solve F (7:3, v./v.), R_f 0.66 in ethyl acetate–Skellysolve F (1:4, v./v.).

3-Phenoxy-4′-methoxyflavylium Chloride.—A solution of salicylaldehyde (1.22 g.) and ω-phenoxy-4-methoxyacetophenone[8] (2.42 g.) in glacial acetic acid (5.0 ml.) was saturated with hydrogen chloride and kept overnight. Ether (50 ml.) was added. The oily product rapidly crystallized on scratching to a mass of orange needles, λ_{max} 462 mμ (3.5 g.).

The flavylium salt was characterized as its **ferrichloride.** This crystallized from glacial acetic acid as orange-red, glistening prisms, m.p. 165–167°.

Anal. Calcd. for $C_{22}H_{17}Cl_4FeO_3$: C, 50.1; H, 3.25. Found: C, 50.2; H, 3.39.

3-Carbophenoxy-2-(4-methoxyphenyl)benzofuran.—The above crude phenoxyflavylium chloride (2.0 g.) was dissolved in warm methanol (40 ml.) and treated with aqueous buffer, pH 5.8 (5.0 ml.) and 30% hydrogen peroxide (5.0 ml.). Decoloration occurred almost instantly and an oily precipitate separated. After 5 min. water was added, whereupon the oil solidified. Recrystallized from methanol, 3-carbophenoxy-2-(4-methoxyphenyl)benzofuran was obtained as long, colorless needles, m.p. 92°, λ_{max}^{EtOH} 319, 228 mμ.

Anal. Calcd. for $C_{22}H_{16}O_4$: C, 76.7; H, 4.68; 1 MeO–, 9.01. Found: C, 76.7; H, 4.78; MeO–, 8.97.

The carbophenoxy compound (4.0 g.) was heated on a steam bath with acetone (100 ml.) and 5% aqueous NaOH (50 ml.) for 15 min. Acidification of the solution with concentrated HCl (20 ml.) then precipitated a crystalline solid. Recrystallized from acetone–methanol, 3-carboxy-2-(4-methoxyphenyl)benzofuran was obtained as colorless needles (3.0 g.), λ_{max}^{EtOH} 311 and 224 mμ, m.p. 217°, undepressed on admixture with the previously described acid.

Anal. Found: C, 71.7; H, 3.55; MeO–, 11.7.

The methyl ester of the acid had m.p. and m.m.p. 81°.

3-Methoxy-4′-hydroxyflavylium Chloride.—Hydrogen chloride was passed into a solution of salicylaldehyde (1.5 g.) and ω-methoxy-4-hydroxyacetophenone (1.9 g.) in ethyl acetate (10 ml.) and ethanol (2.0 ml.) for 5 min. Red crystals rapidly separated from the reaction mixture. After 2 hr. the flavylium salt was collected (3.1 g.) and recrystallized from 5% aqueous hydrochloric acid. 3-Methoxy-4′-hydroxyflavylium chloride was obtained as red-brown, glistening needles with a green reflex, m.p. 135–137° dec.

3-Carbomethoxy-2-(4-hydroxyphenyl)benzofuran.—A solution of the above flavylium salt (2.0 g.) in methanol (40 ml.) and aqueous buffer, pH 5.8 (30 ml.), was treated with 30% hydrogen peroxide (4.0 ml.). Colorless crystals rapidly separated. After 5 min. water was added and the product was collected and recrystallized from methanol. 3-Carbomethoxy-2-(4-hydroxyphenyl)benzofuran was obtained as colorless, glistening needles, m.p. 187°, λ_{max}^{EtOH} 316 mμ (1.0 g.).

Anal. Calcd. for $C_{16}H_{12}O_4$: C, 71.6; H, 4.51; MeO–, 11.6. Found: C, 71.7; H, 4.62; MeO–, 11.5.

Acetylation of the product gave **3-carbomethoxy-2-(4-acetoxyphenyl)benzofuran** which crystallized from methanol as colorless, felted needles, m.p. 135°, λ_{max}^{EtOH} 303 and 224 mμ.

Anal. Calcd. for $C_{18}H_{14}O_5$: C, 69.7; H, 4.55. Found: C, 69.5; H, 4.59.

Methylation of the oxidation product gave the previously described 3-carbomethoxy-2-(4-methoxyphenyl)benzofuran, m.p. and m.m.p. 81°, λ_{max}^{EtOH} 314 and 227 mμ. This methyl ether methyl ester was also obtained by hydrogen peroxide oxidation of 3,4′-dimethoxyflavylium chloride. On alkaline hydrolysis the 3-carboxy-2-(4-methoxyphenyl)benzofuran, m.p. and m.m.p. 217°, was obtained.

Acknowledgment.—The author is indebted to Dr. R. Royer for his generous gift of 2-ethyl-3-anisoylbenzofuran and to L. M. White and Miss G. Secor for elemental analyses.

