110°, 0.07 mm.) gave 266 mg. of pure product. $\bar{\nu}$ in cm.$^{-1}$ (film): 1790 (lactone), 1740 (C=O, ester).

Anal. Calcd. for $C_{12}H_{18}O_5$: C, 59.47; H, 7.48. Found: C, 58.95; H, 7.40.

Action of Zinc and Acetic Acid on the Bromination Product of 3-(4,4-Dimethyl-2,6-dioxocyclohexyl)levulinic Acid (II).—A mixture of 276 mg. (0.830 mmole) of II and 425 mg. of zinc dust in 10 ml. of glacial acetic acid was stirred for 1.5 hr. at 80°. After filtration, 25 ml. of water was added to the filtrate, and the mixture was extracted with ether (3 × 25 ml.). The combined ether extracts were washed with water (3 × 25 ml.) and then extracted with 5% sodium bicarbonate solution (3 × 25 ml.). The ethereal layer, after drying with magnesium sulfate, was evaporated to dryness and gave 16 mg. (8.2%) of X, m.p. 167°. $\bar{\nu}$ in cm.$^{-1}$ (potassium bromide): 1805 (enol lactone), 1645 (α,β-unsaturated ketone). This product was identical with X prepared by a different method.[4] The bicarbonate extracts were acidified with concentrated hydrochloric acid and extracted with ether (3 × 25 ml.). The combined ether extracts after the usual processing gave 101 mg. (52.0%) of 2,6,6-trimethyl-3-carboxymethyl-4-oxo-4,5,6,7-tetrahydrobenzofuran (XI) (m.p. 125°), which was identical with the product previously prepared by a different procedure.[4]

Hydrogenolysis of the Bromination Product of 3-(4,4-Dimethyl-2,6-dioxocyclohexyl)levulinic Acid (II).—A mixture of 666 mg. (2.00 mmoles) of II, 100 mg. of magnesium oxide, and 150 mg. of 5% palladium-on-charcoal catalyst in 200 ml. of absolute ethanol was hydrogenated at an initial pressure of 60 p.s.i. until the theoretical amount of hydrogen had been absorbed. After filtration, the reaction mixture was concentrated *in vacuo* to 10 ml., and the white solid (X), which precipitated from solution, was collected by filtration; the yield of X was 321 mg. (68.2%), m.p. 167°. $\bar{\nu}$ in cm.$^{-1}$ (potassium bromide): 1805 (enol lactone), 1645 (α,β-unsaturated ketone). This product was identical in all respects with compound X prepared by a different procedure.[4]

The Lactone of 3-Acetyl-3-(4,4-dimethyl-2,6-dioxo-1-hydroxycyclohexyl)propionic Acid (XII).—A solution of 333 mg. (1.00 mmole) the bromination product of 3-(4,4-dimethyl-2,6-dioxocyclohexyl)levulinic acid (II) and 50 mg. of magnesium oxide in 100 ml. in 95% ethanol was stirred for 2.5 hr. and allowed to stand overnight. The solution was filtered to remove excess magnesium oxide. The filtrate was concentrated to 50 ml. *in vacuo*, chilled, and the white solid product which precipitated was removed by filtration; yield, 167 mg. (66.2%), m.p. 212°. Sublimation from an oil bath at 130° (0.1 mm.) gave the analytical material, m.p. 210°. $\bar{\nu}$ in cm.$^{-1}$ (potassium bromide): 1790 (lactone), 1745 and 1720 (C=O).

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 62.05; H, 6.58.

Furazan Oxides. III. An Unusual Type of Aromatic Substitution Reaction[1,2]

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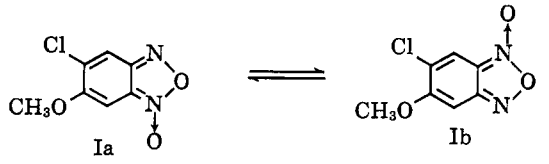
Treatment of either 2,4- or 2,3-dinitroaniline in alkaline methanol solution at 50° with aqueous sodium hypochlorite gives rise to an unusual substitution reaction which proceeds by way of the corresponding nitrobenzofurazan oxide as an intermediate. The product in each case is a chloromethoxybenzofurazan oxide in which the nitro group in the nitrobenzofurazan oxide intermediate has been replaced by a chloro group and an adjacent ring hydrogen in this intermediate has been replaced by a methoxy group. An analogous reaction takes place with each of the two nitrobenzofurazans. The structures of the chloromethoxy products were proved by spectral and chemical means. A mechanism for this reaction is suggested.

In 1912 Green and Rowe reported[4] that 2,4-dinitroaniline underwent an unexpectedly complex reaction when it was treated in alkaline methanol solution at 50° with aqueous sodium hypochlorite. Such treatment constitutes a well known method for the preparation of benzofurazan oxides from *o*-nitroanilines; however, the product from 2,4-dinitroaniline was found not to be the corresponding nitrobenzofurazan oxide but rather a chloromethoxybenzofurazan oxide. The chloro and methoxy groups were formulated by Green and Rowe as having the positions relative to the heterocycle which are indicated in structure I,[5] although the structural evidence consisted only in satisfactory analyses for N, Cl, and CH_3O and also the observations



that the compound underwent several reactions typical of furazan oxides.

The use of ethanol in place of methanol in hypochlorite oxidation of 2,4-dinitroaniline was found[4] to give a chloroethoxybenzofurazan oxide whose structure was formulated on similar grounds to be analogous to I.

There appears to be only one other mention in the literature of this unusual type of substitution reaction in which an aromatic nitro group and a ring hydrogen are replaced by chloro and alkoxy groups; in 1958 Dyall and Pausacker reported[6] that treatment of 2,3-dinitroaniline in alkaline ethanol with aqueous sodium hypochlorite gave a product which they formulated solely on the basis of analyses for C, H, and Cl as X-chloro-4-ethoxybenzofurazan oxide.

We have reinvestigated these reactions and have found that in each case the structure which previously was assigned[4,6] to the product is incorrect. Thus, we have established that the product from 2,4-dinitroaniline in methanol has structure II and the product from 2,3-dinitroaniline in methanol has structure III. It is suggested that in substituted benzofurazan oxides of this sort steric compression of the exocyclic oxygen and the adjacent substituent on the six-membered ring may destabilize significantly the configurations such as IIa and IIIa so that the equilibrium mixture would contain predominantly the configurations such as IIb and

(1) Part II: F. B. Mallory and C. S. Wood, *J. Org. Chem.*, **27**, 4109 (1962).

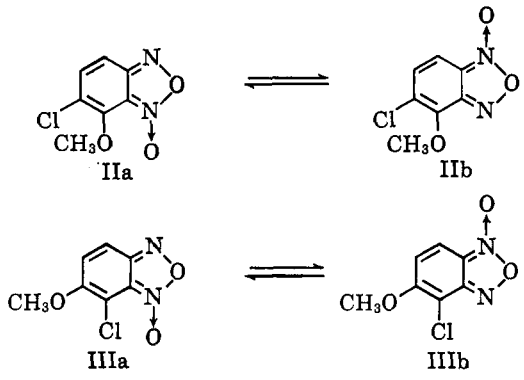
(2) Presented before the Organic Division at the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

(3) National Science Foundation Cooperative Graduate Fellow, 1960–1961.

