appears to be in those of *t*-alkyl halides therefore cannot be decided on the basis of the present experiments.

The structures represented by Figs. 1 and 2 will both account for the observed order of reactivity of *t*-alkylbenzenes,[11] but the former are perhaps preferable because they have one more bond than those of Fig. 2[12]; in addition, the greater stability of the benzyl group than that of the phenyl group should be reflected in the relative contributions of 1 and 2. Structures 1 are more nearly like those suggested for alkylbenzenes which possess *alpha* hydrogens, for which structures of type 2 could not have been decisive.

If the *t*-alkylbenzenes are strained, one could give up a detailed picture and take refuge in the statement that strain in general increases the polarizability of molecules and that this effect alone can account for the data. The inductive effect of alkyl groups also predicts the right order of reactivity. Both statements may be perfectly true, but neither explanation brings us any closer to a real understanding of the effects of *t*-alkyl groups. On the other hand, hyperconjugation, or perhaps a judicious combination of hyperconjugation and steric strain, probably presents a more fruitful approach.

(11) For the similar case of the trifluoromethyl group see Roberts, Webb and McElhill, THIS JOURNAL, **72**, 408 (1950).

(12) Wheland, "The Theory of Resonance," John Wiley and Sons, Inc., New York, N. Y., 1944, p. 16.

Acknowledgment.—We thank Professor R. C. Huston of Michigan State College for generously supplying us with samples of seven hydrocarbons used in this study. We gratefully acknowledge the help afforded us by a Frederick Gardner Cottrell Grant of the Research Corporation.

Summary

The per cent. bromination of twelve *t*-alkylbenzenes in 90% acetic acid in 28 hours has been found to be *t*-butylbenzene, 5.80, *t*-amylbenzene 7.30, dimethyl-*i*-propylcarbinylbenzene 6.95, methyldiethylcarbinylbenzene 9.00, dimethyl-*n*-butylcarbinylbenzene 7.30, triethylcarbinylbenzene 10.20, methyldi-*n*-propylcarbinylbenzene 9.80, methylethyl-*n*-butylcarbinylbenzene 10.00, methylethyl-*i*-butylcarbinylbenzene 10.70, dimethyl-2-methylbutylcarbinylbenzene 11.50, diethyl-*n*-propylcarbinylbenzene 11.70, ethyl-di-*n*-propylcarbinylbenzene 9.10.

The above order of reactivity has been considered in terms of hyperconjugation and steric strain.

BRYN MAWR, PA. RECEIVED JANUARY 3, 1950

[CONTRIBUTION FROM THE WM. H. CHANDLER LABORATORY OF CHEMISTRY, LEHIGH UNIVERSITY]

Studies in the Sulfone Series. VII. The Preparation of 2,8-Diaminophenoxathiin-5-dioxide and Bis-(2-hydroxy-4-aminophenyl) Sulfone

BY E. D. AMSTUTZ

Previous studies in this series of possible antitubercular compounds have dealt with the synthesis of derivatives of bis-(4-aminophenyl) sulfone which possess a direct union of the 2,2′-positions (dibenzothiophene), a carbonyl bridge in the 2,2′-positions (thiaxanthone) and an –NH bridge in the same positions (phenothiazine).[1] The present paper describes a very simple and satisfactory route to the corresponding oxygen bridged structure.

Since the customary substituting agents attack the phenoxathiin system at the position(s) para to the oxygen,[2] our effects have been directed toward those methods dependent upon ring closures. Of the several possible routes to the desired 2,8-disubstituted ring system the only one which proved satisfactory and which was at all thoroughly investigated, involved the dehydrohalogenation of a substituted 2-hydroxy-2′-iododiphenyl sulfide. The following reaction sequence illustrates the reactions employed and the yields obtained.