Furazan Oxides. IV. Extensions of the Scope of the Haloalkoxy Substitution Reaction[1a,b]

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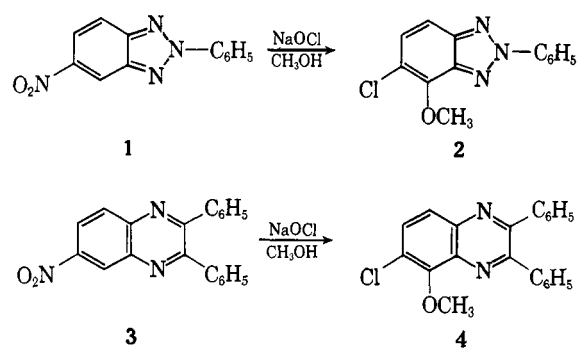
Additional examples are given of the recently described reaction in which an aromatic nitro group and an adjacent ring hydrogen are replaced by a halogen and an alkoxy group, respectively, by treatment of certain aromatic nitro compounds with aqueous sodium hypohalite in alkaline alcohol solution. Improved conditions are given for the reduction of benzofurazan oxides by copper and acid to give *o*-nitroanilines.

In a previous paper in this series[1a] a novel aromatic substitution reaction was described in which the overall result was the replacement of a nitro group by a chloro group and also the replacement of an adjacent ring hydrogen by a methoxy group as a consequence of the treatment of certain aromatic nitro compounds with aqueous sodium hypochlorite in alkaline methanol solution at about 50°. Since this reaction, which we designate as a haloalkoxy substitution reaction, is potentially useful as a means of synthesizing certain aromatic compounds that have several adjacent ring substituents and that are difficult to prepare by other methods, we have investigated the scope and generality of the reaction.

It was reported earlier[1a] that the reaction unfortunately was found not to occur with some of the more common aromatic nitro compounds such as *m*-dinitrobenzene. In the work done thus far, successful haloalkoxy substitution reactions have been achieved only with molecules having a nitrogen heterocycle fused to the ring bearing the replaceable nitro group as in the 4- and 5-nitrobenzofurazans and the corresponding N-oxides; the two new examples of nitro compounds that undergo haloalkoxy substitution that have been found in the present work, 5-nitro-2-phenylbenzotri-

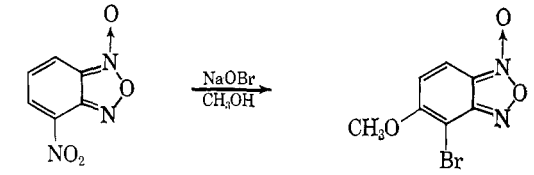


1 2 3 4

(1) (a) Part III: F. B. Mallory and S. P. Varimbi, *J. Org. Chem.*, **28**, 1656 (1963); (b) supported in part by the National Science Foundation through Grant No. GP 1186; (c) Alfred P. Sloan Research Fellow; (d) National Science Foundation Summer Undergraduate Research Program Participant, 1963.

azole (1) and 6-nitro-2,3-diphenylquinoxaline (3), both possess this same structural feature.

We have found that hypobromite can be used in place of hypochlorite in these reactions. Thus, 4-nitrobenzofurazan oxide (5) gives 4-bromo-5-methoxybenzofurazan oxide (6).[2] Also, 2,4-dinitroaniline gives 5-bromo-4-methoxybenzofurazan oxide (7), presumably by way of 5-nitrobenzofurazan oxide as an intermediate.[1a] Attempts to carry out analogous reactions using hypoiodite have not yet been successful.



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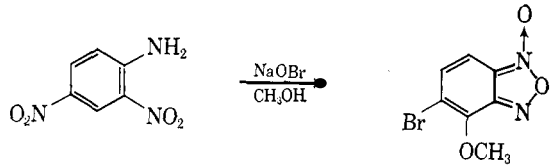

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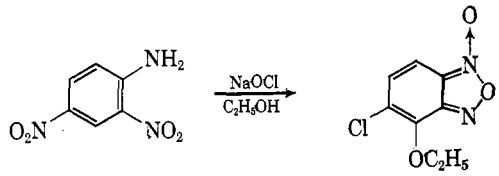
Some limited studies have been carried out using alcohols other than methanol. The reaction of 2,4-dinitroaniline with sodium hypochlorite in alkaline ethanol has been reported previously[4]; we have repeated this work and have shown that the product is 5-chloro-4-ethoxybenzofurazan oxide (8) rather than the 5-chloro-6-ethoxy isomer as proposed by the earlier workers. The reaction of 5 using isopropyl alcohol gave the



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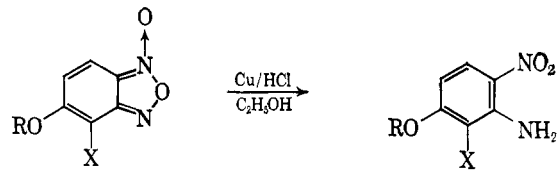
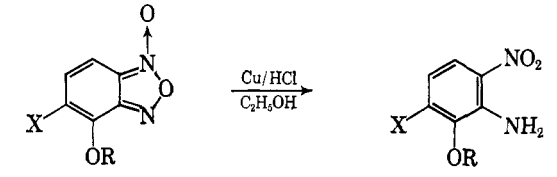
expected product, 4-chloro-5-isopropoxybenzofurazan oxide (9), but the yield was very low. We have thus far been unable to carry out a haloalkoxy substitution reaction successfully using *t*-butyl alcohol.