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

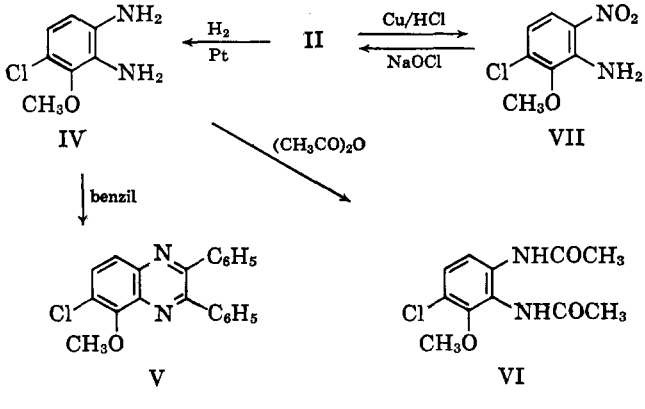
(5) The furazan oxide structure for molecules in this family and the Ia ⇌ Ib type of equilibration by way of *o*-dinitrosobenzenes have been demonstrated by recent work. (See ref. 1 for pertinent references.)

(6) L. K. Dyall and K. H. Pausacker, *Australian J. Chem.*, **11**, 491 (1958).



IIIb in which such steric strain would not be so severe. Thus, to simplify the nomenclature in the present work these two products will be designated as 5-chloro-4-methoxybenzofurazan oxide (IIb) and 4-chloro-5-methoxybenzofurazan oxide (IIIb), respectively.

The proof that the product melting at 80.6–82.0°, which was obtained from the reaction first described by Green and Rowe, has structure II is based on both spectral and chemical evidence. Thus, this product was shown to be a furazan oxide by the characteristic peaks in the 6–7-μ region in its infrared spectrum and also by catalytic hydrogenation to give a compound with properties of an *o*-phenylenediamine; this diamine, which is formulated as 4-chloro-3-methoxy-1,2-phenylenediamine (IV), was characterized by its conversion to a quinoxaline derivative (V) by treatment with benzil and also by its conversion to a diacetyl derivative (VI). Both V and VI gave analyses for C, H, Cl, N, and CH_3O in excellent agreement with the expected values. Further evidence that II is a furazan oxide was obtained by its reduction with copper powder in ethanol containing concentrated hydrochloric acid to give a compound shown by its infrared spectrum and elemental analyses to be a nitroaniline which was formulated as 3-chloro-2-methoxy-6-nitroaniline (VII); this type of reduction is characteristic of benzofurazan oxides.[7] Finally, hypochlorite oxidation of this presumed *o*-nitroaniline VII regenerated II.

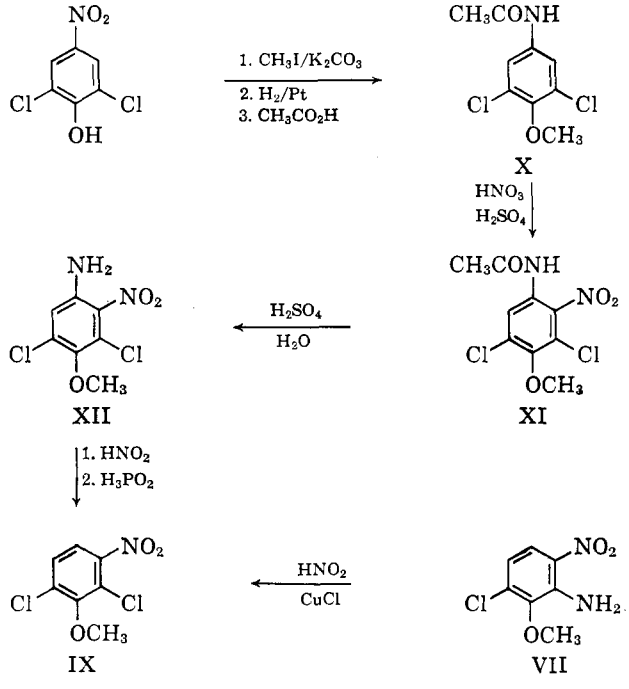


Deamination of VII by diazotization and subsequent treatment with hypophosphorous acid gave 2-chloro-5-nitroanisole (VIII); the identity of VIII was established by comparison with an authentic sample of this known compound which had been synthesized from commercially available 2-amino-5-nitroanisole by a Sandmeyer reaction.

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

All of the structural evidence given thus far is consistent with the formulation of the furazan oxide as II and the nitroaniline derived from II as VII but it would also be consistent with the formulation of the furazan oxide as I and the nitroaniline as 5-chloro-4-methoxy-2-nitroaniline. These two possibilities were distinguished by the proton n.m.r. spectrum of the furazan oxide which showed the resonance pattern for the ring protons to be that of an AB system with a coupling constant of 9.5 c.p.s. This value is typical[8] for adjacent aromatic protons regardless of other neighboring substituents and is an order of magnitude greater than the value that is characteristic[8] for *para* ring protons; thus, the validity of structure II as opposed to structure I for the furazan oxide is established.

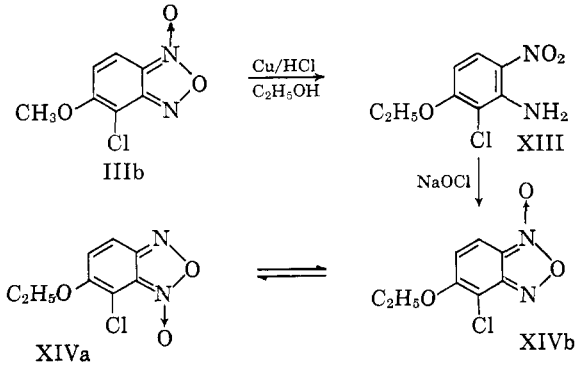
Further proof that structure II is correct was provided by chemical means. The nitroaniline VII was converted to 2,6-dichloro-3-nitroanisole (IX) by a Sandmeyer reaction. Several attempts at reduction of IX followed by diazotization and deamination to give 2,6-dichloroanisole failed to yield any useful product; therefore, the more lengthy process of independent synthesis of IX was carried out as is shown. Commercially available 2,6-dichloro-4-nitrophenol was methylated and the resulting 2,6-dichloro-4-nitroanisole was reduced and subsequently acetylated to give 4-acetamido-2,6-dichloroanisole (X). Mononitration of X gave 4-acetamido-2,6-dichloro-3-nitroanisole (XI) which was hydrolyzed to give 4-amino-2,6-dichloro-3-nitroanisole (XII); both XI and XII were found to have infrared spectra and elemental analyses in agreement with the assigned structures. Deamination of XII gave IX.



