Acknowledgment.—The authors are grateful to members of Spectroscopy Investigations of this Laboratory for many of the infrared spectra, to Dr. Robert Barker and Gordon J. Boudreaux for the nmr spectra, and to Mrs. Ann Alford for the molecular weights.

Application of the Haloalkoxy Reaction to 6-Nitroanthroxanic Acid[1a]

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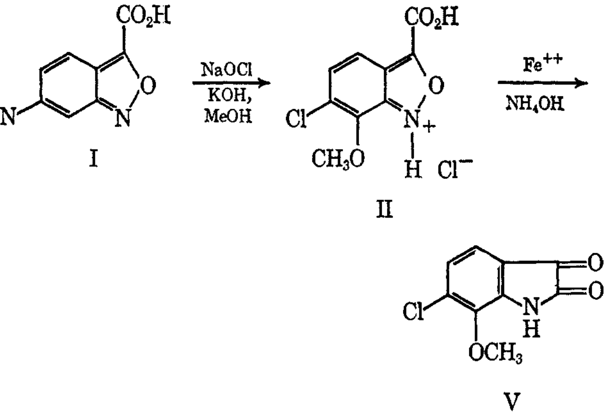
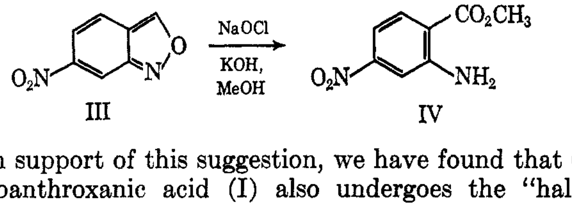
Received November 10, 1965

In a series of papers Mallory[2] and co-workers investigated a novel conversion, called the "haloalkoxy substitution reaction," in which the replacement of a nitro group by a chlorine and of an adjacent ring hydrogen by a methoxy group is effected by treatment of certain aromatic nitro compounds with aqueous sodium hypochlorite in alkaline methanol solution. Mallory demonstrated that this reaction takes place with nitro-substituted benzofurazans and their corresponding N-oxides, with 5-nitro-2-phenylbenzotriazole, and with 6-nitro-2,3-diphenylquinoxaline, and he suggested that the reaction may be general for molecules having a nitrogen heterocycle fused to the ring bearing the replaceable nitro group.





In support of this suggestion, we have found that 6-nitroanthroxanic acid (I) also undergoes the "haloalkoxy substitution reaction." Compound I is converted under the conditions described by Mallory to 6-chloro-7-methoxyanthroxanic acid hydrochloride (II). The structure of II was confirmed by its nmr spectrum, which exhibited two doublets of an AB system due to the two adjacent ring protons ($J = 9.0$ cps). Attempts to carry out an analogous conversion on 6-nitroanthranil (III) were unsuccessful because III is easily ring opened under the basic reaction conditions to methyl 4-nitroanthranilate (IV).

Since anthroxanic acids are easily converted to isatins by reductive cleavage of the isoxazole ring,[3] the "haloalkoxy substitution reaction" applied to nitro-substituted anthroxanic acids is potentially useful as a means of synthesizing certain isatins with adjacent ring substituents. Illustrative of this synthetic potential is the conversion of II to 6-chloro-7-methoxyisatin (V) with ferrous sulfate and ammonia.

Experimental Section[4]

The preparations of 6-nitroanthroxanic acid and 6-nitroanthranil have been described in a previous paper.[5]

6-Chloro-7-methoxyanthroxanic Acid Hydrochloride (II).—A solution of 0.5 g (0.0024 mole) of 6-nitroanthroxanic acid (I) and 0.8 g of potassium hydroxide (0.014 mole) in 50 ml of methanol was stirred magnetically and heated at reflux during the dropwise addition of 65 ml of aqueous sodium hypochlorite solution.[6] The solution was maintained at 60–65° during the addition, over 15 min, of the hypochlorite solution and for 20 min more, after which time most of the methanol was removed at aspirator pressure on a rotating flash evaporator. The flask was cooled in ice and acidified with 2 *N* hydrochloric acid. The yellow crystals of II were collected by filtration and washed with ice-cold water to give 0.25 g (40%): mp 182°; $\lambda_{\max}^{\mathrm{EtOH}}$ 229 mμ (ϵ 26,900); $\nu_{\max}$ 3535, 3450, 1690, 1637, 1546, 1520, 1275, 800, and 780 cm^{-1}.

Anal. Calcd for $C_9H_7N_4Cl \cdot HCl$: C, 40.91; H, 2.67; N, 5.31. Found: C, 40.61; H, 2.36; N, 5.11.

6-Chloro-7-methoxyisatin (V).—To a solution containing 5 ml of water and 1.5 ml of concentrated ammonium hydroxide was added 0.15 g of 6-chloro-7-methoxyanthroxanic acid hydrochloride (II) followed by 1.0 g of $FeSO_4 \cdot 7H_2O$. The solution was allowed to stand at room temperature for 30 min, after which time 20 ml of water was added. The mixture was shaken and filtered, and the filtrate was acidified with 15 ml of 2 *N* hydrochloric acid. The orange crystals of V which separated on standing were collected by filtration to give 0.09 g (74%): mp 179°; $\lambda_{\max}^{\mathrm{EtOH}}$ in mμ (ϵ) 216 (21,600), 248 (17,000), 255 (15,200), 311 (6100); $\nu_{\max}$ 3225, 1770, 1736, 1615, 1325, 1275, 1040, and 760 cm^{-1}.

Anal. Calcd for $C_9H_6NO_3Cl$: C, 51.09; H, 2.86; N, 6.62; Cl, 16.75. Found: C, 50.92; H, 3.00; N, 6.67; Cl, 17.03.

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(1) (a) This work was supported in part by a grant (CA-02551) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service. (b) National Institutes of Health Predoctoral Fellow, 1962–1965.

(2) Part IV: F. B. Mallory, C. S. Wood, and B. M. Hurwitz, *J. Org. Chem.*, **29**, 2605 (1964).

(3) A procedure for reducing anthroxanic acid to isatin was described by A. Reissert, *Ber.*, **41**, 3921 (1908).

(4) All melting points are corrected.

(5) D. R. Eckroth, T. G. Cochran, and E. C. Taylor, in press.

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

Protonolysis of 2-Isopropoxy-2-methyl-1-methylenecyclopropane. A Stable Unsaturated Carbonium Ion

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Received November 1, 1965

The study of carbonium ion structures was greatly facilitated by the discovery that nmr data can be obtained quickly and simply for solutions in strong acids.[2] Ions studied in this way are usually produced by protonation of a double bond or by protonolysis of a hy-

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(2) *Cf.* N. C. Deno, *Chem. Eng. News*, **42**, 88 (1964).