The benzyl ether of 2-bromo-5-nitrophenol, prepared in the usual manner[3] in 80% yield, was converted to 2-benzyloxy-5-nitrothiophenol (II) in 70% yield by treatment with sodium disulfide in alcohol.[4] Refluxing for six hours with 3,4-diiodonitrobenzene and potassium carbonate in ethanol afforded an almost quantitative yield of 2-benzyloxy-2′-iodo-4,4′-dinitrodiphenyl sulfide (III). The benzyl group was removed by refluxing with 48% hydrobromic acid in glacial acetic acid to give the corresponding phenol, IV, in 72% yield. Precipitation of the potassium salt of the phenol was carried out by addition of strong potassium hydroxide solution to a dilute aqueous solution of the salt. The ring-closure step was found to give no difficulty if performed in a sealed tube in the absence of oxygen since the dry salt is quite unstable in air above 100°, particularly in the presence of a small amount of potassium hydroxide. The 2,8-dinitrophenoxathiin was oxidized to the 5-dioxide with 30% hydrogen peroxide in glacial acetic acid after which the nitro groups were reduced with stannous chloride in acetic acid.

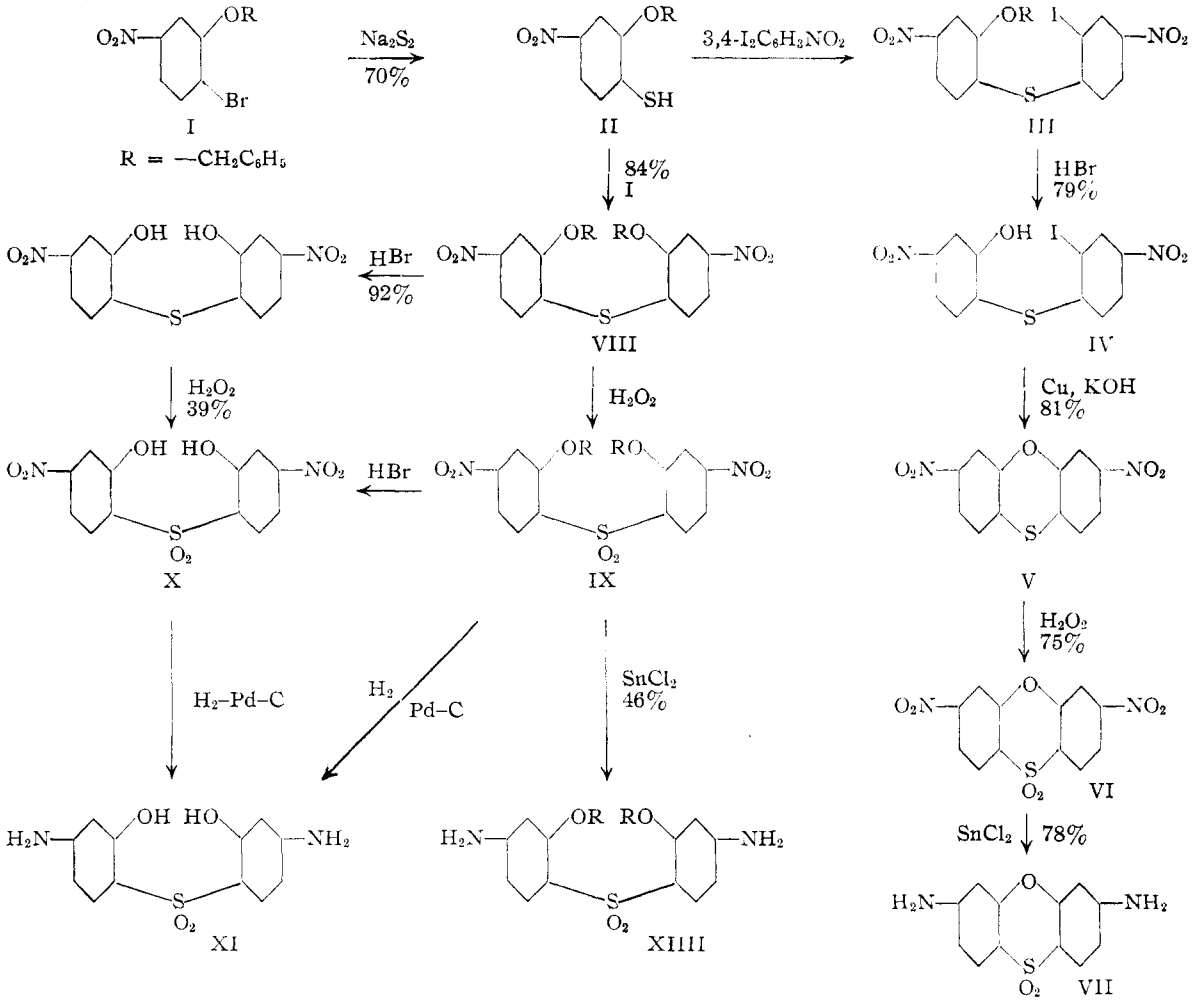
(1) Michels and Amstutz, THIS JOURNAL, **72**, 888 (1950).