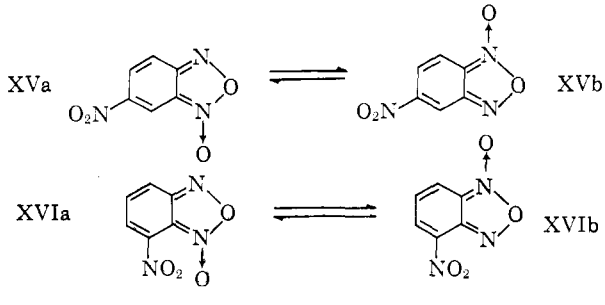
The structure of the furazan oxide, melting at 136.2–137.2° which was obtained from the hypochlorite oxidation of 2,3-dinitroaniline in methanol, was readily established to be III. The method of synthesis, the elemental analyses, and the characteristic peaks in the

(8) (a) H. S. Gutowsky, C. H. Holm, A. Saika, and G. A. Williams, *ibid.*, **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).

infrared spectrum of this product indicate that it is a chloromethoxybenzofurazan oxide. The proton n.m.r. spectrum of this compound exhibits an AB resonance pattern for the ring protons with a coupling constant of 9.5 c.p.s. which demonstrates that these two protons are on adjacent ring carbons.[8] Reduction of this furazan oxide with copper powder and hydrochloric acid in ethanol gave a product characterized by its infrared spectrum and elemental analyses as a nitroaniline and formulated as 2-chloro-3-ethoxy-6-nitroaniline (XIII); the exchange of the methoxy group for an ethoxy group under these reaction conditions presumably is due to the influence of the *para* nitro group in XIII. Deamination of XIII gave 2-chloro-4-nitrophenetole as shown by comparison with an authentic sample of this known compound which had been synthesized by ethylation of commercially available 2-chloro-4-nitrophenol. That XIII is an *o*-nitroaniline was shown by its conversion to a furazan oxide by hypochlorite oxidation; this compound is formulated as 4(7)-chloro-5(6)-ethoxybenzofurazan oxide (XIV) and agrees in melting point with the compound obtained[6] from the hypochlorite oxidation of 2,3-dinitroaniline in ethanol. The only structure for the furazan oxide, melting at 136.2–137.2°, which is in accord with all of these observations is III.

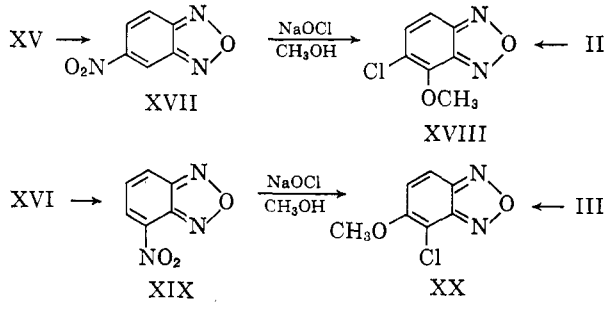


We have shown from two lines of evidence that the substitution reactions leading to II and III are not reactions characteristic of the dinitroanilines themselves, but rather proceed by way of the corresponding nitrobenzofurazan oxides which are presumed to be formed by hypochlorite oxidation of the dinitroanilines under the reaction conditions. Thus, 5(6)-nitrobenzofurazan oxide (XV), synthesized independently by

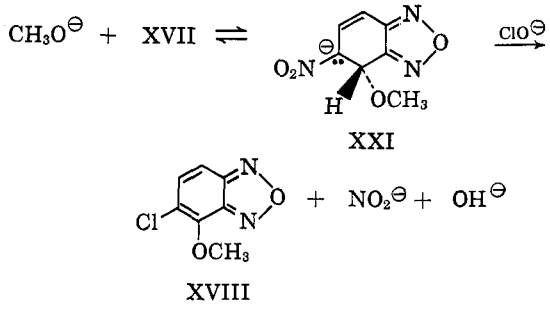


pyrolysis of 2,4-dinitrotriazobenzene, and 4(7)-nitrobenzofurazan oxide (XVI), synthesized independently by nitration of benzofurazan oxide, were found to be converted to the corresponding chloromethoxybenzofurazan oxides II and III, respectively, by treatment in alkaline methanol solution with aqueous sodium hypochlorite.[9] Furthermore, no chloromethoxy products were observed from any of the several compounds related to 2,4-dinitroaniline but having structural modifications that precluded furazan oxide formation which have been subjected to the conditions of this substitution reaction; the compounds investigated were *N*-methyl-2,4-dinitroaniline, 2,4-dinitro-*N*-phenylaniline, 2,2′,4,4′-tetranitrodiphenylamine, 2,4-dinitrophenol, and *m*-dinitrobenzene.

In accord with the presumption that this substitution reaction is not a general one for aromatic nitro compounds but rather depends on the presence of the heterocycle it was found that the nitrobenzofurazans also undergo this reaction: 5-nitrobenzofurazan (XVII), a new compound prepared by deoxygenation of the related furazan oxide XV with triphenylphosphine,[10] gave 5-chloro-4-methoxybenzofurazan (XVIII); and 4-nitrobenzofurazan (XIX) gave 4-chloro-5-methoxybenzofurazan (XX). The structures of XVIII and XX were proved by comparison in each case with a sample which had been obtained by deoxygenation with triphenylphosphine of the corresponding furazan oxide II or III, respectively.



The most satisfactory mechanism that we have been able to devise for this type of substitution reaction is presented for the case of the reaction of 5-nitrobenzofurazan (XVII). The postulate of the reversible



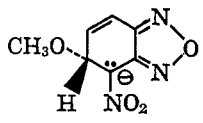
formation of the adduct of XVII and methoxide ion is reasonable by analogy with other systems[11]; the furazan ring would help accommodate the negative charge in this adduct, for which structure XXI is only one of the possible resonance forms. It is suggested that hypochlorite ion could react with XXI to give XVIII, nitrite ion, and hydroxide ion in a concerted process by way of a five-membered cyclic transition state in-

(9) The instability of both XV and XVI in alkaline solution necessitated carrying out these reactions by simultaneous addition of the furazan oxide and the hypochlorite solution to hot alkaline methanol; also, this method was chosen in order to approximate the reaction conditions under which XV and XVI are presumed to be generated *in situ* from the corresponding dinitroanilines. Reactions carried out in this way gave variable yields owing to difficulties in reproducing the technique exactly.

(10) G. Englert and H. Prinzbach, *Z. Naturforsch.*, **17b**, 4 (1962).

(11) J. Meisenheimer, *Ann.*, **323**, 205 (1902).

volving synchronous attack of the chlorine of the hypochlorite ion on C-5 and of the oxygen of the hypochlorite ion on the hydrogen attached to C-4 with concomitant aromatization of the six-membered ring and expulsion of nitrite ion. An analogous mechanism involving attack of hypochlorite ion on the adduct XXII that is shown is proposed as a plausible path from 4-



XXII

nitrobenzofurazan (XIX) to 4-chloro-5-methoxybenzofurazan (XX). Similar mechanisms are suggested for the corresponding reactions of the nitrobenzofurazan oxides XV and XVI to give the chloromethoxybenzofurazan oxides II and III, respectively.