Although the haloalkoxy substitution reaction is clearly useful for the preparation of certain substituted heterocycles, the synthetic value of the reaction may be more widely appreciated as an approach to those highly substituted benzenes that are available from subsequent reactions of the haloalkoxybenzofurazan oxides. For example, benzofurazan oxides can be reduced to *o*-phenylenediamines by various strong reducing agents, and can be reduced to *o*-nitroanilines by copper metal in ethanol containing concentrated hydrochloric acid. Five of the possible eight copper–acid reduction reactions represented below have been carried out either in the present work or in previous work,[1a] and in all five cases the products had the indicated structures (11 or



10 11



12 13

X=Cl or Br; R=CH_3 or C_2H_5

13) rather than the structures with the positions of the amino and nitro groups reversed. Thus, it appears in general that compounds of type 11 can be obtained in three steps from benzofurazan oxide[5] (nitration[1a] to give 5, haloalkoxy substitution to give 10, and copper–acid reduction), and compounds of type 13 can be obtained in two steps from 2,4-dinitroaniline (haloalkoxy substitution to give 12, and copper–acid reduction).

This reduction of benzofurazan oxides to give *o*-nitroanilines as described originally[6] and employed previously[1a] involved heating the N-oxide in ethanol solution with 1.5 equiv. of copper powder, and subsequently treating the filtered reaction mixture with refluxing aqueous sodium hydroxide solution. We have found it advantageous to introduce certain modifications of this procedure. In the present work only 1.1–1.2 equiv. of copper was used since it was found that the nitroanilines produced in these reactions are subject to further reduction by copper under the reaction conditions. Light copper turnings, cut into short pieces, were found to be more convenient to handle than copper powder. The alkaline treatment originally specified was omitted since it is apparently unnecessary; the nitroanilines can be obtained by sublimation of the crude products that are precipitated by dilution of the reaction mixtures with saturated aqueous sodium chloride solution. Furthermore, the unwanted exchange of alkoxy groups that was observed[1a] when 4-chloro-5-methoxybenzofurazan oxide was reduced in ethanol solution by the original procedure to give 2-chloro-3-ethoxy-6-nitroaniline presumably occurred during the alkaline treatment; this same furazan oxide was reduced in ethanol solution using the new procedure without exchange of the methoxy group for an ethoxy group.

The structures of the benzofurazan oxides 6, 7, and 8 were established by methods analogous to those used previously.[1a] In each case, copper–acid reduction gave a nitroaniline (14, 15, or 16, respectively) that was deaminated by diazotization followed by treatment with hypophosphorous acid to give the known haloalkoxynitrobenzene with the halo and alkoxy groups *ortho* to each other. It was shown by proton n.m.r. spectroscopy that these two groups are at the 4- and 5-positions rather than the 5- and 6-positions in the furazan oxides 6, 7, and 8. Thus, the spectrum of each of these furazan oxides exhibited an AB quartet due to the two

(2) The specification throughout this paper of single structures for furazan oxides such as 5 and 6 is done for symbolistic simplicity only; for example, the so-called 4-nitrobenzofurazan oxide exists in solution as a mixture of 4- and 7-nitrobenzofurazan oxides undergoing rapid interconversion.[1a,3]

(3) F. B. Mallory and C. S. Wood, *J. Org. Chem.*, **27**, 4109 (1962).

(4) A. G. Green and F. M. Rowe, *J. Chem. Soc.*, **101**, 2452 (1912).

(5) F. B. Mallory, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p. 74.

(6) J. H. Boyer, R. F. Reinisch, M. J. Danzig, G. A. Stoner, and F. Sahhar, *J. Am. Chem. Soc.*, **77**, 5688 (1955).

TABLE I

Compd.	δ_A	δ_B	J, c.p.s.
2	7.38	7.25	8.9
6[a]	7.64	7.48	10.0
7	7.24	6.90	9.5
8	7.09	6.95	9.2
9	7.28	7.06	10.0
14	8.14	6.33	9.8
15	7.76	6.81	9.5
16	7.76	6.58	9.5
b	8.10	6.36	9.8

[a] Spectrum obtained in dimethyl sulfoxide solution since **6** was not sufficiently soluble in deuteriochloroform. [b] 2-Chloro-3-methoxy-6-nitroaniline.

ring protons with a coupling constant of 9.2–10.0 c.p.s. (see Table I); this value is typical for adjacent aromatic protons[1a,7] as are present in the 4,5-disubstituted structure, but is an order of magnitude greater than the value that is characteristic[7] for *para* aromatic protons as would be present in the alternative 5,6-disubstituted structure. In addition, the coupling constant for the ring protons in each of the corresponding nitroanilines **14**, **15**, and **16** was found to be 9.5–9.8 c.p.s.

