak at 332 nm increased. At the same time, two sets of doublets, one at 384 and 370 nm, and the second at 364 and 354 nm, joined to form a lower intensity shoulder at 373 nm and a broad peak at 360 nm. The very broad peak at 450 nm did not shift but its intensity increased in proportion to the other peaks.

Control Reaction. 1,2-Dibromoacenaphthylene in Moist Ether.—A solution of 4.8 mg (15 μmol) of 1,2-dibromoacenaphthylene in 75 ml of moist ether was allowed to stand in the dark. The spectrum of the solution was periodically monitored and during 2 weeks remained unchanged.

Control Reaction. 1,2-Dibromoacenaphthylene-5,6-sultone in Methanol.—A solution of 10.46 mg (27 μmol) of 1,2-dibromoacenaphthylene-5,6-sultone in 75 ml of methanol was allowed to stand in the dark, and the progress of the reaction was followed by visible–ultraviolet spectroscopy. During a 2-week interval the peak at 334 nm slowly disappeared, while a peak at slightly lower intensity appeared at 332 nm. A peak at 256 nm, during the same period, slowly shifted to 360 nm and gained in relative intensity. A slightly lower intensity peak at 370 nm initially grew in intensity while shifting to 375 nm. As the reaction proceeded, however, the relative intensity at 375 nm decreased. The broad, low intensity peak at 450 nm remained at the same position, but its relative intensity increased. The solvent was removed from the solution by rotary evaporation. The dark brown solid dissolved readily in 3 ml of water to form a solution whose resulting pH was approximately 2. Treatment of the aqueous solution with barium chloride immediately gave a precipitate.

Photolysis of 1,2-Dibromoacenaphthylene-5,6-sultone in Methanol.—A solution of 0.2 g (0.52 mmol) of 1,2-dibromoacenaphthylene-5,6-sultone in 500 ml of methanol was purged with dry nitrogen for 15 min and irradiated for 40 min in a quartz immersion apparatus, equipped with a magnetic stirrer and a Hanovia 450-W medium-pressure mercury lamp and fitted with a Pyrex filter. The progress of the reaction was followed by tlc. The solvent was removed from the reaction mixture by rotary evaporation and the residue treated with 20 ml of chloroform. The chloroform solution was filtered, the filtrate rotary evaporated, and the bright red solid crystallized from hexane: yield 0.17 g (0.40 mmol) (77%); mp 107.0–107.5°; ir (CCl_4) OH 3290 (m), CH 2950) (w); ir (KBr) 1620 (C=C) (m), SO_2 1165 (s), ArH 1180 (m), 1105 (m), 1038 (m), 995 (w), 820 cm^{-1} (m); nmr δ ($CDCl_3$) 3.82 (s, 3, OCH_3), 7.09 (d, 1, J = 8.0 Hz), 7.28 (s, 1, OH), 7.62 (d, 1, J = 8.0), 7.70 (d, 1, J = 8.0), 8.32 ppm (d, 1, J = 8.0); uv (C_6H_{12}) 480 nm (ϵ 1290), 373 (6750), 367 (6560), 355 (8210), 335 (9750), 289 (5660), 247 (22,900), 207 (13,800). *Anal.* Calcd for $C_{13}H_8Br_2O_4S$: C, 37.17; H, 1.92; Br, 38.04; S, 7.63. Found: C, 37.31; H, 1.91; Br, 38.29; S, 7.83.

Reaction of 1,2-Dibromoacenaphthylene-5,6-sultone and Sodium Methoxide.—A solution of 1.2 mg (52.8 μg-atoms) of sodium dissolved in 2 ml of dry methanol was added to a solution of 20.5 mg (52.8 μmol) of 1,2-dibromoacenaphthylene-5,6-

(15) Private communication from Mr. Richard Hall of these laboratories. See also the report by B. F. Plummer, and R. A. Hall, *Chem. Commun.*, 44 (1970).

(16) No physical constants were reported for this compound.[6]

sultone in 40 ml of dry methanol. The mixture, which turned dark blue, was stirred at room temperature for 15 min. Upon acidification with hydrogen chloride the solution turned red. After removal of the solvent by rotary evaporation, the residue was chromatographed with ethyl acetate on Chrom AR-1000. A fraction moving with the solvent front was recovered as a dark red solid that had melting point, ir, and nmr identical with those of the red photoproduct (4) described above. A small second fraction which was difficult to elute was not characterized.

Reaction of 1,2-Dibromoacenaphthylene-5,6-sultone and Pyrrolidine.—A solution of 75.8 mg (0.195 mmol) of 1,2-dibromoacenaphthylene-5,6-sultone in 100 ml of dry ether was treated with 70 mg (0.975 mmol) of pyrrolidine at room temperature and the solution immediately turned a dark purple. The ether was removed from the solution by rotary evaporation. The residue was heated at 85° *in vacuo* for 4 hr and the solid chromatographed on Chrom AR-1000 using benzene to elute the bright red product: yield 72.4 mg (0.158 mmol) (81%); mp 180–181°; ir (KBr) 3190 (OH) (m), 2920 (CH) (w), 1620 (C=C) (m), 1140 (SO_2–N) (s), 1175 (ArH) (w), 1095 (w), 1060 (w), 1025 (w), 835 cm^{-1} (w); nmr δ ($CDCl_3$) 1.77 (m, 4, CH_2), 3.25 (m, 4, NCH_2), 6.98 (d, 1, J = 7.4 Hz), 7.52 (d, 1, J = 7.4), 7.65 (d, 1, J = 7.4), 8.21 (d, 1, J = 7.4), 10.73 ppm (s, 1, O–H); uv (C_6H_{12}) 470 nm (ε 1320), 377 (7390), 359 (9040), 335 (9280), 289 (5910), 248 (22,400), 208 (21,400). *Anal.* Calcd for $C_{16}H_{13}NBr_2O_3S$: C, 41.85; H, 2.85; N, 3.05; Br, 34.81; S, 6.98. Found: C, 42.00; H, 2.99; N, 2.93; Br, 34.80; S, 6.73.

Photolysis of 1,2-Dibromoacenaphthylene-5,6-sultone in Acrylonitrile.—A solution of 20.0 mg (51.5 μmol) of 1,2-dibromoacenaphthylene-5,6-sultone in 5 ml of freshly distilled acrylonitrile was irradiated in a Pyrex container for 8 hr, employing a Hanovia 450-W medium-pressure mercury lamp. A small amount of solid precipitated during the irradiation. Upon removal of the remaining acrylonitrile, a red crystalline material was recovered which had infrared absorptions identical with 1,2-dibromoacenaphthylene-5,6-sultone. A small amount of a dark oil was also obtained whose structure was not identified.

