[Contribution from the Chemistry Department, New Mexico Highlands University]

NITRATION AND BROMINATION OF *m*-PHENOXYANISOLE

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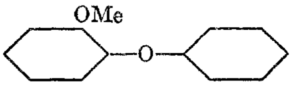
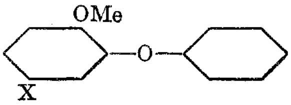
The orientation in substitution reactions of *o*-phenoxyanisole (I) is largely determined by the methoxy group. Thus, bromination (1), nitration (2, 3), and Friedel-Crafts acylation (4) yield 5-substituted ethers (II) as main products.[2]

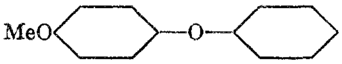


I

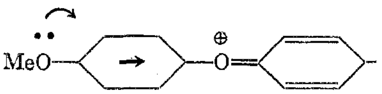


II

In *p*-phenoxyanisole (III) nitration occurs *ortho* to the methoxy group (3, 5)



III



IV

while bromination (6), iodination (3) and acylation (7, 8) take place first in the *para* position of the unsubstituted nucleus. The rate of bromination in III exceeds that in diphenyl ether and it was therefore proposed by Brewster and Slocombe (9) that electronic effects are transmitted across the ether linkage (structure IV). Since chlorination, bromination, and nitration substitute *p*-phenoxyphenol in the *ortho* position (10), the orientation to the unsubstituted ring in III may be attributed to the methoxy group.

m-Phenoxyanisole (V) has not been previously investigated. Evidence is now presented which indicates that it yields 6-substituted ethers on bromination and nitration, *i.e.* that the orientation is *apparently* determined by the phenoxy group.

The nitration products from V represent a complex mixture which proved difficult to separate. Only a single nitro compound (VI, m.p. 70–71°) has been isolated by crystallization. This substance has been identified as the 6-nitro derivative by synthesis from 3-chloro-6-nitroanisole.[3]

The alkaline demethylation of the nitration mixture similarly yields a single crystalline nitrophenol which is identical with synthetic 3-phenoxy-6-nitrophenol.

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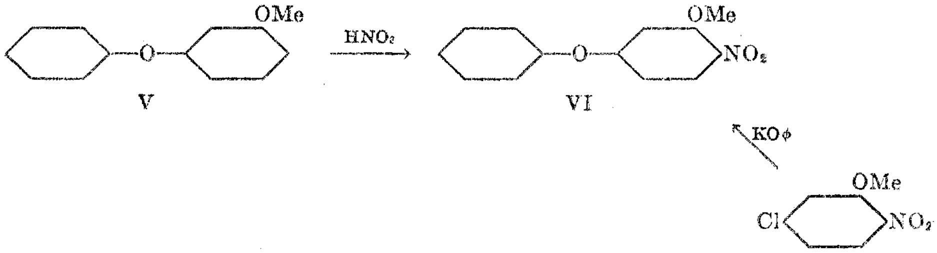
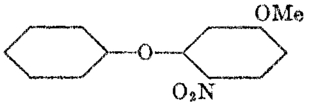
[2] Lions and Willison (2) report 80% 4-nitro- and 20% 5-nitro-2-phenoxyanisole. Bromination and acylation fail to attack the 4-position and the disubstitution products have the second substituent in the *para* position of the unsubstituted nucleus.

[3] Since the completion of this work, compounds VI and VII have been reported by Yamaguchi [*J. Pharm. Soc. Japan*, **71**, 1447 (1951)] who gives m.p. 109° for the high-melting form of VI and 89–90° for VII.

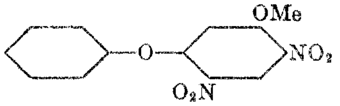


V VI

In an effort to identify other nitro derivatives, the 4-nitro isomer (VII) and the 4,6-dinitro compound (VIII) have been synthesized by unambiguous methods. The spectrum of VIII bears some resemblance to that of the nitration oil but attempts to isolate VII or VIII from the mixture have been unsuccessful. Alkaline demethylation of VII under conditions similar to those used for the nitration mixture results in cleavage to give 4-nitroresorcinol. The dinitro compound VIII is converted to the corresponding phenol by cautious demethylation under very mild conditions.