The structure of 5-chloro-4-methoxy-2-phenylbenzotriazole (**2**) is assigned on the basis of elemental analyses, the method of synthesis, and infrared and proton n.m.r. spectra. The infrared spectrum of **2** was very similar to that of the starting material, 5-nitro-2-phenylbenzotriazole (**1**), in the 1350–1650-cm.$^{-1}$ region except for the absence of the two intense peaks associated with the nitro group stretching modes. The proton n.m.r. spectrum exhibited a sharp singlet at δ 4.43 with area corresponding to three protons attributed to the methoxy group, a complex multiplet of at least ten lines between δ 8.07 and 8.33 with area corresponding to two protons attributed possibly to the two protons *ortho* to nitrogen in the phenyl group, and a complex multiplet of at least ten lines between δ 7.13 and 7.58 with area corresponding to five protons attributed possibly to the three protons *meta* and *para* to nitrogen in the phenyl group and the two protons on the fused benzene ring. These latter two protons are believed to give rise to the AB quartet (see Table I) that is clearly discernible within the δ 7.13–7.58 multiplet.

Experimental[8]

5-Nitro-2-phenylbenzotriazole (**1**).[10]—A solution of 40.6 g. (0.2 mole) of 2,4-dinitrochlorobenzene and 21.6 g. (0.2 mole) of phenylhydrazine in 350 ml. of 95% ethanol was stirred magnetically and heated at reflux for 24 hr. The solvent was removed from the reaction mixture at reduced pressure. The dark residue was heated at reflux for 6 hr. with 50 ml. of glacial acetic acid. The reaction mixture was cooled and a gummy, dark red precipitate was collected. The crude material was digested with petroleum ether (b.p. 30–40°), the solvent was decanted and discarded, and the remaining solid was sublimed. Recrystallization of the sublimate from 2 l. of 95% ethanol gave 9.28 g. (19%) of 5-nitro-2-phenylbenzotriazole, m.p. 175.9–176.9° (lit.[11] m.p. 178°). A small sample was purified further by chromatography on alumina and recrystallization from benzene to give material melting at 176.6–177.0°.

Anal. Calcd. for $C_{12}H_8N_4O_2$: C, 60.00; H, 3.36; N, 23.32. Found: C, 60.21; H, 3.50; N, 23.39.

5-Chloro-4-methoxy-2-phenylbenzotriazole (**2**).—A mixture of 1.20 g. (0.005 mole) of 5-nitro-2-phenylbenzotriazole (**1**) in 150 ml. of methanol was stirred magnetically and heated at reflux for 15 min. after which time nearly all the material had dissolved. A solution of 1.32 g. (0.02 mole) of potassium hydroxide pellets in 15 ml. of methanol was added and then the addition of 150 ml. of aqueous sodium hypochlorite solution[12] was begun. After the first 10 ml. of the hypochlorite solution had been added, no material remained undissolved in the pale orange reaction mixture. The mixture was maintained at 60–65° during the addition, over 10 min., of the remainder of the hypochlorite solution and then for 5 min. more. The flask was cooled in ice and the white precipitate was collected by suction filtration and sublimed to give 1.00 g. (77%) of material that was recrystallized from 95% ethanol to give 0.90 g. (69%) of 5-chloro-4-methoxy-2-phenylbenzotriazole, m.p. 111.8–113.2°. A small sample of this material that was purified further by several recrystallizations from methanol melted at 113.0–114.0°.

Anal. Calcd. for $C_{13}H_{10}ClN_3O$: C, 60.13; H, 3.88; N, 16.18. Found: C, 60.24; H, 4.09; N, 16.23.

6-Nitro-2,3-diphenylquinoxaline (**3**).[10]—A solution prepared from 10.5 g. (0.05 mole) of benzil and 7.65 g. (0.05 mole) of 4-nitro-1,2-phenylenediamine in 225 ml. of 95% ethanol was stirred magnetically and heated at reflux for 24 hr. The reaction mixture was cooled in ice and the precipitate was collected by suction filtration. The crude product was sublimed and the sublimate was recrystallized from 2 l. of 95% ethanol to give 9.36 g. (57%) of 6-nitro-2,3-diphenylquinoxaline, m.p. 187.5–187.9° (lit.[13] m.p. 188°).

6-Chloro-5-methoxy-2,3-diphenylquinoxaline (**4**).—A solution of 1.64 g. (0.005 mole) of 6-nitro-2,3-diphenylquinoxaline (**3**) and 3.3 g. (0.05 mole) of potassium hydroxide pellets in 500 ml. of methanol was stirred magnetically and heated to 60°. The reaction mixture was maintained at 58–62° during the dropwise addition, over a 30-min. period, of 500 ml. of aqueous sodium hypochlorite[12] and then was maintained at 60° for 5 min. more. The mixture was cooled in ice and the precipitate that was collected by suction filtration amounted to 1.55 g. (90%) of material melting at 133.6–136.0°. This material was sublimed to free it from inorganic impurities and the sublimate was recrystallized from methanol to give 1.10 g. (64%) of 6-chloro-5-methoxy-2,3-diphenylquinoxaline, m.p. 135.8–137.0° (lit.[1a] m.p. 137.2–137.5°). Infrared spectral comparison and a mixture melting point determination showed this material to be identical with that obtained[1a] from the reaction of 4-chloro-3-methoxy-1,2-phenylenediamine with benzil.