Control Reaction. Acenaphthene-5,6-sultone and Pyrrolidine in Ether.—To a solution of 20.0 mg (0.086 mmol) of acenaphthene-5,6-sultone in 100 ml of dry ether was added 0.5 ml (0.43 g, 5.98 mmol) of pyrrolidine. Monitoring of the solution by tlc indicated that no reaction occurred during a period of 1 hr.

Registry No.—1, 26988-41-0; sodium acenaphthene-5-sulfonate, 26988-42-1; sodium 6-nitroacenaphthene-5-sulfonate, 26988-43-2; 6-aminoacenaphthene-5-sulfonic acid, 26988-44-3; 1,2-dibromoacenaphthylene-5,6-sultone with methanol, 26988-49-8; 1,2-dibromoacenaphthylene-5,6-sultone with pyrrolidine, 26988-50-1.

Acknowledgment.—We gratefully acknowledge support from the Robert A. Welch Foundation and a matching fund grant from the National Science Foundation for purchase of the T-60 nmr spectrometer.

Reaction of Nitroprusside with Amines[1]

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In the course of our studies of pentacyanoferrates ($Fe(CN)_5X^{3-}$), we came across a report which described the preparation of aminepentacyanoferrates ($Fe(CN)_5NH_2R^{3-}$) by reaction of nitroprusside ($Fe(CN)_5NO^{2-}$) with primary amines.[2] The reaction of nitroprusside with ammonia and amines was, in fact, first studied by Hofmann and Manchot who also noticed that a gas (presumably nitrogen) was evolved.[3] However, although 2 mol of amine is consumed for each mole of complex produced, no reports have appeared on the *organic* products of this reaction.

$$2RNH_2 + Fe(CH)_5NO^{2-} \longrightarrow Fe(CN)_5NH_2R^{3-} + N_2 + \text{organic products}$$

We have found that the organic products (Table I)

TABLE I
PRODUCTS OF REACTION OF NITROPRUSSIDE WITH AMINES

Amine	Products (yield, %)[a]	Additional products (yield, %) (in air)[b,c]
Benzylamine	Benzyl alcohol (120)	Benzonitrile (20), benzaldehyde (trace)
Allylamine	Allyl alcohol (38)	Acrylonitrile (trace)
Cyclohexylamine	Cyclohexanol (120), cyclohexene (9)	Cyclohexanone (3)
2-Octylamine	2-Octanol (70), 1- and 2-octene (16)	2-Octanone (10)
1-Butylamine	1-Butanol (42), 2-butanol (8)	...[d]
Diethylamine	*N*,*N*-Diethyl-*N*-nitrosamine (44)	

[a] Yields are based on a stoichiometry of 2 amine: 1 nitroprusside; formation of some $Fe(CN)_5OH_2^{3-}$ in place of $Fe(CN)_5NH_2R^{3-}$, however, may also occur; *cf.* yields for benzylamine and cyclohexylamine. [b] Yields of oxidized products varied with pH and with concentration of nitroprusside; average yields are reported. Yields of nitrosation products (in air) were *ca.* 10% lower than under nitrogen. [c] Infrared spectra of all product mixtures showed weak absorptions at *ca.* 1640 cm^{-1} (>C=N–). [d] The expected oxidation product, *n*-butyraldehyde, reacts with nitroprusside; see ref 10.

are substances derived from *N*-nitrosamines, which indicates that nitroprusside functions as a nitrosating agent. Moreover, nitroprusside is unique in being a nitrosating (and deaminating) agent which is stable in *alkaline aqueous solution. Thus, the deamination of benzylamine can be carried out at an initial pH as high as 12.7.* At higher pH's, nitroprusside is destroyed, according to[4]

$$Fe(CN)_5NO^{2-} + 2OH^- \longrightarrow Fe(CN)_5NO_2^{4-} + H_2O$$

Primary amines give deaminated products (alcohols and olefins), while a secondary amine gives the *N*-nitrosamine. Tertiary and aromatic amines are largely inert. The deaminations are of interest since they probably involve generation of diazonium and carbonium ions in *alkaline solution.*

Moss[5] recently studied the reactions of diazonium ions (prepared from hydrolysis of diazotates) in alkaline solution. He found that the diazotates prepared from primary carbinamines gave predominantly diazoalkanes on hydrolysis, *e.g.*

$$C_4H_9N{=}N{-}O^- \xrightarrow{H_2O} C_4H_9N{\equiv}N^+OH^- \longrightarrow C_3H_7CHN_2 + H_2O$$

We have not observed diazoalkanes with nitroprusside, probably because the hydroxide ion concentration is

(1) Taken from the M.S. Theses of M. A. G. and M. C. N., Boston College, 1970.

(2) D. J. Kenney, J. P. Flynn, and J. B. Gallini, *J. Inorg. Nucl. Chem.*, **20**, 75 (1961).

(3) (a) K. A. Hofmann, *Justus Liebigs Ann. Chem.*, **312**, 1 (1900); (b) W. Manchot and P. Woringer, *Ber.*, **46**, 3514 (1913).

(4) J. H. Swinehart and P. A. Rock, *Inorg. Chem.*, **5**, 573 (1966).

(5) R. A. Moss, *J. Org. Chem.*, **31**, 1082 (1966).

still too low for proton abstraction from the diazonium ion.[6]

On the other hand, there is a qualitative parallel between the products of nitrous acid and nitroprusside deaminations. Thus, with nitrous acid, cyclohexylamine gave 68% cyclohexanol and 20% cyclohexene,[7] and 2-octylamine gave 20% 1- and 2-octene and 27% 2-octanol.[8] There are differences in product *ratios*, however, which indicate that hydroxide ion is involved in the nitroprusside deamination. The higher ratio of 1- to 2-butanol with nitroprusside (5:1 *vs.* 2:1[9]) is evidence for an SN2 attack of hydroxide ion on the 1-butyldiazonium ion. Alternatively, the possibility exists that all the products are formed directly from an amine–nitroprusside complex.

The first step in these nitrosations almost certainly involves addition of the amine to the coordinated nitric oxide.[10]

$$RNH_2 + Fe(CN)_5NO^{2-} \rightleftharpoons RNH_2NOFe(CN)_5^{2-}$$

The lower basicity of aromatic amines is consistent with their inertness to nitroprusside.