In the absence of specific evidence for the existence of more than one mechanism for this unusual type of substitution reaction it is reasonable on simplicity grounds to reject as a working hypothesis any mechanism which can be demonstrated not to be applicable to all four examples of this reaction (involving the 4- and 5-nitrobenzofurazans and the two corresponding nitrobenzofurazan oxides) which have been found to date. On this basis a mechanism involving cine-substitution of a methoxy group for a nitro group[12] followed by electrophilic chlorination *ortho* to the methoxy group can be excluded since 5(6)-methoxybenzofurazan oxide has been found not to undergo chlorination to give the chloromethoxy compound III under the conditions that III is formed from 4(7)-nitrobenzofurazan oxide. Similarly, mechanisms involving initial replacement of the nitro group by a chloro group can be discarded since 5(6)-chlorobenzofurazan oxide has been found not to give the chloromethoxy compound II under the conditions that II is formed from 5(6)-nitrobenzofurazan oxide.

Experimental[13]

5-Chloro-4-methoxybenzofurazan Oxide (II) from 2,4-Dinitroaniline.—The deep red solution obtained by dissolving 0.92 g. (0.005 mole) of 2,4-dinitroaniline and 1.0 g. (0.015 mole) of potassium hydroxide in 50 ml. of methanol was heated at 48–50° and stirred magnetically during the addition over a period of 5 min. of 80 ml. of an aqueous solution (*ca.* 5%) of sodium hypochlorite.[15] The resulting yellow solution was maintained at 48–50° for an additional 2 min. and then was cooled rapidly using an ice bath to give a precipitate which was collected by suction filtration. This crude solid was sublimed to give 0.64 g. (63%) of bright yellow 5-chloro-4-methoxybenzofurazan oxide (II), m.p. 80.6–82.0° (lit.[4] m.p. 80°). The yields were much lower (*ca.* 30%) from reactions carried out on twenty times this scale.

The 60-Mc. proton n.m.r. spectrum[16] of II in carbon tetrachloride solution with tetramethylsilane as an internal standard showed a singlet for the methoxy group protons with $\tau = 5.47$ and an AB quartet for the ring protons with the resonance of the A proton centered at $\tau = 2.72$ and the resonance of the B proton centered at $\tau = 2.86$ with a coupling constant of 9.5 c.p.s.

Hydrogenation of 5-Chloro-4-methoxybenzofurazan Oxide (II).—A solution of 10.0 g. (0.050 mole) of II in 100 ml. of ethyl acetate was shaken for 21 hr. with 0.1 g. of platinum dioxide in a Parr apparatus under an initial pressure of 30 p.s.i. of hydrogen. The catalyst was removed by gravity filtration under a nitrogen atmosphere and the filtrate was divided into three portions.

A 10-ml. portion of the filtrate was evaporated to dryness under reduced pressure and the residue was sublimed. Recrystallization of the sublimate from water under a nitrogen atmosphere gave gray crystals of **4-chloro-3-methoxy-1,2-phenylenediamine (IV)**, m.p. 49–51°.

A second 10-ml. portion of the original filtrate was added to a solution of 1.0 g. (0.005 mole) of benzil in 100 ml. of glacial acetic acid and the resulting solution was refluxed for 30 min. The ethyl acetate was removed by distillation and the remaining dark colored solution was poured into 500 ml. of ice–water. Treatment of the resulting turbid mixture with dilute hydrochloric acid gave a precipitate which was collected by suction filtration and sublimed. Two recrystallizations of the sublimate from methanol gave 0.10 g. of white, crystalline **6-chloro-5-methoxy-2,3-diphenylquinoxaline (V)**, m.p. 137.2–137.5°.

Anal. Calcd. for $C_{21}H_{15}ClN_2O$: C, 72.73; H, 4.36; Cl, 10.22; N, 8.08; CH_3O, 8.95. Found: C, 72.56; H, 4.25; Cl, 10.41; N, 7.92; CH_3O, 8.99.

The solvent from the remaining portion of the original filtrate was removed under reduced pressure to give a dark red oil which was dissolved by the addition of 200 ml. of water and 3 ml. (0.036 mole) of concentrated hydrochloric acid. This solution was stirred magnetically and treated at room temperature with 16 g. (0.16 mole) of acetic anhydride followed by 8 g. (0.10 mole) of sodium acetate; three 8-g. portions of acetic anhydride were added during the subsequent 2 hr. The precipitate was collected by suction filtration and sublimed to give 5.8 g. of ***N,N'*-diacetyl-4-chloro-3-methoxy-1,2-phenylenediamine (VI)**, m.p. 209.4–210.0°. Five recrystallizations from 95% ethanol gave white crystals of VI melting at 209.6–210.0°.

Anal. Calcd. for $C_{11}H_{13}ClN_2O_3$: C, 51.47; H, 5.10; Cl, 13.81; N, 10.91; CH_3O, 12.09. Found: C, 51.62; H, 5.23; Cl, 13.84; N, 10.92; CH_3O, 12.18.

3-Chloro-2-methoxy-6-nitroaniline (VII).—The reduction of II was accomplished by a method previously described.[7] To a solution of 20.0 g. (0.10 mole) of II in 500 ml. of 95% ethanol was added 9.5 g. (0.15 g.-atom) of copper powder and 20 ml. of concentrated hydrochloric acid. The mixture was heated under reflux and stirred magnetically for 24 hr. after which it was concentrated to about 350 ml. and filtered by gravity to remove inorganic material. The filtrate was treated with 150 ml. of 25% aqueous sodium hydroxide solution and the resulting mixture was refluxed for 2 hr. and then the hot mixture was filtered by gravity. The filtrate was refrigerated for 10 hr. and the precipitate was collected by suction filtration and sublimed to give 11.6 g. (57%) of orange crystals of 3-chloro-2-methoxy-6-nitroaniline (VII) with m.p. 86.0–87.4°. Four recrystallizations from 95% ethanol gave a sample of VII with m.p. 87.2–87.6°.

Anal. Calcd. for $C_7H_7ClN_2O_3$: C, 41.50; H, 3.48; N, 13.83. Found: C, 41.54; H, 3.44; N, 13.65.

5-Chloro-4-methoxybenzofurazan Oxide (II) from 3-Chloro-2-methoxy-6-nitroaniline (VII).—The red solution prepared by heating 1.0 g. (0.005 mole) of VII and 0.3 g. (0.005 mole) of potassium hydroxide in 25 ml. of 95% ethanol was cooled to 0° using an ice–salt bath. The reaction temperature was maintained at 0° during the slow addition of 50 ml. of aqueous sodium hypochlorite solution.[15] A red gummy material was removed by suction filtration and sublimed to give 0.10 g. (10%) of yellow crystals melting at 68.5–74.0°. This material was identified as II by comparison of its infrared spectrum with that of the material obtained by hypochlorite oxidation of 2,4-dinitroaniline as described above.