4-Bromo-5-methoxybenzofurazan Oxide (**6**).—Aqueous sodium hypobromite was prepared by adding slowly 57.5 g. (0.36 mole) of bromine to an ice-cold, well-stirred solution of 36.0 g. (0.90 mole) of sodium hydroxide in 400 ml. of water.

A solution of 5.95 g. (0.09 mole) of potassium hydroxide pellets in 150 ml. of methanol in a three-necked flask was stirred magnetically and maintained at 47–50° during the simultaneous addition of the cold hypobromite solution prepared above and of a solution of 5.44 g. (0.03 mole) of 4-nitrobenzofurazan oxide (**5**)[1a] in 350 ml. of warm methanol. The rates of addition were regulated so that the addition time for each solution was 35 min. The reaction mixture was held at 48° for an additional 10 min. and was then cooled in ice. The flocculent yellow precipitate was collected by suction filtration to give 3.05 g. (42%) of 4-bromo-5-methoxybenzofurazan oxide, m.p. 156.4–157.6°. A small sample was recrystallized three times from 95% ethanol and finally sublimed to give material melting at 157.4–157.8°.

Anal. Calcd. for $C_7H_5BrN_2O_3$: C, 34.31; H, 2.06; Br, 32.61; N, 11.43. Found: C, 34.46; H, 2.14; Br, 32.72; N, 11.49.

2-Bromo-3-methoxy-6-nitroaniline (**14**).—To a magnetically stirred mixture of 1.00 g. (0.0041 mole) of 4-bromo-5-methoxybenzofurazan oxide (**6**) and 0.29 g. (0.0046 g.-atom) of copper turnings[14] in 25 ml. of methanol was added 0.85 ml. (0.0102 mole) of

(7) (a) H. S. Gutowsky, C. H. Holm, A. Saika, and G. A. Williams, *J. Am. Chem. Soc.*, **79**, 4596 (1957); (b) R. E. Richards and T. P. Schaefer, *Trans. Faraday Soc.*, **54**, 1280 (1958); (c) J. B. Leane and R. E. Richards, *ibid.*, **55**, 707 (1959).

(8) All melting points are corrected. Elemental analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Sublimations were carried out at a pressure of about 0.03 mm. using equipment described elsewhere.[9]

(9) F. B. Mallory, *J. Chem. Educ.*, **39**, 261 (1962).

(10) These reactions were carried out by Miss Ellen J. Halpern.

(11) C. Willgerodt and B. Hermann, *J. prakt. Chem.*, **40**, 252 (1889).

(12) The aqueous sodium hypochlorite solution used in this work was the commercial product Clorox.

(13) O. Hinsberg, *Ann.*, **292**, 245 (1896).

(14) The copper used in this work was Baker and Adamson light turnings cut into pieces about 5 mm. long.

concentrated hydrochloric acid. The reaction mixture was heated at reflux for 4 hr. by which time all the copper had dissolved. To the hot solution was added 50 ml. of saturated aqueous sodium chloride solution; the reaction mixture was then cooled in ice and the precipitate was collected by suction filtration. The crude product was sublimed and the sublimate was dissolved in a minimum volume of warm cyclohexane and chromatographed on alumina. After a small amount of the yellow starting material **6** was eluted with a 3:1 mixture of cyclohexane and benzene, the orange product was eluted with benzene and recrystallized from 95% ethanol to give 0.80 g. (79%) of 2-bromo-3-methoxy-6-nitroaniline, m.p. 127.4–128.0°. Further purification of the sample by recrystallization and sublimation did not change the melting point.

Anal. Calcd. for $C_7H_7BrN_2O_3$: C, 34.03; H, 2.85; N, 11.34. Found: C, 34.12; H, 2.87; N, 11.24.

The same procedure was followed for all the other copper–acid reductions described below.

2-Bromo-4-nitroanisole.—A solution of 0.49 g. (0.0020 mole) of 2-bromo-3-methoxy-6-nitroaniline (**14**) in 9.0 ml. of glacial acetic acid was added dropwise to a magnetically stirred solution of 0.16 g. (0.0023 mole) of sodium nitrite in 1.5 ml. of concentrated sulfuric acid maintained in an ice–salt bath. To the resulting solution was added 3.1 ml. (0.03 mole) of 50% aqueous hypophosphorous acid. The reaction mixture was stirred in the ice–salt bath for 1 hr. and then at room temperature for 22 hr. The solution was diluted with 40 ml. of water and cooled in ice. The precipitate was collected by suction filtration and washed first with 15 ml. of 20% aqueous sodium hydroxide solution and then with water. The crude product was sublimed and the sublimate was recrystallized from 95% ethanol to give 0.40 g. (86%) of 2-bromo-4-nitroanisole, m.p. 103.7–104.4°. This sample was recrystallized again from 95% ethanol and then from methanol–water to give material with m.p. 104.1–104.8° (lit.[15] m.p. 106°). This material was shown by infrared spectral comparison and a mixture melting point determination to be identical with an authentic sample of 2-bromo-4-nitroanisole that was prepared from 2-amino-4-nitroanisole by a Sandmeyer reaction.