The resulting complex might react directly with a molecule of amine, with displacement of the *N*-nitrosamine.

$$\underset{\mathbf{1}}{RNH_2NOFe(CN)_5^{2-}} + RNH_2 \longrightarrow RNHNO + H^+ + RNH_2Fe(CN)_5^{3-}$$

$$RNHNO \longrightarrow RN{\equiv}N^+{:}OH^- \longrightarrow R^+ \longrightarrow \text{products}$$

Another possibility involves loss of water from **1**, leading to a diazonium ion complex which would then react with a molecule of amine.

$$\underset{\mathbf{1}}{RNH_2NOFe(CN)_5^{2-}} \xrightarrow{-H_2O} RN{\equiv}N{-}Fe(CN)_5^{2-} \xrightarrow{RNH_2} RNH_2Fe(CN)_5^{3-} + RN{\equiv}N^+ \longrightarrow R^+ \longrightarrow \text{products}$$

The intermediates apparently are too short-lived to be detected by conventional spectrophotometry.

When nitroprusside is allowed to react with amines in presence of air, small amounts of oxidized products are formed, together with the compounds listed above. These materials (Table I) are produced only in the presence of *both* nitroprusside and air, and their yields increase when the reactions are carried out under pure oxygen. Control experiments show that they are *not* produced by reaction of the corresponding alcohols with nitroprusside. Autoxidation of an intermediate nitroprusside–amine complex seems to be a reasonable pathway for these oxidative deaminations.

Experimental Section[11]

Materials.—Allylamine, benzylamine, 1-butylamine, cyclohexylamine, diethylamine, and 2-octylamine were obtained from the usual commercial sources and were distilled prior to use. Sodium nitroprusside dihydrate (Fisher) was used without further purification.

Reaction of Nitroprusside with Amines.—The reaction of cyclohexylamine (under nitrogen) and benzylamine (under oxygen) with nitroprusside will be described in detail. Procedure and product identification were similar in all other cases.

A solution of sodium nitroprusside dihydrate (24.0 g, 0.084 mol) in 90 ml of water was flushed with nitrogen and was added dropwise, under nitrogen, to a deaerated solution of cyclohexylamine (1.4 g, 0.014 mol) and sodium carbonate (0.75 g, 0.007 mol) in 30 ml of water. An immediate, but slow, evolution of gas occurred. The reaction mixture was stirred for *ca.* 10 hr, during which a small amount of brown solid gradually precipitated. Potassium carbonate (*ca.* 20 g) was then added (to salt out organic materials) and the mixture extracted with five 40-ml portions of ether. The ethereal extract was dried (magnesium sulfate) and the ether taken off. There remained 0.9 g of a pale yellow oil, the infrared spectrum of which was identical with that of cyclohexanol. When the oil was submitted to vpc (135°, 6 ft × 0.25 in., 20% Carbowax 20M on 80–100 Chromosorb P column, He pressure 18 psi), two peaks were observed. Retention times corresponded to cyclohexene (9%) and cyclohexanol (120%), respectively.

A solution of sodium nitroprusside dihydrate (25.5 g, 0.086 mol) in 100 ml of water was added dropwise to a solution of benzylamine (1.5 g, 0.014 mol) and sodium carbonate (1.5 g, 0.014 mol) in 45 ml of water. The solution was stirred under oxygen for *ca.* 24 hr. Potassium carbonate (*ca.* 20 g) was then added and the mixture extracted with five 20-ml portions of ether. The ethereal extract was dried (magnesium sulfate) and the ether stripped off. There remained 1.1 g of an orange oil. When the oil was submitted to preparative vpc (125°, 20 ft × 0.375 in., 30% SE-30 on 60–80 Chromosorb W column, He pressure 20 psi), two peaks were observed, the retention times and infrared spectra of which corresponded to benzonitrile (40%) and benzyl alcohol (116%), respectively.

Registry No.—Nitroprusside, 1784-20-9; benzylamine, 100-46-9; allylamine, 107-11-9; cyclohexylamine, 108-91-8; 2-octylamine, 693-16-3; 1-butylamine, 109-73-9; diethylamine, 109-89-7.

Acknowledgment.—This work was partially supported by the Petroleum Research Fund (Grant 1316-G1), administered by the American Chemical Society.

(6) No carbon-deuterated benzyl alcohol was obtained from reaction of benzylamine with nitroprusside in D_2O, indicating that phenyldiazomethane is not an intermediate in the deamination.

(7) H. Söll in Houben-Weyl, "Methoden der Organischen Chemie," 4th ed, XI/2, G. Thieme Verlag, Stuttgart, 1958, p 133 ff.

(8) R. A. Moss and S. M. Lane, *J. Amer. Chem. Soc.*, **89**, 5655 (1967).

(9) F. C. Whitmore and D. P. Langlois, *ibid.*, **54**, 3441 (1932).

(10) C-Nitrosations of ketones with nitroprusside have been observed; *cf.* J. H. Swinehart, *Coord. Chem. Rev.*, **2**, 387 (1967).

(11) Infrared spectra were determined with a Beckman IR-10 instrument. Vpc determinations were performed on a Varian Aerograph 1700 instrument; vpc peak areas were calibrated with standards.

Reaction of Perfluoroalkyl Halides with Grignard Reagents

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The reactions of perfluorocarbon halides (Cl, Br, or I) with Grignard reagents reported in the literature[2-6] were mainly for the syntheses of fluorocarbon Grignard reagents. These alkyl or aryl exchange reactions were carried out at low temperatures (0 to −70°), because of the thermal instability of the fluorocarbon Grignard reagents. The present investigation was a study of this reaction at higher temperatures (>25°).

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(2) R. N. Haszeldine, *J. Chem. Soc.*, 3423 (1952).

(3) O. R. Pierce, A. F. Meiners, and E. T. McBee, *J. Amer. Chem. Soc.*, **75**, 2516 (1953).

(4) R. J. DePasquale and C. Tamborski, *J. Organometal. Chem.*, **13**, 273 (1968).

(5) W. L. Respress and C. Tamborski, *ibid.*, **11**, 619 (1968).

(6) R. J. DePasquale, *ibid.*, **15**, 233 (1968).

Haszeldine[2] reported that the reflux of heptafluoropropylmagnesium chloride in butyl ether gave mainly C_3F_7H (76%) and C_3F_6 (6%). The present study indicated that the addition of methylmagnesium chloride to hot linear perfluoroalkyl iodides, $CF_3(CF_2)_nI$ (n = 7, 9) gave essentially terminal olefins and some internal olefins. Small amounts of condensation products were also present as indicated by gas chromatography. The amount of 1-hydroperfluoroalkanes $CF_3(CF_2)_nH$, if present, was small.