(2) Suter, McKenzie and Maxwell, *ibid.*, **58**, 717 (1936).

(3) Powell and Adams, *ibid.*, **42**, 646 (1920).

(4) Price and Stacy, *ibid.*, **68**, 498 (1946).

REACTION DIAGRAM



While we were engaged in this work we considered it worthwhile to prepare bis-(2-hydroxy-4-aminophenyl) sulfone (XI) which, because of its unique relationship to both bis-(4-aminophenyl) sulfone and *p*-aminosalicylic acid should prove to be of considerable interest in the correlation of chemical structure with the chemotherapy of tubercular infections. The reaction diagram above also indicates the routes employed to this compound. Hydrogen peroxide in acetic acid was used throughout as the sulfide oxidant since chromic acid apparently disrupted the molecule affording lower yields of impure products. In all the stannous chloride reductions of nitrobenzyl ethers some debenzylation took place as evidenced by a yield lower than usual and by the odor of benzyl chloride. At higher temperatures (over 90°) the debenzylation was quite extensive. It is worthy of mention also that it was found possible in one step to reduce two nitro groups and split two benzyloxy groups on the diphenyl sulfone nucleus.

The author thanks Dr. J. F. Feeman for certain preliminary work and Mr. W. C. Thomas, Jr., for his assistance with several of the preparations and for four of the analyses.

Experimental

2-Benzyloxy-4-nitrobromobenzene (I).—A stirred suspension of 15.87 g. (0.073 mole) of 2-bromo-5-nitrophenol (m. p. 118–119°),[5] 9.2 g. (0.073 mole +) of benzyl chloride and 10.01 g. (0.073 mole) of anhydrous potassium carbonate in dry acetone was refluxed for seven and one-half hours and poured into cold water. The solid was triturated with dilute alkali, washed and recrystallized from alcohol. The fine colorless needles were obtained in 80.5% yield (4.82 g. of phenol recovered) and melted at 111.5–112.5°.

Anal. Calcd. for $C_{13}H_{10}O_3NBr$: Br, 25.95. Found: Br, 25.60, 25.80.

2-Benzyloxy-4-nitrothiophenol (II).—A solution of 10.64 g. (0.0346 mole) of 2-benzyloxy-4-nitrobromobenzene (I) in hot alcohol was treated with an alcoholic solution of 5.97 g. (0.0249 mole) of sodium sulfide nonahydrate and 0.8 g. of sulfur according to the procedure of Price and Stacey.[4] The bright yellow crystalline product, after dissolution in alkali and precipitation with acid sev-

(5) Henley and Turner, *J. Chem. Soc.*, 928 (1930), found m. p. 118.5–121°.

eral times, weighed 6.26 g. (70% yield) and melted at 103.2–105°. This material was the quality used in all preparative work even though it contained excess sulfur.

Anal. Calcd. for $C_{13}H_{11}O_3NS$: S, 12.27. Found: S, 13.41. After two recrystallizations from alcohol (95%) the yellow crystalline material melted at 100–103°. Found: S, 12.42.

Oxidation of an alkaline alcoholic solution of the mercaptan with an alcoholic solution of iodine yielded the yellow disulfide, which was purified by extraction with water and hot alcohol. It melted at 159–161°.

Anal. Calcd. for $C_{26}H_{20}O_6N_2S_2$: S, 12.30. Found: S, 12.35.

2-Benzyloxy-2′-iodo-4,4′-dinitrodiphenyl Sulfide (III).—A stirred suspension of 15.54 g. (0.0596 mole) of 3,4-diiodonitrobenzene (m. p. 110–111.5°)[6] and 8.3 g. (0.0596 mole) of anhydrous potassium carbonate in alcohol was refluxed for a period of six hours although the reaction appeared to be complete after about three hours. After cooling, the solid was removed, washed well with water and cold alcohol and dried. The crude light tan colored solid (28.25 g., 96% yield) melted at 132–136°. Recrystallization from glacial acetic acid or nitromethane reduced the yield slightly but raised the melting point to 136.2–138.2°.