The same deamination procedure was used in several other cases described below.

5-Bromo-4-methoxybenzofurazan Oxide (7).—A solution of 1.83 g. (0.01 mole) of 2,4-dinitroaniline and 2.0 g. (0.03 mole) of potassium hydroxide pellets in 90 ml. of methanol was stirred magnetically and heated to 50°. To this solution was added dropwise an aqueous solution of sodium hypobromite prepared by adding 16.0 g. (0.10 mole) of bromine to a cold solution of 10.0 g. (0.25 mole) of sodium hydroxide in 150 ml. of water. The addition was complete in 10 min. during which time the reaction temperature was maintained at 46–48°. The reaction mixture was kept at 48° for an additional 5 min. and was then cooled in ice. The yellow precipitate was collected by suction filtration, sublimed, and recrystallized from 95% ethanol to give 1.18 g. (48%) of crude 5-bromo-4-methoxybenzofurazan oxide melting at 86.0–95.2°. A small sample was purified by three more recrystallizations from 95% ethanol and finally by sublimation to give 5-bromo-4-methoxybenzofurazan oxide with m.p. 95.0–95.6°. This material was observed to undergo a change in crystalline form at 91.0° when heated slowly in a capillary tube.

Anal. Calcd. for $C_7H_5BrN_2O_3$: C, 34.31; H, 2.06; Br, 32.61; N, 11.43. Found: C, 34.40; H, 2.19; Br, 32.86; N, 11.29.

A small amount of an unidentified side product melting at 105.5–109.4° was separated from the crude 5-bromo-4-methoxybenzofurazan oxide by chromatography on alumina followed by two recrystallizations from 95% ethanol. This material survived copper–acid reduction and therefore does not appear to be a benzofurazan oxide. The same side product was also formed, along with **7** as the major product, when 5-nitrobenzofurazan oxide was used as the starting material in place of 2,4-dinitroaniline.

3-Bromo-2-methoxy-6-nitroaniline (15).—From 0.59 g. (0.0024 mole) of 5-bromo-4-methoxybenzofurazan oxide (**7**), 0.17 g. (0.0027 g.-atom) of copper turnings,[14] 10 ml. of methanol, and 0.50 ml. (0.0060 mole) of concentrated hydrochloric acid, there was obtained 0.35 g. (71% based on recovered starting material) of 3-bromo-2-methoxy-6-nitroaniline that was recrystallized from methanol–water to give 0.31 g. (63%) of material with m.p. 88.8–89.4°. A small sample that was recrystallized again from methanol–water and then sublimed melted at 88.9–89.4°.

Anal. Calcd. for $C_7H_7BrN_2O_3$: C, 34.03; H, 2.85; N, 11.34. Found: C, 34.12; H, 3.11; N, 11.58.

2-Bromo-5-nitroanisole.—From 0.49 g. (0.0020 mole) of 3-bromo-2-methoxy-6-nitroaniline (**15**), 5.5 ml. of glacial acetic acid, 0.17 g. (0.0025 mole) of sodium nitrite, 2.0 ml. of concentrated sulfuric acid, and 3.5 ml. (0.034 mole) of 50% aqueous hypophosphorous acid there was obtained 0.38 g. (82%) of 2-bromo-5-nitroanisole, m.p. 102.8–103.7° (lit.[16] m.p. 104°). This material was shown by infrared spectral comparison and a mixture melting point determination to be identical with an authentic sample of 2-bromo-5-nitroanisole, m.p. 102.6–103.6°, that was prepared from 2-amino-5-nitroanisole by a Sandmeyer reaction.

5-Chloro-4-ethoxybenzofurazan Oxide (8).[10]—In a typical preparation 500 ml. of an aqueous solution of sodium hypochlorite[12] was added over a period of 12 min. to the deep red solution prepared from 3.66 g. (0.02 mole) of 2,4-dinitroaniline and 4.0 g. (0.06 mole) of potassium hydroxide pellets in 200 ml. of 95% ethanol and maintained at 42–44°. The reaction mixture was cooled in ice and the ethanol was removed at reduced pressure. The aqueous mixture was then refrigerated for 2 days before a gummy yellow solid was collected by suction filtration. This crude solid was dissolved in a 1:1 mixture of cyclohexane and benzene and chromatographed on alumina using the same solvent mixture as the eluent. The eluate was evaporated to dryness at reduced pressure and the residue was recrystallized from 60–70° ligroin, sublimed, and recrystallized once more to give 0.90 g. (21%) of 5-chloro-4-ethoxybenzofurazan oxide, m.p. 51.8–53.0° (lit.[4] m.p. 55°).