The reaction of CH_3MgCl with $I(CF_2)_4I$ at 60° gave perfluorobutadiene as the major product. A small amount of perfluorobutene-1 was also present indicating that some fluorination of the iodo compound took place. When $CF_3CFClCFClCF_3$ was allowed to react with Grignard reagent, 2-butenes were the major products, not the butadiene. In this case the dechlorination reaction was preferred. There was, however, some terminal olefin present as shown by the infrared analysis. A similar reaction was run with ICF_2CF_2I.[7] The major product was tetrafluoroethylene. The reaction of perfluoroheptyl bromide with methylmagnesium chloride at 70° gave heptene-1 and hepteres-2.[8]

The formation of terminal olefins by the present method has not been reported previously. Up to now terminal perfluoroalkenes ($>C_3$) were prepared by the pyrolysis[9] of the sodium salts of the corresponding carboxylic acids. The lack of 1-hydroperfluoroalkanes among the major products in the present study may indicate the absence of a regular Grignard intermediate $CF_3(CF_2)_nCF_2MgX$.[10] Thus the formation of terminal olefins may be best explained by an E2 elimination mechanism.[11] The internal olefins were the result of

$$CH_3MgCl \longrightarrow {}^-CH_3 + {}^+MgCl$$

$$^-CH_3 + I-\underset{F}{\overset{\overset{F}{\downarrow}}{C}}-\underset{C_6F_{13}}{\overset{F}{C}}-F \longrightarrow CH_3I + CF_2{=}CFC_6F_{13} + F^-$$

isomerization[12] of the terminal olefins by the fluoride ions present in the reaction media.

A similar dehalofluorination reaction of perfluoroalkyl halides reported in the literature[13] was the exothermic reaction of C_3F_7I with lithium at −74°, which gave essentially C_3F_6 and only a trace of C_3F_7H. No information concerning such reactions with a longer alkyl chain was described.

Experimental Section

Spectra.—The ^{19}F nmr spectra were obtained with a 60-MHz Varian DP-60 spectrometer. The gas chromatographic data were obtained with a Nester–Faust "Prepkro" unit using a column (0.25 in. × 24 ft) packed with 30% SF-96 on Chromosorb P. Infrared spectra were run on a Beckman IR-2 spectrophotometer and also on a Perkin–Elmer Model 137 double-beam spectrophotometer. A Bendix time-of-flight mass spectrometer (Model 12-101) was employed to record the mass spectra at 70 eV.

Materials.—Methylmagnesium chloride in tetrahydrofuran (THF) (2.9 mol/l.) was purchased from Fisher Scientific Co. Perfluoroalkyl iodides and diiodides were purchased from Thiokol Chemical Corp. These iodides were linear as shown by ^{19}F nmr analysis. Perfluoroheptyl bromide and perfluoro-2,3-dichlorobutane were purchased from Peninsular ChemResearch Co.

Reaction of Perfluoroalkyl Iodides with Methylmagnesium Chloride.—In a typical experiment a round-bottom flask was equipped with a stirrer, a thermometer, a dropping funnel, a dry nitrogen inlet, and a vapor trap connected to a condenser. The dropping funnel and the condenser were capped with Drierite tubes. Perfluoroalkyl iodides (109 g), containing $C_8F_{17}I$ (85%) and $C_{10}F_{21}I$ (15%), were placed in the flask and heated to 60°. The heat was turned off before the addition of CH_3MgCl (0.445 mol) in THF (150 ml). The dropping rate of the Grignard reagent was such that the exotherm of the reaction maintained the solution temperature at 70–75°. The distillate (95 ml), collected in the vapor trap in 1 hr, was drained into an ice-cooled separatory funnel. Upon standing a colorless lower layer was separated, washed with water, dried ($MgSO_4$), and fractionated. The fraction (52 g) boiling at 100–115° was further fractionated by gas chromatography at 105°. The major peaks were collected and identified by mass, infrared, and ^{19}F nmr spectroscopy. The following perfluoro compounds were found: octene-1 (63%), *trans*-octene-2 (20%), decene-1 (8%), three other decenes (5%), and two unknown peaks (4%).

The residue in the flask was a light brown, thick solution. Water (100 ml) was added to dissolve some of the inorganic salts and the mixture was then filtered. The filtrate separated into two layers. The upper aqueous layer gave a positive iodine test. The lower layer (23.5 g) was dried ($MgSO_4$). Infrared analysis indicated the presence of –CH, –CF=CF– [5.6 (w) and 5.8 μ (m)], and –CF groups. Gas chromatography showed that the major peak was that of the solvent. Numerous small peaks were those found in the distillate and the unreacted alkyl iodides. A few minor new peaks, at longer retention times, were also present indicating some higher molecular weight fractions.

Reaction of Perfluoroheptyl Bromide with Methylmagnesium Chloride.—Perfluoroheptyl bromide (44.9 g, 0.1 mol) was heated to 65° in a flask equipped as described above. The heat was turned off before the addition of CH_3MgCl (0.29 mol in 100 ml of THF). During the 0.5-hr addition, the solution temperature was maintained at 68–70° by the exotherm of the reaction. Colorless distillate was collected in the vapor trap. It was drained into a separatory funnel and cooled by Dry Ice. The lower fluorocarbon layer (14.5 g) was analyzed by gas chromatography and infrared. The following perfluoro components were identified: *n*-heptene-1 (50.2%), *trans*-heptene-2[8] (20.6%), *cis*-heptene-2[8] (6.7%), CH_3Br (4.3%), and THF (6.9%); other small peaks composed 12.3%. The residue in the flask was a dark liquid containing a substantial amount of inorganic salts. Infrared analysis indicated the presence of –COH, –CH, and –CF=CF– (5.75 and 5.85 μ). Gas chromatographic analysis indicated the presence of THF, unreacted $C_7F_{15}Br$, and some higher condensation products.

Reaction of Perfluoroalkylene Diiodides with Methylmagnesium Chloride.—In this experiment, the equipment was slightly modified. A Dry Ice trap was connected to the top of the condenser. A sample of perfluoro telomer diiodide (100 g) containing the following diiodides, $I(CF_2)_4I$ (47%), $I(CF_2)_6I$ (21%), and higher diiodides (32%), was heated to 50°. The heat was turned off before the addition of the Grignard reagent. Methylmagnesium chloride (1.16 *M* in 400 ml of THF) was added rapidly (1.5 hr) to the diiodides. The colorless liquid (21.5 g) collected in the Dry Ice trap was fractionated by gas chromatography at 0°. Five peaks were collected and identified by infrared as $CF_3CF_2CF{=}CF_2$[14] (5.5%), $CF_2{=}CFCF{=}CF_2$[14] (45.5%), perfluorocyclohexene (12.5%), CH_3Cl (8.9%), CH_3I (11.9%), and four other small peaks (total 16.7%).