2-Chloro-5-nitroanisole (VIII).—The deamination of VII was carried out by a procedure previously reported.[17] A solution of 1.0 g. (0.005 mole) of VII in 15 ml. of glacial acetic acid was added slowly to a magnetically stirred solution of 0.4 g. (0.006 mole) of sodium nitrite in 3 ml. of concentrated sulfuric acid, maintained at 0–5°, using an ice–salt bath. To this cold solution

(12) An example of such a reaction, the conversion of 2,3-dinitronaphthalene to 1-methoxy-3-nitronaphthalene by treatment with sodium methoxide in methanol at 45°, has been reported by D. C. Morrison, *J. Org. Chem.*, **27**, 296 (1962).

(13) All melting points are uncorrected. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were obtained with a Perkin-Elmer Infracord spectrophotometer. Sublimations were carried out at a pressure of about 0.05 mm. using an apparatus described elsewhere.[14]

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

(15) The aqueous sodium hypochlorite solution used in all of our work was the commercial product "Clorox."

(16) This spectrum was obtained with a Varian HR-60 spectrometer through the courtesy of Mr. E. Anderson of the Bell Telephone Laboratories, Murray Hill, N. J.

(17) H. H. Hodgson and J. Walker, *J. Chem. Soc.*, 1620 (1933).

was added 7 ml. (0.067 mole) of 50% aqueous hypophosphorous acid. The resulting mixture was stirred for one additional hour at 0–5° and then allowed to stand at room temperature for 24 hr. The mixture was diluted with water to 100 ml. and the yellow solid was collected by suction filtration and washed with 50 ml. of 20% aqueous sodium hydroxide solution followed by several portions of water. Sublimation of the crude product gave 0.70 g. (76%) of 2-chloro-5-nitroanisole (VIII), m.p. 81.0–81.8°. Three recrystallizations from 95% ethanol gave 0.60 g. (65%) of VIII with m.p. 81.8–82.5° (lit.[18] m.p. 83°).

A solution prepared by heating 3.4 g. (0.020 mole) of 2-methoxy-4-nitroaniline, 10 ml. of concentrated hydrochloric acid, and 10 ml. of water was cooled to 0° using an ice–salt bath. To this cold mixture was added slowly a solution of 1.6 g. (0.023 mole) of sodium nitrite in 3 ml. of water. The resulting diazonium chloride solution was then added cautiously to a cold solution of 2.0 g. (0.020 mole) of cuprous chloride in 15 ml. of concentrated hydrochloric acid. When the gas evolution had subsided the mixture was warmed to room temperature and diluted to 400 ml. with water. The precipitate was collected by suction filtration, washed with 10% aqueous sodium hydroxide solution, and sublimed to give 2.4 g. (69%) of 2-chloro-5-nitroanisole (VIII), m.p. 81.0–82.6°. After two recrystallizations from 95% ethanol this sample of VIII melted at 82.4–83.0° (lit.[18] m.p. 83°). Comparison of infrared spectra and a mixture melting point determination showed this material to be identical with that obtained by deamination of 3-chloro-2-methoxy-6-nitroaniline (VII) as described.

2,6-Dichloro-4-nitroanisole.—A previously described method[19] was employed. A suspension prepared from 10.4 g. (0.050 mole) of 2,6-dichloro-4-nitrophenol, 20 ml. (46 g., 0.32 mole) of methyl iodide, 27 g. (0.20 mole) of anhydrous potassium carbonate, and 80 ml. of acetone was heated under reflux for 6 hr. and was then allowed to stand at room temperature for 12 hr. The reaction mixture was evaporated to dryness under reduced pressure and the residue was treated with 100 ml. of water. The insoluble yellow solid was collected by suction filtration and sublimed to give 9.5 g. (86%) of 2,6-dichloro-4-nitroanisole, m.p. 95.2–97.4° (lit.[20] m.p. 98°).

4-Amino-2,6-dichloroanisole.—Hydrogenation of 4.5 g. (0.02 mole) of 2,6-dichloro-4-nitroanisole in 70 ml. of ethyl acetate was carried out by shaking the solution in a Parr apparatus for 1 hr. with 0.2 g. of platinum dioxide under an initial pressure of 25 p.s.i. of hydrogen. Sublimation of the crude product gave 3.4 g. (87%) of 4-amino-2,6-dichloroanisole, m.p. 76.5–79.0° (lit.[20] m.p. 80.0–80.5°).

4-Acetamido-2,6-dichloroanisole (X).—A solution of 6.3 g. (0.033 mole) of 4-amino-2,6-dichloroanisole in 80 ml. (1.4 mole) of glacial acetic acid was heated under reflux for 8 hr. and then slowly poured into a solution of 52 g. (1.3 mole) of sodium hydroxide in 100 ml. of water. The precipitate was removed by suction filtration and sublimed to give 5.5 g. (72%) of 4-acetamido-2,6-dichloroanisole (X), m.p. 196.2–197.6° (lit.[20] m.p. 196–197°).

4-Acetamido-2,6-dichloro-3-nitroanisole (XI).—A solution of 0.80 g. (0.0034 mole) of X in 1.6 ml. of glacial acetic acid and 4 ml. of concentrated sulfuric acid was cooled to −10° in a Dry Ice–acetone bath. Fuming nitric acid (0.4 ml., min. 90%) was added, the mixture stirred magnetically and maintained at −10 to 0° for 1.75 hr., and then poured into 25 ml. of ice–water. The resulting yellow crystalline solid was collected by suction filtration and amounted to 0.93 g. (98%) of 4-acetamido-2,6-dichloro-3-nitroanisole (XI), m.p. 162.8–163.4°. A small sample of XI which was recrystallized four times from 95% ethanol melted at 163.4–163.8°.

Anal. Calcd. for $C_9H_5Cl_2N_2O_4$: C, 38.73; H, 2.89. Found: C, 38.55; H, 2.70.

4-Amino-2,6-dichloro-3-nitroanisole (XII).—A solution of 6 ml. of concentrated sulfuric acid and 6 ml. of water was added to 0.60 g. (0.002 mole) of XI and the mixture was stirred magnetically and maintained at 100° for 1.5 hr. The resulting orange solution was cooled to room temperature and then poured into a solution of 8 g. of sodium hydroxide in 35 ml. of water. The precipitate was collected by suction filtration and amounted to 0.40 g. (79%) of 4-amino-2,6-dichloro-3-nitroanisole (XII), m.p. 82.5–87.0°. Four recrystallizations from ethanol–water and one sublimation gave orange needles of XII with m.p. 88.2–89.0°.

Anal. Calcd. for $C_7H_6Cl_2N_2O_3$: C, 35.47; H, 2.55. Found: C, 35.68; H, 2.73.