3-Chloro-2-ethoxy-6-nitroaniline (16).—From 1.07 g. (0.005 mole) of 5-chloro-4-ethoxybenzofurazan oxide (**8**), 0.38 g. (0.006 g.-atom) of copper turnings,[14] 20 ml. of 95% ethanol, and 1.0 ml. (0.012 mole) of concentrated hydrochloric acid there was obtained after recrystallization from cyclohexane 0.65 g. (60%) of 3-chloro-2-ethoxy-6-nitroaniline, m.p. 98.8–99.2°. A small sample that was recrystallized again from cyclohexane melted at 98.9–99.4°.

Anal. Calcd. for $C_8H_9ClN_2O_3$: C, 44.36; H, 4.19; N, 12.93. Found: C, 44.37; H, 4.23; N, 12.78.

2-Chloro-5-nitrophenetole.—From 0.43 g. (0.0020 mole) of 3-chloro-2-ethoxy-6-nitroaniline (**16**), 5.5 ml. of glacial acetic acid, 0.17 g. (0.0025 mole) of sodium nitrite, 2.0 ml. of concentrated sulfuric acid, and 3.5 ml. (0.034 mole) of 50% aqueous hypophosphorous acid there was obtained 0.21 g. (52%) of 2-chloro-5-nitrophenetole, m.p. 63.1–64.4° (lit.[17] m.p. 64.5°).

4-Chloro-5-isopropoxybenzofurazan Oxide (9).—A solution of 1.0 g. (0.015 mole) of potassium hydroxide pellets in 25 ml. of isopropyl alcohol was stirred magnetically and maintained at 48–52° during the simultaneous addition over a period of 12 min. of 150 ml. of aqueous sodium hypochlorite solution[12] and of a solution of 0.91 g. (0.005 mole) of 4-nitrobenzofurazan oxide (**5**)[1a] in 100 ml. of hot isopropyl alcohol. The reaction mixture was maintained at 50° for an additional 8 min. and was then concentrated to about 200 ml. at reduced pressure. The solution was refrigerated overnight and then filtered to give 0.13 g. (11%) of yellow solid. This material was recrystallized several times from 95% ethanol and finally sublimed to give 4-chloro-5-isopropoxybenzofurazan oxide melting at 99.6–100.1°.

Anal. Calcd. for $C_9H_9ClN_2O_3$: C, 47.28; H, 3.97; N, 12.25. Found: C, 47.14; H, 4.02; N, 12.50.

The n.m.r. spectrum showed an AB quartet attributed to the ring protons (see Table I), a seven-line multiplet attributed to the single proton α to the ether oxygen centered at δ 4.72 with a coupling constant of 6.2 c.p.s., and a doublet attributed to the two methyl groups centered at δ 1.42 with a coupling constant of 6.2 c.p.s.

2-Chloro-3-methoxy-6-nitroaniline.—From 1.00 g. (0.005 mole) of 4-chloro-5-methoxybenzofurazan oxide,[1a] 0.38 g. (0.006 g.-atom) of copper turnings,[14] 25 ml. of 95% ethanol, and 1.0 ml. (0.012 mole) of concentrated hydrochloric acid there was obtained on sublimation 0.81 g. (80%) of 2-chloro-3-methoxy-6-nitroaniline that melted at 126.5–127.5° after undergoing some change in appearance at 123.5°. This material was chromatographed on alumina using a 1:1 mixture of cyclohexane and benzene as the eluent. The solvent was evaporated from the

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(16) W. E. Hanford and R. Adams, *J. Am. Chem. Soc.*, **57**, 1592 (1935).

(17) H. van Erp, *J. prakt. Chem.*, **127**, 20 (1930).

eluate at reduced pressure and the residue was recrystallized three times from 95% ethanol to give material with a constant m.p. of 123.7–124.4°. After sublimation, this material melted at 127.0–128.0° with a change in appearance at 123.8°; recrystallization of this sublimate from 95% ethanol gave material melting at 123.8–124.4°.

Anal. Calcd. for $C_7H_7ClN_2O_3$: C, 41.50; H, 3.48; N, 13.83. Found: C, 41.43; H, 3.49; N, 14.05.

2-Chloro-4-nitroanisole.—From 0.40 g. (0.0020 mole) of 2-chloro-3-methoxy-6-nitroaniline, 8 ml. of glacial acetic acid, 0.17 g. (0.0025 mole) of sodium nitrite, 1.5 ml. of concentrated sulfuric acid, and 2.5 ml. (0.024 mole) of 50% aqueous hypophosphorous acid there was obtained 0.27 g. (73%) of 2-chloro-4-nitroanisole, m.p. 93.8–94.6° (lit.[18] m.p. 95°). This material was shown by infrared spectral comparison and a mixture melting point determination to be identical with an authentic sample of 2-chloro-4-nitroanisole, m.p. 93.6–94.9°, that was prepared[19] by methylation of 2-chloro-4-nitrophenol.