Reaction of Perfluoro-2,3-dichlorobutane with Methylmagnesium Chloride.—Methylmagnesium chloride (0.87 mol) in 300 ml of THF was placed in a 1-l. flask. $CF_3CFClCFClCF_3$ (81 g) was added to the Grignard reagent with stirring. The exotherm of the reaction raised the solution temperature from 25 to 60° during the 50-min addition period. The temperature dropped

(7) E. S. Lo, unpublished data.

(8) E. S. Lo, J. D. Readio, and H. Iserson, *J. Org. Chem.*, **35**, 2051 (1970).

(9) J. D. LaZerte, L. J. Hals, T. S. Reid, and G. H. Smith, *J. Amer. Chem. Soc.*, **75**, 4525 (1953).

(10) H. Gilman and R. G. Jones, *ibid.*, **65**, 2037 (1943).

(11) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1962, p 478.

(12) D. J. Burton and F. E. Herkes, *J. Org. Chem.*, **33**, 1854 (1968), and the references cited therein.

(13) J. A. Beel, H. C. Clark, and D. Whyman, *J. Chem. Soc.*, 4423 (1962).

(14) Identified by infrared spectrum according to R. N. Haszeldine, *ibid.*, 4423 (1952).

almost immediately upon completion of the addition. Heat was applied to maintain the temperature at 60° for 0.5 hr. The lower fluorocarbon layer (50 g) collected in the Dry Ice trap showed a major peak and a few minor peaks in the gas chromatographic analysis. Infrared analysis indicated the presence of terminal olefin (5.6 μ, weak) and internal olefins (5.75 and 5.85 μ). The major component (80%) was identified as a mixture of *cis*- and *trans*-butene-2 (5.75 μ).[14]

Registry No.—Perfluoroheptyl bromide, 375-88-2; perfluoro-2,3-dichlorobutane, 355-20-4; methylmagnesium chloride, 676-58-4.

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An Improved Aldehyde Synthesis from 1,3-Dithianes

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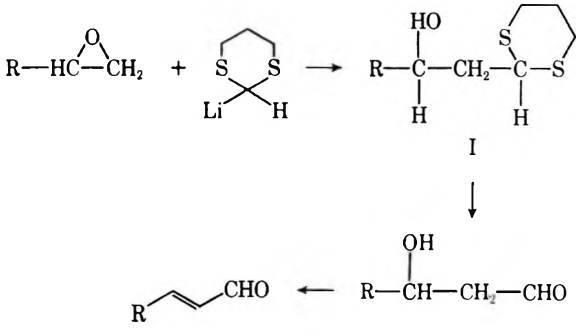
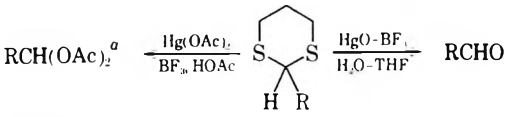
As part of a synthetic project, we required a general route to substituted acroleins. The dithiane method seemed to hold considerable promise in this direction since 2-(hydroxyalkyl)dithianes are readily available from epoxides,[1] and hydrolysis followed by dehydration should result in the desired products.



However, it became apparent that hydrolysis of I would pose difficulties. A thorough search of the literature for experimental details revealed only one example of hydrolysis of a 2-substituted 1,3-dithiane to an aldehyde, 2-phenyl-1,3-dithiane to benzaldehyde.[2,3] Accordingly, we examined the hydrolysis of some simple 2-alkyl-1,3-dithianes under conditions which hydrolyze 2,2-dialkyl-1,3-dithianes to ketones. Disappointingly low yields (20–40%) of heptanal were obtained from 2-*n*-hexyl-1,3-dithiane using $HgCl_2$ with HgO or $CdCO_3$ in refluxing aqueous methanol. Other published conditions[1a] such as the *N*-bromosuccinimide method or the silver nitrate method were even less successful and initial experiments failed to produce any aldehyde (nmr analysis) from 2-isopropyl-1,3-dithiane. Poor material balance was the rule in the various experiments, and in the mercuric chloride reactions, 30–40% of the starting material was lost, presumably due to the formation of insoluble mercury derivatives.

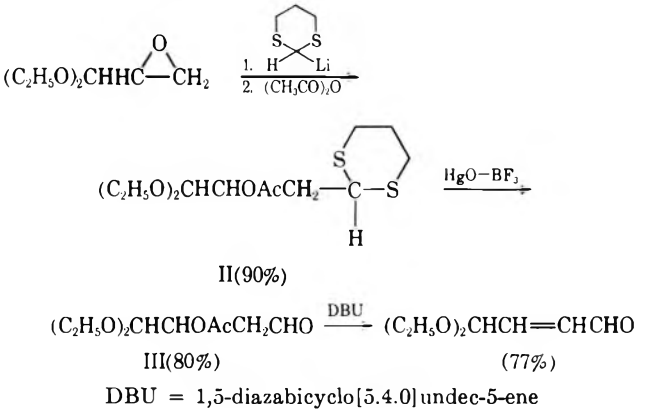
After screening a number of potential reagents,[4] we examined the combination of mercuric acetate and boron trifluoride etherate. Remarkably, a solution of this reagent in acetic acid effected the transacetalization of several 2-substituted 1,3-dithianes into the known acetaldiacetates (Table I) within a few minutes at room temperature. Under similar conditions, red mercuric oxide and boron trifluoride etherate in aqueous tetrahydrofuran hydrolyzed 1,3-dithianes to the corresponding aldehydes[5] in high yield. This method proved to be especially advantageous in the case of II, which was prepared from the epoxide of acrolein diethyl acetal.[6] The $HgO–BF_3$ reagent afforded the aldehyde in 80% yield, while $HgCl_2$ served only to destroy starting material. In addition to demonstrating the mildness of our condi-

TABLE I



Entry no.	Yield of acetaldiacetate, %	R	Registry no.	Yield of aldehyde, %
1	76[b]	C_6H_5–	5425-44-5	90[c]
2	73[b]	C_6H_5CH=CH–	26958-41-8	86[c]
3	78[c]	*i*-C_3H_7–	6007-25-6	78[e]
4		*n*-C_6H_{13}–	26958-42-9	60[d]
5		$(C_2H_5O)_2CHCHOAcCH_2$–		80[c]
6		$C_6H_5OCOC_6H_{10}$–	26958-43-0	84[e,f]

[a] E. Späth, *Monatsh. Chem.*, **36**, 29 (1915). [b] Yield of recrystallized product. [c] Yield of crude product, homogeneous by nmr. [d] Yield of pure aldehyde isolated by distillation. [e] Yield of aldehyde determined by glpc. [f] 1-Benzoyloxycyclohexanecarboxaldehyde.