Anal. Calcd. for $C_{19}H_{13}O_5N_2IS$: S, 6.31. Found: S, 6.36.

2-Hydroxy-2′-iodo-4,4′-dinitrodiphenyl Sulfide (IV).—The debenzylation was performed by refluxing a solution of 17.53 g. (0.0353 mole) of III and 9.7 ml. of 48% hydrobromic acid for four hours in sufficient glacial acetic acid to dissolve the reactants. After cooling, the solid was removed and washed with cold acetic acid and water. The yield of quite pure, slightly greenish-tan colored phenol was 10.55 g. (72%), melting at 226–228° (after recrystallization from acetic acid).

Anal. Calcd. for $C_{12}H_7O_5N_2IS$: S, 7.66. Found: S, 7.46.

2,8-Dinitrophenoxathiin (V).—The free phenol IV (10.55 g.) was converted to the potassium salt by precipitation with approximately 30% aqueous potassium hydroxide solution from a dilute aqueous solution. The dry, dark-red powder, which undoubtedly contained a small amount of free caustic, weighed 11.5 g. It (11.2 g.) was mixed with 0.7 g. of powdered copper and an approximately equal volume of clean, dry sand and sealed up, under nitrogen, in 12 mm. glass tubes. The tubes were heated in a stirred oil-bath at 175° for a total of two hours although the red color had faded to bright yellow almost completely in three quarters of an hour. The contents of the tubes were then removed and extracted in a Soxhlet with acetone until all colored material had been removed. Evaporation of the acetone extracts afforded a light-brown solid which was converted to 5.12 g. (81.7%) of bright yellow crystals (m. p. 204–205°) by trituration with warm concentrated hydrochloric acid.

Anal. Calcd. for $C_{12}H_6O_5N_2S$: S, 11.05. Found: S, 11.02.

2,8-Dinitrophenoxathiin-5-dioxide (VI).—A solution of 5 g. of 2,8-dinitrophenoxathiin in approximately 350 ml. of glacial acetic acid was refluxed for three and one-half hours in the presence of a considerable excess of 30% hydrogen peroxide. The product, obtained as an almost colorless powder, was removed after cooling and was washed with cold acetic acid and water. Drying afforded 4.16 g. (75%) of sulfone melting at 246–247° (block, uncor.). Dilution of the oxidation mother liquors with water produced an additional 0.91 g. of less pure material melting at 235–246°.

Anal. Calcd. for $C_{12}H_6O_7N_2S$: S, 9.95. Found: S, 9.87.

2,8-Diaminophenoxathiin-5-dioxide (VII).—To a solution of 5.94 g. (0.0264 mole) of stannous chloride dihydrate in a minimum amount of glacial acetic acid saturated with dry hydrogen chloride was added, at once, 1.01 g. (0.0033 mole) of 2,8-dinitrophenoxathiin-5-dioxide (VI). A slightly exothermic reaction set in and the solid soon dissolved. After three hours stirring and heating at 80° the suspension was cooled and filtered. The solid was dispersed in water and treated twice with a large excess of approximately 30% potassium hydroxide solution, washed well with water and dried over phosphorus pentoxide. The yield of crude white amine shrinking at 209–211° and completely melting at 224–225.5° was 0.8 g. All of the product (excepting small portions used in preliminary trials) was dissolved in hot dilute hydrochloric acid, filtered and saturated in the cold with dry hydrogen chloride. The hydrochloride salt was removed, converted to the free amine with aqueous bicarbonate, washed and dried. There was thus obtained 0.65 g. (78%) of fine white powder melting at 224–225.5° with slight softening at 210°.

Anal. Calcd. for $C_{12}H_{10}O_3N_2S$: N, 10.68; S, 12.22. Found: N, 10.42; S, 12.19.

The above amine (0.246 g.) was converted to the diacetyl derivative in 90% yield by refluxing with acetic anhydride (0.25 g.) in acetic acid. The derivative melted at 359–362° (block, uncor.).

Anal. Calcd. for $C_{12}H_{14}O_5N_2S$: N, 8:09. Found: N, 8.06.