Proton N.m.r. Spectra.—Proton n.m.r. spectra were obtained at 60 Mc. in deoxygenated deuteriochloroform solution (except where noted) with tetramethylsilane as an internal standard using a Varian Associates A-60 spectrometer. The spectrum of each of the compounds exhibited an AB quartet attributed to the two aromatic protons that were present in each case; the chemical shifts in parts per million downfield from tetramethylsilane and the coupling constants in cycles per second for these aromatic protons are given in Table I.

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(19) This preparation was carried out by Dr. Suzanne P. Varimbi.

Substitution of the Exocyclic Secondary Hydroxyl Group by an Amino Group in a D-Glucofuranose Structure[1]

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A route to the synthesis of 5-amino-5-deoxy derivatives of D-glucose is provided by double inversion at the exocyclic asymmetric carbon atom, C-5, in a D-glucofuranose structure. Both inversions involve nucleophilic displacement on carbon atom C-5.

3-*O*-Benzyl-1,2-*O*-isopropylidene-5-*O*-tolylsulfonyl-6-*O*-triphenylmethyl-α-D-glucofuranose[2] can be converted, by selective hydrolysis and subsequent acetylation, to crystalline 6-*O*-acetyl-3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose in a yield of 56%. Exposure of this acetyl derivative to base gives 5,6-anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-idofuranose (I). Reaction of I with sodium benzoxide produces 3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-β-L-idofuranose (II), which on tosylation gives 3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-β-L-idofuranose (III). Hydrazinolysis of the latter compound affords 3,6-di-*O*-benzyl-5-deoxy-5-hydrazino-1,2-*O*-isopropylidene-α-D-glucofuranose (IV) and this on catalytic hydrogenolysis produces crystalline 5-amino-5-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (V).

N-Acetylation, followed by mild methanolysis of V, similar to conditions employed by Jones and Szarek,[3] gives a product suggested to be methyl 5-acetamido-5-deoxy-α,β-D-glucoside. Since formic acid is not detected when the N-acetylated D-glucosides are subjected to periodate oxidation, it is concluded that a piperidine sugar derivative is not present.

Experimental conditions would suggest that the uncharacterized product is probably 5-acetamido-5-deoxy-α,β-D-glucofuranoside (VI).

Experimental

Analytical Methods.—Chromatographic identification of sugar derivatives was made at 25° on Whatman No. 1 filter paper, developed in irrigants (A) 1-butanol–ethanol–water (40:11:19, v./v.) or (B) ethyl acetate–pyridine–water (10:4:3, v./v.). Spray indicators employed were (C) potassium permanganate–periodate and (D) iodine vapor. Purity of crystalline products were determined by thin layer chromatography on 25 × 75 mm. silica gel G[4] coated microscope slides irrigated with (G) 1-butanol saturated with water or (H) chloroform–acetone (1:1, v./v.). Plates were sprayed with a dilute ethanolic solution containing 5% sulfuric acid and charred at 110° until permanent spots were visible. A calibrated Fisher-Johns apparatus was used for melting point determinations. Evaporations were done at reduced pressure.

6-*O*-Acetyl-3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose.—Ninety grams of 3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-6-*O*-triphenylmethyl-α-D-glucofuranose[2] were dissolved in 800 ml. of an ice-cold solution of anhydrous acetone which contained 36 g. of dry hydrogen chloride per liter. This mixture was kept for 10 min. at 0°, then for an additional 1.5 hr. at 20° and slowly neutralized with solid sodium bicarbonate. On filtration and concentration, a colorless sirup was obtained. The product was dissolved in 100 ml. of chloroform and the organic extract was washed with two 25-ml. portions of water, dried over anhydrous magnesium sulfate, filtered, and evaporated to a sirup. Acetylation of this material in a mixture of pyridine and acetic anhydride gave a product which crystallized from a mixture of benzene and petroleum ether (b.p. 40–60°) and which was identified as 6-*O*-acetyl-3-*O*-benzyl-1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-glucofuranose; yield 36 g. (the yield from the 6-*O*-trityl derivative was 56%), m.p. 132°, $[\alpha]^{25}D$ −4.8° (c 2.1, chloroform).

Anal. Calcd. for $C_{25}H_{30}O_9S$ (506.49): C, 59.28; H, 5.97; S, 6.33. Found: C, 59.54; H, 6.04; S, 6.24.

5,6-Anhydro-3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-idofuranose (I).—A 30-g. portion of the acetyl derivative described above was dissolved in 60 ml. of alcohol-free chloroform. The mixture was cooled to 15° and 30 ml. of absolute methanol containing 3 g. (2.3 mole) of sodium were added. The solution was stirred for 2 hr. at −15° and then for an additional 12 hr. at 0°. After the addition of a saturated solution of potassium bicarbonate, the mixture was evaporated at 5° to remove methanol. The residue was extracted four times with 60-ml. portions of chloroform and the latter extracts were combined, washed with water, dried over anhydrous magnesium sulfate, and evaporated to

(1) Journal Paper No. 2306 of the Purdue University Agricultural Experiment Station.

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