II(90%)

$(C_2H_5O)_2CHCHOAcCH_2CHO \xrightarrow{DBU} (C_2H_5O)_2CHCH{=}CHCHO$

III(80%) (77%)

DBU = 1,5-diazabicyclo[5.4.0]undec-5-ene

(1) (a) D. Seebach, *Synthesis*, 17 (1969); (b) D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **8**, 639 (1969); E. J. Corey and D. Seebach, *ibid.*, **4**, 1075, 1077 (1965).

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

(3) Hydrolysis of a 2-alkyl-1,3-dithiane ($HgCl_2$, yield unspecified) is mentioned briefly by J. A. Marshall and H. Roebke, *Tetrahedron Lett.*, 1555 (1970). Transacetalization of a 2-alkyl-1,3,5-trithiane to the methoxyacetal is also reported in ref 1 without experimental details.

(4) Salts of Pb(III), Zn(II), and Tl(I) were tried without success. Copper(II) acetate with BF_3 produced some aldehyde (25% in the case of 2-*n*-hexyl-1,3-dithiane), but 50% of the starting material could not be accounted for.

(5) Aldehydes were also isolated from the reaction of dithianes with $Hg(OAc)_2$–BF_3 in dry *tert*-butyl alcohol, presumably *via* fragmentation of the corresponding *tert*-butyloxonium ion to aldehyde and isobutylene. Thus, cinnamaldehyde (78%) and cinnamaldehyde acetaldiacetate (13%) were produced from the corresponding dithiane, 2 mol of mercuric acetate, and 2 mol of boron trifluoride etherate in 200 mol of dry *tert*-butyl alcohol.

(6) D. I. Weisblat, B. J. Magerlein, D. R. Myers, A. R. Hanze, E. I. Fairburn, and S. T. Rolfson, *J. Amer. Chem. Soc.*, **75**, 5893 (1953).

tions, this example shows that substituted acroleins can be synthesized readily by the dithiane method.

We have encountered several limitations to the HgO–BF_3 procedure. Thus, attempted hydrolysis of 2-benzoyl-1,3-dithiane to the α-ketoaldehyde afforded benzoic acid (73%) as the only isolable product. Also, the dithianes of enolizable ketones could not be hydrolyzed successfully by our method. Poor material balance was obtained, and yields of only 20–30% of the ketone could be isolated from cyclohexanone or cyclopentanone dithianes.[7] However, 2,2-diphenyl-1,3-dithiane was hydrolyzed readily to benzophenone (86%).

Experimental Section

With the exception of II, the dithianes in Table I were prepared according to ref 1 and literature cited therein. Commerical red mercuric oxide and tetrahydrofuran were used directly unless otherwise specified. Boron trifluoride etherate was distilled at reduced pressure from calcium hydride before use.

General Procedure for Hydrolysis of 2-Substituted 1,3-Dithianes.—Red mercuric oxide (2 molar equiv), 2 molar equiv of boron trifluoride etherate, and 15% aqueous tetrahydrofuran (10 ml/g of dithiane) were stirred vigorously in a three-neck flask equipped with a dropping funnel and a nitrogen inlet tube. The dithiane (1 molar equiv) was dissolved in the minimum of tetrahydrofuran and was added *via* the dropping funnel in the course of 10–15 min under nitrogen. Stirring was maintained for 10–20 min after addition was complete. In the course of this time, the red mercuric oxide gradually dissolved and a white precipitate appeared. All hydrolyses were carried out at room temperature except for entry 6, Table I. The latter case required 30 min at reflux to complete the reaction. Ethyl ether (2 vol) was then added, the precipitated salts were filtered, and the ether was washed to pH 10 with saturated sodium carbonate and to neutrality with saturated sodium chloride. After drying over magnesium sulfate, the ether was evaporated under vacuum to yield crude aldehyde. Analysis by nmr indicated complete consumption of starting material and formation of aldehyde (>90% pure) in the yields reported in Table I.

Acetaldiacetates. General Procedure.—The procedure described for hydrolysis was used except that mercuric acetate was substituted for mercuric oxide and dry acetic acid was used as the solvent. A white precipitate appeared immediately upon addition of the dithiane. The same work-up method as before afforded crude acetaldiacetates free of starting material and homogeneous by nmr spectroscopy.

2-(2-Acetoxy-3,3-diethoxypropyl)-1,3-dithiane (II).—2-Lithiodithiane was prepared by the usual method[1] from 8.03 g (0.067 mol) of 1,3-dithiane in 75 ml of dry tetrahydrofuran at −50°. A solution of 1,1-diethoxy-2,3-epoxypropane[6] (9.78 g, 0.067 mol) in 10 ml of dry tetrahydrofuran was then added dropwise at such a rate that the temperature was maintained at −30°. After 3 hr at −35°, the reaction was allowed to warm to room temperature. The reaction mixture was diluted with an equal volume of ether, washed with saturated sodium chloride, dried over magnesium sulfate, and evaporated under vacuum. Removal of residual solvent and unreacted dithiane was accomplished at 0.05 mm, 12 hr at room temperature, to yield 17 g of crude alcohol.

The alcohol was dissolved in pyridine (25 ml) and acetic anhydride (18 ml) was added. After 18 hr at room temperature, the mixture was poured into ice water and extracted twice with ether (100 ml). The ether layer was washed with copper sulfate solution to remove pyridine, dried over magnesium sulfate, and evaporated under vacuum to afford the crude acetate. Molecular distillation at 130° and 0.1 mm afforded 10–12 g of II as a colorless oil, pure by nmr analysis: ($CDCl_3$) δ 5.15 (1 H, d t, J = 5, 7 Hz), 4.45 (1 H, d, J = 5 Hz), 4.04 (1 H, t, J = 7 Hz), 3.62 (4 H, m), 2.81 (4 H, m), 2.13 (4 H, m), 2.05 (3 H, s), 1.20 (6 H, t, J = 7 Hz).

4,4-Diethoxy-2-butenal (III).—The distilled acetate II was hydrolyzed by the usual method (mercuric oxide–BF_3). The crude product, 3-acetoxy-4,4-diethoxybutanal, was homogenous by nmr: ($CDCl_3$) δ 9.72 (1 H, t, J = 2 Hz), 5.52 (1 H, m), 4.55 (1 H, d, J = 4.5 Hz), 3.61 (4 H, m), 2.72 (2 H, m), 2.03 (3 H, s), 1.18 (6 H, t, J = 7 Hz). The crude 3-acetoxy-4,4-diethoxybutanal (6.42 g) was dissolved in chloroform (10 ml) and 1,5-diazabicyclo[5.4.0]undec-5-ene (5.35 g) (Aldrich) was added dropwise with cooling to keep the temperature below 30°. The reaction was stirred 0.25 hr after addition was complete and then was diluted with hexane, washed twice with water, and dried over magnesium sulfate. After evaporation of solvent, the crude product was distilled at 45–50° (0.15 mm) to yield 4,4-diethoxy-2-butenal (3.6 g, 77%) as a colorless liquid. The nmr spectrum was in excellent agreement with that of known material:[8] ($CDCl_3$) δ 9.62(1 H, d, J = 7 Hz), 6.7 (1 H, d d, J = 16, 3 Hz), 6.32 (1 H, d d, J = 16, 7 Hz), 5.15 (1 H, d, J = 3 Hz), 3.60 (4 H, m), 1.22 (6 H, (t, J = 7 Hz).