2,6-Dichloro-3-nitroanisole (IX).—The procedure for deamination of XII was the same as that[17] described before for the preparation of 2-chloro-5-nitroanisole (VIII). From 0.50 g. (0.0021 mole) of XII, 0.20 g. (0.0029 mole) of sodium nitrite, and 7 ml. (0.067 mole) of 50% aqueous hypophosphorous acid was obtained after sublimation 0.25 g. (53%) of 2,6 dichloro-3-nitroanisole (IX), m.p. 46.0–46.8°. A mixture melting point determination and infrared spectral comparisons showed this sample of IX to be identical with that obtained from VII as described.

Diazotization of 3-chloro-2-methoxy-6-nitroaniline (VII) was carried out by the method[17] described in connection with the preparation of VIII. A solution of 4.0 g. (0.020 mole) of VII in 30 ml. of glacial acetic acid was added slowly to a magnetically stirred solution of 1.6 g. (0.023 mole) of sodium nitrite in 16 ml. of concentrated sulfuric acid which was maintained at 10–20°. The resulting solution was added dropwise to a solution of 2.0 g. (0.020 mole) of cuprous chloride in 15 ml. of concentrated hydrochloric acid while the reaction temperature was maintained below 30°. The mixture was stirred for an additional 2 hr. and then poured onto crushed ice. The crude solid was collected by suction filtration and sublimed to give 3.8 g. (87%) of 2,6-dichloro-3-nitroanisole (IX), m.p. 45.8–46.4°. Four recrystallizations from 95% ethanol gave yellow crystals of IX melting at 46.4–46.8°.

Anal. Calcd. for $C_7H_5Cl_2NO_3$: C, 37.85; H, 2.27; Cl, 31.93. Found: C, 37.90; H, 2.44; Cl, 31.74.

3-Chloro-2-methoxy-6-nitrobenzonitrile.—This nitrile was synthesized using a previously reported method[21] as the first step in a scheme for proving the structure of VII which was abandoned owing to experimental difficulties later in the scheme. Solutions of 18.0 g. (0.28 mole) of potassium cyanide in 75 ml. of water, 8.3 g. (0.035 mole) of nickel chloride hexahydrate in 25 ml. of water, and 75 g. (0.71 mole) of anhydrous sodium carbonate in 150 ml. of water were combined and cooled to 5° using an ice bath. To this cooled, magnetically stirred solution was added over a period of 5 hr. the diazonium sulfate solution which had been prepared from 10.0 g. (0.049 mole) of 3-chloro-2-methoxy-6-nitroaniline (VII) in 90 ml. of glacial acetic acid and 4.0 g. (0.058 mole) of sodium nitrite in 30 ml. of concentrated sulfuric acid by the method[17] described in connection with the preparation of VIII. During the 5-hr. addition period an additional 75 g. of anhydrous sodium carbonate in 150 ml. of water was added in three equal portions. The reaction mixture was then heated at 80° on a steam bath for 30 min. before it was poured onto crushed ice. The resulting solid was collected by suction filtration and sublimed to give 7.7 g. (73%) of 3-chloro-2-methoxy-6-nitrobenzonitrile, m.p. 108.5–110.0°. A small sample of this nitrile was recrystallized three times from 95% ethanol to give pale yellow needles melting at 110.5–111.2°.

Anal. Calcd. for $C_8H_5ClN_2O_3$: C, 45.20; H, 2.37; N, 13.18. Found: C, 45.32; H, 2.66; N, 13.14.

4-Chloro-5-methoxybenzofurazan Oxide (III) from 2,3-Dinitroaniline.—Acetylation of *m*-nitroaniline with acetic anhydride by a previously reported procedure[22] gave *m*-nitroacetanilide, m.p. 152.2–153.0° (lit.[22] m.p. 152°).

Nitration of *m*-nitroacetanilide followed by recrystallization of the crude mixture of isomers from benzene–acetone (2:1) according to a procedure previously described[23] gave **2,3-dinitroacetanilide**, m.p. 185.8–187.0° (lit.[23] m.p. 187°).

The 2,3-dinitroacetanilide was hydrolyzed by a previously reported method.[24] A mixture of 1.0 g. (0.004 mole) of 2,3-dinitroacetanilide, 5 ml. of concentrated hydrochloric acid, and 15 ml. of absolute ethanol was heated under reflux for 1 hr. The resulting yellow solution was poured into 100 ml. of ice–water and the precipitate was collected by suction filtration. Recrystallization of the crude product from 95% ethanol gave 0.5 g. (61%) of **2,3-dinitroaniline**, m.p. 129.6–130.8° (lit.[25] m.p. 127°).

A solution of 1.0 g. (0.015 mole) of potassium hydroxide in 15 ml. of methanol was added to a solution of 0.92 g. (0.005 mole) of

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2,3-dinitroaniline in 10 ml. of methanol at 50° to give a pale red solution which was stirred magnetically and heated at 48–52° during the addition over a period of 6 min. of 100 ml. of an aqueous solution of sodium hypochlorite.[15] The resulting pale orange solution was maintained at 48–52° for an additional 1 min. and then cooled using an ice bath to give a precipitate which was collected by suction filtration. The crude product was sublimed and the sublimate recrystallized from 95% ethanol to give 0.20 g. (20%) of yellow 4-chloro-5-methoxybenzofurazan oxide (III), m.p. 134.0–134.8°. This material was identified as III by comparison of its infrared spectrum with that of the sample of III obtained from the hypochlorite oxidation of 4(7)-nitrobenzofurazan oxide (XVI) as described later.

The 60-Mc. proton n.m.r. spectrum[26] of III in deuteriochloroform solution with tetramethylsilane as an internal standard showed a singlet for the methoxy group protons with $\tau = 5.97$ and an AB quartet for the ring protons with the resonance of the A proton centered at $\tau = 2.73$ and the resonance of the B proton centered at $\tau = 2.93$ with a coupling constant of 9.5 c.p.s.

2-Chloro-3-ethoxy-6-nitroaniline (XIII).—The method was similar to that[7] described previously for the preparation of VII. Treatment of 2.5 g. (0.012 mole) of III with 1.1 g. (0.017 mole) of copper powder, 2.5 ml. of concentrated hydrochloric acid, and 87 ml. of 95% ethanol gave on sublimation 1.40 g. (55%) of XIII melting at 86–94°. Six recrystallizations from 95% ethanol gave 2-chloro-3-ethoxy-6-nitroaniline (XIII) with m.p. 100.0–100.8°.

Anal. Calcd. for $C_8H_9ClN_2O_3$: C, 44.35; H, 4.19. Found: C, 44.59; H, 4.22.

2-Chloro-4-nitrophenetole.—The deamination of XIII was carried out by the procedure[17] described above for the preparation of VIII. Treatment of 0.50 g. (0.0023 mole) of XIII with 0.20 g. (0.0029 mole) of sodium nitrite and 3.5 ml. (0.034 mole) of 50% aqueous hypophosphorous acid gave on sublimation 0.30 g. (65%) of material melting at 79.8–80.6°. Three recrystallizations from 95% ethanol gave 2-chloro-4-nitrophenetole with m.p. 81.0–82.6° (lit.[27] m.p. 82°).