Bis-(2-benzyloxy-4-nitrophenyl) Sulfide (VIII).—To a solution of 2.36 g. (0.00767 mole) of 2-benzyloxy-4-nitrobromobenzene and 2.0 g. (0.00767 mole) of 2-benzyloxy-4-nitrothiophenol in 95% ethanol was added 1.06 g. (0.00768 mole) of anhydrous potassium carbonate. After an eighteen and one-half-hour period of stirring and refluxing the mixture was cooled and filtered and the solid was washed thoroughly with water and dried. The fine bright yellow crystals weighed 3.15 g. (84.5%) and melted at 164.5–166°. A small sample recrystallized (from acetic acid) for analysis melted at 165.2–166°.

Anal. Calcd. for $C_{26}H_{20}O_6N_2S$: S, 6.65. Found: S, 6.42.

Bis-(2-hydroxy-4-nitrophenyl) Sulfide (XII).—A solution of 2.44 g. (0.005 mole) of bis-(2-benzyloxy-4-nitrophenyl) sulfide and 1.7 g. (0.01 mole) of 48% hydrobromic acid was refluxed in approximately the minimum amount of acetic acid for about nine hours. Most of the acetic acid was evaporated off and the residue was taken up in dilute alkali and extracted with ether. Acidification of the alkaline solution afforded over the theoretical yield of material melting at 241–246°. The debenzylation operation was therefore repeated with 0.5 ml. of hydrobromic acid affording 1.42 g. (92%) of bright yellow powder melting at 243.5–246.4°.

Anal. Calcd. for $C_{12}H_8O_6N_2S$: S, 10.40. Found: S, 10.20.

Bis-(2-benzyloxy-4-nitrophenyl) Sulfone (IX).—The oxidation of the sulfide VIII was carried out as before with 30% hydrogen peroxide in acetic acid. From 3.3 g. of sulfide there was obtained 3.25 g. (90%) of pale yellow sulfone melting at 259–264°. Recrystallization from acetic acid raised the melting point to 263–264.5°.

Anal. Calcd. for $C_{26}H_{20}O_8N_2S$: S, 6.12. Found: S, 6.27.

Bis-(2-hydroxy-4-nitrophenyl) Sulfone (X). A. From the Dibenzyl Ether, IX.—A solution of 3.25 g. (0.00625 mole) of IX and 2.5 g. of 48% hydrobromic acid in about 450 ml. of glacial acetic acid was refluxed for five hours after which most of the solvent was removed by distillation and the residue poured into water. The suspension was rendered alkaline and extracted with ether to remove the benzyl bromide after which acidification with hydrochloric acid in the cold and filtration afforded 1.46 g. of crude phenol X, melting at 200–212°. The material was retreated with hydrobromic acid in acetic acid to complete the splitting after which there was obtained 1.16 g. of material melting at 225–227°. By recrystallization from acetic acid this was raised to 233–235.5°.

(6) Brenans, *Bull. soc. chim.*, [3] **29**, 603 (1903), found m. p. 112.5°.

Anal. Calcd. for $C_{12}H_8O_8N_2S$: S, 9.42. Found: S, 9.22.

B. From the Phenolic Sulfide, XII.—The hydrogen peroxide oxidation in acetic acid of the sulfide XII was carried out by refluxing over a twelve-hour period. The lustrous light yellow needles which separated on cooling were removed, washed and dried after which they weighed 0.51 g. (39%) and melted at 233–237°. The melting point was not depressed by admixing with material obtained by procedure A. The mother liquor on dilution yielded 0.11 g. melting at 230–232°.

Bis-(2-hydroxy-4-aminophenyl) Sulfone (XI).—One gram of the benzyloxysulfone IX and 5 g. of 5% Pd–C catalyst were dispersed in about 200 ml. of hot acetic acid and shaken under 30 lb. of hydrogen pressure for one hour. The filtrate was distilled under 20 mm. pressure of nitrogen. The residue, which was rather dark and caramel-like, slowly crystallized. Two recrystallizations from water afforded about 100 mg. of well-shaped light tan-colored crystals, melting at 180–184°.

Anal. Calcd. for $C_{12}H_{12}O_4N_2S$: S, 11.43. Found: S, 11.25.

The tetraacetyl derivative, **bis-(2-acetoxy-4-acetoamidophenyl) sulfone**, was obtained in about 30% yield by the catalytic (Pd–C) reduction of 0.34 g. of X in acetic acid solution and immediate acetylation of the reduction product. The light salmon-colored powder was insoluble in cold dilute alkali and melted at 289–290.5°.