Registry No.—II, 26958-39-4.

(7) Tentative explanations for the poor recovery of starting material include acid-catalyzed mercuration of product ketone *via* the enol, and oxymercuration of possible thioenol ether intermediates. Some precedent exists for both reactions: A. Morton and H. Penner, *J. Amer. Chem. Soc.*, **73**, 3300 (1951); W. H. Watanabe and L. E. Conlon, *ibid.*, **79**, 2828 (1957).

(8) Prepared according to the method of L. Yanovskaya, B. Rudenko, V. Kucherov, R. Stepanova, and G. Kogan, *Izv. Akad. Nauk SSSR*, **12**, 2189 (1962).

Anomalous Dimerization of 5,5-Dimethyl-2-cyclohexene-1-one

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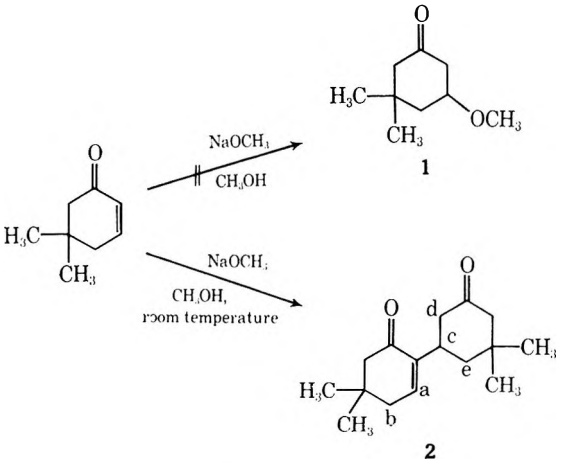
Esso Research and Engineering Company, Linden, New Jersey 07036

Received January 30, 1970

We recently became interested in preparing 3,3-dimethyl-5-methoxycyclohexanone (**1**) by the base-catalyzed addition of methanol to 5,5-dimethyl-2-cyclohexen-1-one utilizing a procedure described by Puetzer[2] for the preparation of 4-methoxy-2-butanone. Addition of 5,5-dimethyl-2-cyclohexen-1-one to anhydrous methanol containing a catalytic amount of sodium methoxide followed by neutralization with glacial acetic



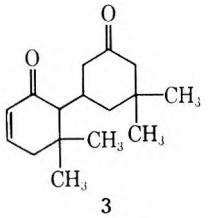
acid resulted in the precipitation of a colorless crystalline solid. The product obtained showed twin carbonyl peaks at 5.85 and 6.0 μ ($CHCl_3$) in the infrared. The absence of the $-OCH_3$ signal in the nmr definitely eliminated **1** as the structure. Elemental analysis and the m/e peak at 248 mass units pointed to a dimer of the starting material.

(1) Esso Agricultural Products Laboratory. To whom inquiries should be addressed: Union Camp Corp., P.O. Box 412, Princeton, N. J. 08540.

(2) B. Puetzer, C. H. Nield, and R. H. Barry, *J. Amer. Chem. Soc.*, **67**, 832 (1945).

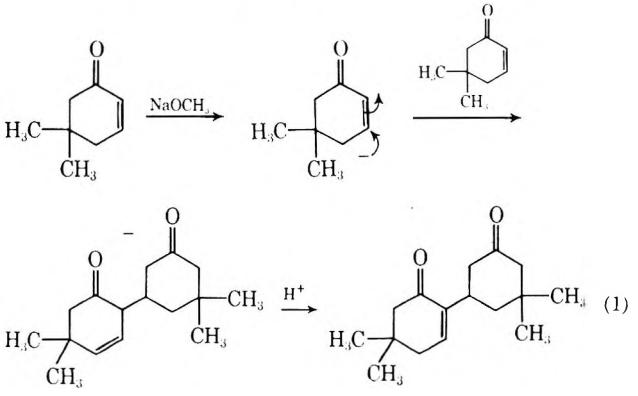
The peak area ratios, chemical shift values, and spin–spin splittings in the 100-MHz nmr spectrum of the reaction product were consistent with the dimer structure 2. The triplet (J = 4.5 Hz) at 6.61 ppm was assigned to proton a of the dimer. In comparison, the chemical shift of the proton at this ring position in the starting material occurred at 6.78 ppm while the olefinic proton α to the carbonyl had a chemical shift of 5.87 ppm. From double irradiation at 6.61 Hz, protons b were identified as a doublet at 2.28 ppm. A complex multiplet at 3.12 ppm, having a peak area equal to proton a, was assigned to methine proton c. Upon double irradiation at 3.12 Hz, protons d were assigned to a doublet (J = 8.5 Hz) at 2.26 ppm and magnetically nonequivalent protons e were assigned to doublets (J = 7.0, J = 9.5 Hz) at 1.58 and 1.57 ppm. The ring methylene protons between the carbonyl and *gem*-dimethyl groups were recorded as singlets at 2.10 ppm for the cyclohexanone ring and at 2.25 ppm for the cyclohexenone ring of the dimer. The methyl groups on the cyclohexanone ring were magnetically nonequivalent and occurred at 1.05 and 0.95 ppm. The methyl groups on the cyclohexenone ring of the dimer were observed as a singlet at 1.00 ppm.

Recently, House[3] isolated a different dimer from the reaction of 5,5-dimethyl-2-cyclohexen-1-one with dilithium tris(1-hexynyl)cuprate. He has assigned structure **3** to this compound. We are postulating that our



3

dimer, **2**, is formed by way of the mechanism of eq 1.



(1)

Alternatively, the dimer could arise by 1,4 addition of methoxide to the cyclohexenone, followed by dimerization, proton transfer, and ultimate loss of methoxide to yield the isolated product. Attempts to dimerize 2-cyclohexen-1-one in this manner were unsuccessful, only starting material or resinous products being obtained.

However, in related work, we have found that methyl mercaptan and propyl mercaptan added normally and in high yield to the double bond of both 2-cyclohexen-1-one and 5,5-dimethyl 2-cyclohexen-1-one in the presence of a basic catalyst (Triton B).