A mixture of 0.87 g. (0.005 mole) of 2-chloro-4-nitrophenol, 4.1 ml. (5.9 g., 0.054 mole) of ethyl bromide, 2.5 g. (0.018 mole) of anhydrous potassium carbonate, and 20 ml. of acetone was heated under reflux and stirred magnetically for 16 hr. The reaction mixture was evaporated to dryness under reduced pressure and the residue was treated with 50 ml. of water. The insoluble material was collected by suction filtration to give 1.0 g. (99%) of 2-chloro-4-nitrophenetole, m.p. 80.8–82.0° (lit.[27] m.p. 82°). This material was shown by a mixture melting point determination and infrared spectral comparisons to be identical with the 2-chloro-4-nitrophenetole obtained from deamination of XIII as described above.

4-Chloro-5-ethoxybenzofurazan Oxide (XIV) from 2-Chloro-3-ethoxy-6-nitroaniline (XIII).—The red solution obtained by adding 0.10 g. (0.0005 mole) of XIII to a solution of 0.20 g. (0.003 mole) of potassium hydroxide in 3 ml. of 95% ethanol was stirred magnetically at room temperature during the addition over a period of 5 min. of 10 ml. of an aqueous solution of sodium hypochlorite.[15] The reaction mixture was extracted with ether and the ether extract was dried over anhydrous sodium sulfate. The ether was removed by evaporation under reduced pressure and the residual solid was sublimed and the sublimate recrystallized from 95% ethanol to give yellow crystals of 4-chloro-5-ethoxybenzofurazan oxide (XIV) melting at 99.8–102.0° (lit.[6] m.p. 101–102°). This material was shown by a mixture melting point determination and comparison of infrared spectra to be identical with the sample of XIV obtained from 4(7)-nitrobenzofurazan oxide (XVI) as described later.

5-Chloro-4-methoxybenzofurazan Oxide (II) from 5(6)-Nitrobenzofurazan Oxide (XV).—The method for the preparation of XV was essentially that described.[28] A solution of 22.0 g. (0.12 mole) of 2,4-dinitroaniline in 175 ml. of glacial acetic acid and 88 ml. of concentrated sulfuric acid was stirred magnetically and maintained at 0–5° during the slow addition of 9.8 g. (0.14 mole) of sodium nitrite dissolved in a minimum volume of water. To the resulting clear solution was added slowly a solution of 17.6 g. (0.27 mole) of sodium azide in 50 ml. of water. The precipitated **2,4-dinitrotriazobenzene** was collected by suction filtration and washed with water. A mixture of this crude material in 50 ml. of water was heated on a steam bath for 2 hr. until the evolution of gas had ceased. The reaction mixture was cooled and the solid was removed by suction filtration. Sublimation of the crude solid gave 18.1 g. (83%) of **5(6)-nitrobenzofurazan oxide (XV)**, m.p. 68.8–70.6° (lit.[28] m.p. 72°).

A solution of 1.0 g. (0.015 mole) of potassium hydroxide in 25 ml. of methanol in a 200-ml. 3-neck flask was stirred magnetically and maintained at 48–50° during the simultaneous addition to this flask of a solution of 0.91 g. (0.005 mole) of XV in 25 ml. of methanol from a dropping funnel and 100 ml. of an aqueous solution of sodium hypochlorite[15] from another dropping funnel. The rates of addition were regulated so that the time required for the addition of each solution was 25 min. The stirred reaction mixture was maintained at 48–50° for an additional 10 min. and then cooled using an ice bath. The precipitate was collected by suction filtration and sublimed to give 0.37 g. (37%) of material melting at 70.6–75.4°. Recrystallization of the sublimate from 95% ethanol gave 0.25 g. (25%) of 5-chloro-4-methoxybenzofurazan oxide (II), m.p. 79.0–79.5°, shown by a mixture melting point determination and infrared spectral comparisons to be identical with the sample of II obtained from 2,4-dinitroaniline as described.

4-Chloro-5-methoxybenzofurazan Oxide (III) from 4(7)-Nitrobenzofurazan Oxide (XVI).—The technique was similar to that described for the preparation of II from XV. Simultaneous addition over a period of 12 min. of 125 ml. of an aqueous solution of sodium hypochlorite[15] and a solution of 0.91 g. (0.005 mole) of XVI in 60 ml. of methanol to a magnetically stirred solution of 1.0 g. (0.015 mole) of potassium hydroxide in 25 ml. of methanol maintained at 48–52° followed by an additional 8 min. of stirring at 48–52° gave 0.40 g. (40%) of yellow 4-chloro-5-methoxybenzofurazan oxide (III), m.p. 137.4–138.2°. A small sample of III from a similar preparation was recrystallized four times from 95% ethanol to give a m.p. of 136.2–137.2°.

Anal. Calcd. for $C_7H_5ClN_2O_3$: C, 41.91; H, 2.51; N, 13.97. Found: C, 42.06; H, 2.68; N, 13.80.

4-Chloro-5-ethoxybenzofurazan Oxide (XIV) from 4(7)-Nitrobenzofurazan Oxide (XVI).—The procedure was identical to that described for the conversion of XVI to III except that ethanol was used in place of methanol and that it was necessary at the completion of the reaction to concentrate the reaction mixture using a rotary evaporator in order to obtain a precipitate. Recrystallization of the crude product from 95% ethanol gave 4-chloro-5-ethoxybenzofurazan oxide (XIV) melting at 102.4–103.2° (lit.[6] m.p. 101–102°).

5-Chloro-4-methoxybenzofurazan (XVIII).—The deoxygenation of 5(6)-nitrobenzofurazan oxide (XV) was carried out using a method previously described.[10] A solution of 0.91 g. (0.0050 mole) of XV and 1.44 g. (0.0055 mole) of triphenylphosphine in 50 ml. of xylene was heated under reflux for 2 hr. The reaction mixture was evaporated to dryness under reduced pressure and the residue was sublimed to give 0.63 g. (76%) of **5-nitrobenzofurazan (XVII)**, m.p. 64.6–65.4°. Two recrystallizations from 95% ethanol gave material melting at 65.4–66.2°.

Anal. Calcd. for $C_6H_3N_3O_3$: C, 43.64; H, 1.83. Found: C, 43.54; H, 1.69.

A solution of 0.20 g. (0.0030 mole) of potassium hydroxide in 5 ml. of methanol was stirred magnetically and maintained at 48–52° during the simultaneous addition over a period of 5 min. of 30 ml. of an aqueous solution of sodium hypochlorite[15] and a solution of 0.20 g. (0.0012 mole) of XVII in 5 ml. of methanol. The stirred reaction mixture was maintained at 48–52° for an additional 5 min. and then cooled using an ice bath. The precipitate was collected by suction filtration and sublimed to give 0.10 g. (45%) of material melting at 62.2–64.6°. Recrystallization of the crude product from 95% ethanol gave 5-chloro-4-methoxybenzofurazan (XVIII), m.p. 69.6–70.6°, shown by comparisons of infrared spectra and a mixture melting point determination to be identical with the material obtained by deoxygenation of II as subsequently described.