Anal. Calcd. for $C_{20}H_{20}O_8N_2S$: N, 6.24; S, 7.15. Found: N, 6.15; S, 7.03.

Bis-(2-benzyloxy-4-aminophenyl) Sulfone (XIII).—To a stirred solution of 3.52 g. (0.0156 mole) of stannous chloride dihydrate in 25 ml. of acetic acid clarified with hydrogen chloride was added 1.0 g. (0.00195 mole) of the dinitro sulfone, IX. By means of mild external heating the temperature was increased to 75° at which point the reaction mixture solidified. After cooling to room temperature the solid was removed and worked up in the usual way. Recrystallization from acetic acid afforded about 0.4 g. of almost colorless leaflets melting at 237–238.5°.

Anal. Calcd. for $C_{26}H_{24}O_4N_2S$: S, 6.96. Found: S, 6.72, 6.91.

It is suspected that the yield in this preparation was diminished by a partial splitting off of the benzyl groups since the odor of benzyl chloride was detected during the working up of the amine salt. In a larger run of the same type the reaction mixture was permitted to heat up to about 102° after the precipitate had formed. The solid then dissolved and failed to reappear, even upon concentrating the solution. In this run, which produced no pure product (and which was therefore discarded), the odor of benzyl chloride was pronounced and unmistakable.

Summary

A method has been devised for the synthesis, in good yield, of 2,8-diaminophenoxathiin-5-dioxide, which is the *o,o'*-oxygen bridged derivative of the potent antitubercular agent 4,4'-diaminodiphenyl sulfone. Also prepared for antitubercular testing was 2,2'-dihydroxy-4,4'-diaminodiphenyl sulfone, a compound having interesting structural similarities to both *p*-aminosalicylic acid and 4,4'-diaminodiphenyl sulfone.

BETHLEHEM, PENNA. RECEIVED FEBRUARY 9, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

The Action of Elementary Fluorine upon Organic Compounds. XIII. The Vapor Phase Fluorination of Trichloroethylene[1]

BY MURRAY HAUPTSCHEIN[2] AND LUCIUS A. BIGELOW

This paper is one of several[3] which deal with the direct fluorination of deactivated organic molecules, that is, molecules whose central structures either aliphatic or aromatic are electron deficient, due to the inductive effect of negative substituents such as fluorine and chlorine. Trichloroethylene has been chosen for the present study for two reasons, first because it is a simple deactivated molecule, most of whose halogen derivatives are already known, and second in order to compare the vapor phase fluorination of this molecule with the liquid phase fluorination of the same substance, which has been described in detail by Miller.[4]

The olefin was fluorinated over a close metal packing at molar reaction ratios (F_2:CHCl=CCl_2:N_2) of 2:1:8, 1:1:6, 1:1:15 and 1:1:15, and corresponding reaction zone temperatures of 71, 45 and 120°. The complex crude products after the removal of most of the hydrogen fluoride were washed, dried and carefully rectified. Altogether, seven distinct products were isolated, together with some polymeric material and fragments due to cleavage. The formation of these substances and their progressive conversion into one another may be illustrated conveniently by the scheme as shown.

Although this diagram indicates that the transition from the original compound to the final products presumably followed several alternative routes involving both addition and substitution, the experimental evidence shows that certain of these are highly favored. Actually under the less vigorous conditions (fluorination ratio 1:1), all the above compounds were isolated in considerable proportions except III and IV; while under the stronger conditions (ratio 2:1) I, V and VII were not isolated, but II, III and VI were formed in much larger amounts instead. Thus far it is indicated that I, V and VII should be considered as the immediate precursors of II or VI, VI and III, respectively, although not exclusively so. However, since I and V were formed in approxi-

(1) This paper has been constructed from portions of the Doctorate Thesis presented by Murray Hauptschein to Duke University in June, 1949.

(2) Allied Chemical and Dye Corporation Fellow, 1948–1949. Grateful acknowledgment is also made to the Duke University Research Council for financial support. Present address: The Research Institute, Temple University, Philadelphia, Pa.

(3) Preceding paper in this group, THIS JOURNAL, **68**, 2187 (1946).

(4) Miller, *ibid.*, **62**, 341 (1940).