Presumably, the less basic character of the mercaptide anion precluded proton abstraction at the activated 4 position of the ring as depicted for the mechanism of eq 1.

Experimental Section

Boiling points are uncorrected; melting points are corrected. Infrared measurements were carried out with a Beckman IR-8 spectrophotometer. Nmr studies were made with the Varian A-60 and Varian HA-100 instruments.

5,5-Dimethyl-2-cyclohexen-1-one.—The general procedure of Gannon and House[4] was used to prepare this compound. A yield of 107 g (86%) was obtained from 1.0 mol of 3-ethoxy-5,5-dimethyl-2-cyclohexen-1-one after distillation through a 12-in. Vigreux column, bp 61–63° (15 mm).

Anal. Calcd for $C_8H_{12}O$: C, 77.4; H, 9.7. Found: C, 77.2; H, 9.7.

Dimerization of 5,5-Dimethyl-2-cyclohexen-1-one.—To a solution of 6.2 g (0.05 mol) of 5,5-dimethyl-2-cyclohexen-1-one in 10 ml of methanol was added 100 mg of sodium methoxide, and the resulting solution was stirred as the temperature slowly rose from 25 to 35°. The reaction mixture sustained itself at 35° for several hours after which stirring was continued for 3 days at room temperature. Neutralization of the solution with 0.5 ml of glacial acetic acid resulted in the precipitation of 1.2 g of a white solid, which was filtered and washed with water. The filtrate yielded an additional 2.9 g of product; the total yield of dimer was 4.1 g: mp 98–99°; ir ($CHCl_3$) 5.85 (C=O) and 6.0 μ (conjugated C=O); mass spectrum m/e 248.

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.4; H, 9.7. Found: C, 77.3; H, 10.1.

Registry No.—2, 10517-07-4; 5,5-dimethyl-2-cyclohexen-1-one, 4694-17-1.

Acknowledgments—We thank Professor P. Skell of The Pennsylvania State University for helpful discussions on the nature of the dimeric product. Thanks are also extended to Dr. R. Pancirov for carrying out the mass spectrometry measurements.

(3) H. O. House and W. F. Fischer, *J. Org. Chem.*, **34**, 3615 (1969).
(4) W. Gannon and H. O. House, *Org. Syn.*, **40**, 14 (1960).

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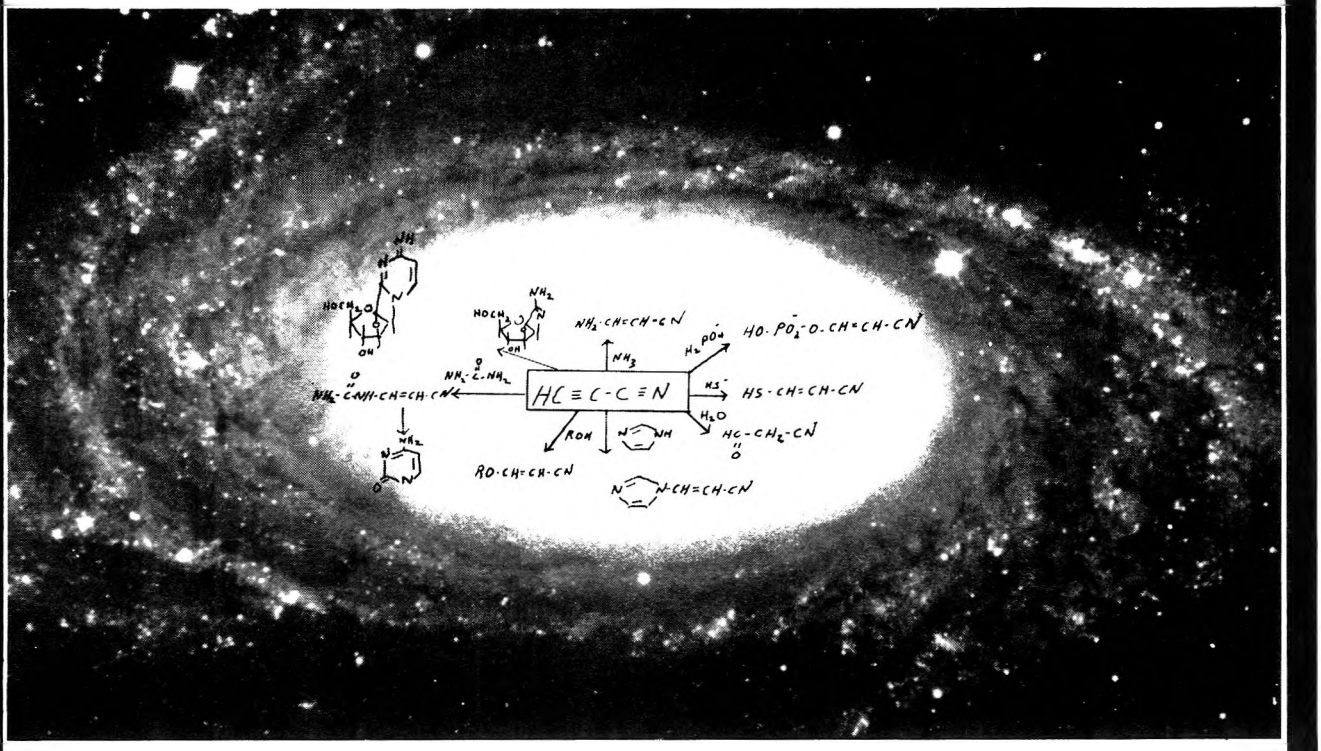

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1. G. R. Wick, Science *170*, 149 (1970). 2. R. A. Sanchez, J. P. Ferris & L. E. Orgel, Science *154*, 784 (1966).

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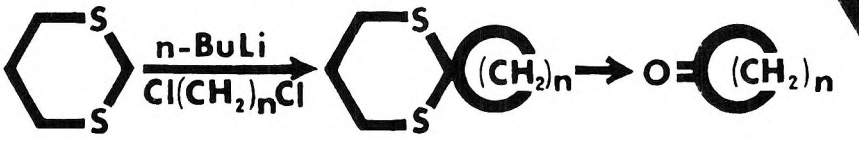

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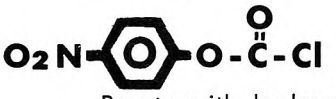

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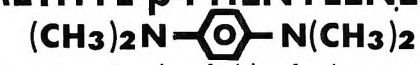

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1. G. Briegleb, Elektronen-Donator-Acceptor-Komplex, Springer Verlag. (1961).
2. A. R. Forrester, J. M. Hay and R. H. Thomson, Organic Chemistry of Stable Free Radicals, Academic Press, (1968).

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