Reduction of 1.0 g. (0.005 mole) of 5-chloro-4-methoxybenzofurazan oxide (II) with triphenylphosphine in refluxing xylene by the method[10] described for the preparation of 5-nitrobenzofurazan (XVII) gave 0.73 g. (79%) of sublimed XVIII with m.p. 71.0–72.4°. A small sample of the product from a similar preparation was recrystallized three times from 95% ethanol to give pale yellow 5-chloro-4-methoxybenzofurazan, **m.p. 71.6–72.6°.**

(26) This spectrum was obtained with a Varian A-60 spectrometer through the courtesy of Dr. H. C. Beachell, University of Delaware, Newark, Del.

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(28) R. J. Gaughran, J. P. Picard, and J. V. R. Kaufman, *J. Am. Chem. Soc.*, **76**, 2233 (1954).

Anal. Calcd. for $C_7H_5ClN_2O_2$: C, 45.54; H, 2.73. Found: C, 45.33; H, 2.78.

4-Chloro-5-methoxybenzofurazan (XX).—A solution of 13.6 g. (0.1 mole) of benzofurazan oxide, prepared by a method previously described,[29] in 44.5 ml. of concentrated sulfuric acid was stirred magnetically and maintained at 5–12° during the addition over a period of 45 min. of a mixture of 5 ml. of fuming nitric acid (min. 90%) and 20 ml. of concentrated sulfuric acid. The stirred reaction mixture was cooled in an ice bath for an additional 1.5 hr. and then poured into ice–water. The solid was collected by suction filtration, washed with water, and recrystallized from 100 ml. of glacial acetic acid (Norit) to give 9.8 g. (54%) of **4(7)-nitrobenzofurazan oxide (XVI)**, m.p. 141.6–143.2° (lit.[28] m.p. 143°).

Reduction of 0.91 g. (0.005 mole) of XVI with triphenylphosphine in refluxing xylene according to the procedure[10] described for the preparation of 5-nitrobenzofurazan (XVII) gave on sublimation 0.37 g. (45%) of **4-nitrobenzofurazan (XIX)**, m.p. 96.6–98.2° (lit.[30] m.p. 98°).

The procedure for the conversion of XIX to 4-chloro-5-methoxybenzofurazan (XX) was identical to that described for the conversion of XVII to 5-chloro-4-methoxybenzofurazan (XVIII). From 0.20 g. (0.0012 mole) of XIX was obtained on sublimation 0.15 g. (67%) of 4-chloro-5-methoxybenzofurazan (XX) with m.p. 130.2–130.8°. Three recrystallizations of the sublimate from 95% ethanol sharpened the m.p. to 130.4–130.8°. Mixture melting point determination and comparison of infrared spectra showed this material to be identical with sample of XX obtained by deoxygenation of 4-chloro-5-methoxybenzofurazan oxide (III) as subsequently described.

Treatment of 0.70 g. (0.0035 mole) of III with 1.0 g. (0.0038 mole) of triphenylphosphine in 35 ml. of refluxing xylene according to the method[10] described for the preparation of 5-nitrobenzofurazan (XVII) gave 0.53 g. (82%) of 4-chloro-5-methoxybenzofurazan (XX) which melted at 129.0–130.2° after one recrystallization from 95% ethanol. Two subsequent recrystallizations from 95% ethanol gave pale yellow crystals of XX melting at 130.2–130.6°.

Anal. Calcd. for $C_7H_5ClN_2O_2$: C, 45.54; H, 2.73. Found: C, 45.60; H, 2.80.

Mechanistic Evidence.—A mechanically stirred solution of 3.4 g. (0.02 mole) of 4-methoxy-2-nitroaniline and 3.4 g. (0.05 mole) of potassium hydroxide in 200 ml. of methanol was heated to 50° and 400 ml. of an aqueous solution of sodium hypochlorite[15] was added. The reaction mixture was cooled and filtered by suction to give 2.4 g. (72%) of **5(6)-methoxybenzofurazan oxide**, m.p. 112–115° (lit.[28] m.p. 118°). The infrared spectrum of this material showed the absence of several intense peaks characteristic of 4-chloro-5-methoxybenzofurazan oxide (III).

A mechanically stirred solution of 3.4 g. (0.02 mole) of 4-chloro-2-nitroaniline and 5.3 g. (0.08 mole) of potassium hydroxide in 200 ml. of methanol was heated to 50° and 400 ml. of an aqueous solution of sodium hypochlorite[15] was added. The reaction mixture was cooled and the precipitate was collected and recrystallized from methanol to give 2.1 g. (63%) of **5(6)-chlorobenzofurazan oxide**, m.p. 43–45° (lit.[28] m.p. 48°). The infrared spectrum of this material was essentially identical with that of an authentic sample of 5(6)-chlorobenzofurazan oxide and showed the absence of several intense peaks characteristic of 5-chloro-4-methoxybenzofurazan oxide (II).

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Electron Density and Orientation of Nucleophilic Substitution in the Purine Ring[1]

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The poor correlation between various electron density calculations and experimental observations relative to the purine ring has resulted in a careful re-examination of nucleophilic substitution in that ring system. It now has been observed that the position of nucleophilic attack can be changed by temporarily blocking the imidazole hydrogen which prevents anion formation in the presence of strong nucleophiles. Acid-catalyzed nucleophilic displacement also may result in a change of orientation. These effects are discussed in terms of a unified theory. It is suggested that similar results might be expected from other related nitrogen heterocyclic systems.

Nucleophilic attack by various reagents on 2,6,8-trichloropurine was first studied by Fischer[2] and extended by later investigators.[3–8] In all cases, with strong bases, nucleophilic displacement occurs first at position 6 followed by position 2 and finally position 8. The reactivities of the various chlorine atoms are such that selective substitution often can be accomplished under the appropriate reaction conditions. When 7-methyl-2,6,8-trichloropurine (I) or 9-methyl-2,6,8-trichloropurine (II) was similarly studied by Fischer,[9] he found that in most instances substitution occurred first at position 8. This would seem at first inspection to be at variance with expectation since modern theory would require that the methyl group at position 7 or 9 should, by the inductive effect, increase the electron density in the imidazole ring and thus favor attack by a nucleophilic reagent in the pyrimidine ring (position 6). Recent electron density calculations for purine[10] would predict nucleophilic substitution at position 6 followed by 2 then 8. Pullman[11] has calculated the localization energy for nucleophilic attack on the purine nucleus and has taken into account induced polarization under these conditions. According to these calculations there is an equal possibility for nucleophilic attack at either position 6 or 8 of the purine ring. Electron density calculations by Mason[12] for nucleophilic attack predict position

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