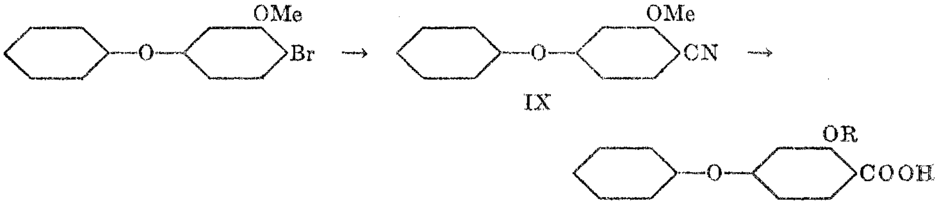


VII



VIII

The bromination product of V has been converted to the cyanide through the Rosenmund-von Braun synthesis. The oily cyanide (IX) is hydrolyzed in acid or basic medium and it is possible to obtain either the hydroxy acid or the methoxy acid as end product. Comparison with the known acids (11) has established that the acids X possess a carboxyl group in the 6-position.



IX

X (a, R = H)
(b, R = Me)

In view of poor yields and tedious separations the presence of other isomers has not been excluded. It may be concluded, however, that a considerable amount of the substitution takes place in the 6-position of *m*-phenoxyanisole. Since it is known that the methoxy group determines the orientation in the isomers, and since it has been established that substitution reactions are subject to steric effects (12), it seems likely that such effects may need to be considered in these reactions.

Absorption spectra have been determined for all the new compounds (Table I, Fig. 1–3). A satisfactory explanation of the bands and their intensities can be

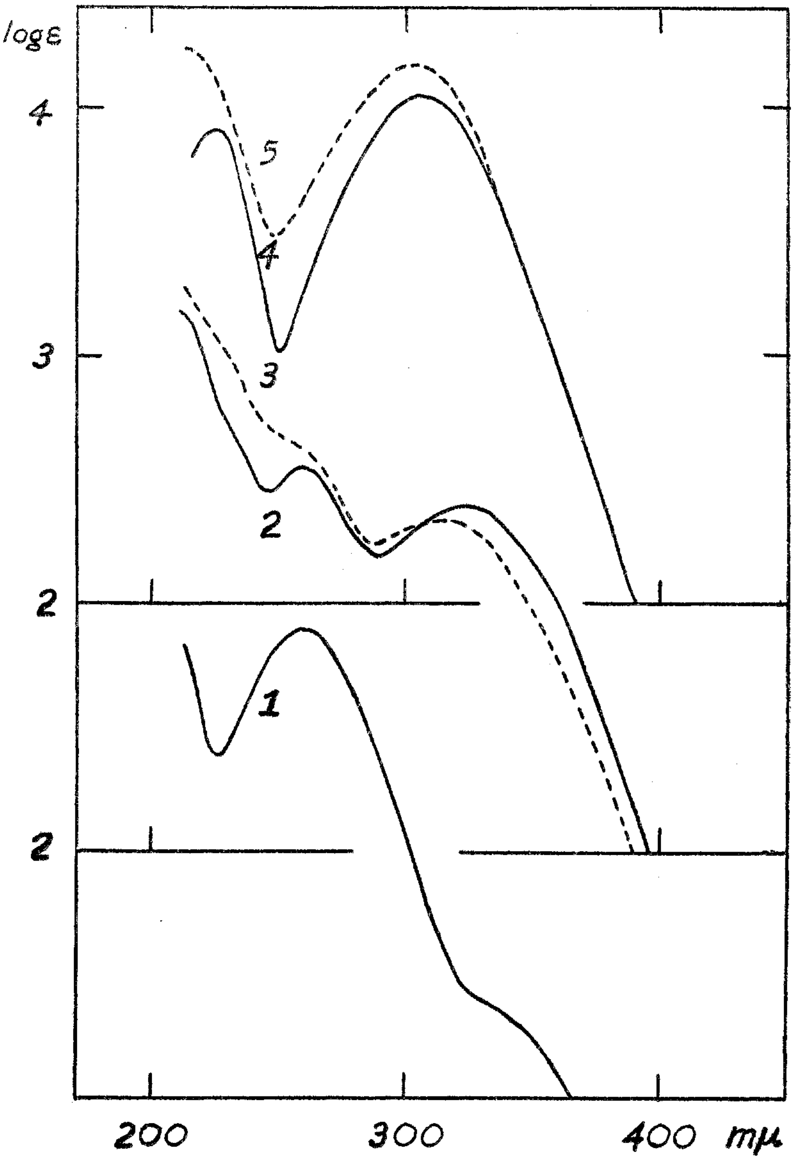


FIG. 1. 1, NITROBENZENE; 2, *o*-METHOXYNITROBENZENE; 3, *o*-PHENOXYNITROBENZENE; 4, *p*-METHOXYNITROBENZENE; 5, *p*-PHENOXYNITROBENZENE

made on the assumption that the resonance between the nitro group and the ring is interfered with by *ortho* methoxy and phenoxy groups.

EXPERIMENTAL

All melting points uncorrected.

Nitration of m-phenoxyanisole. m-Phenoxyanisole (V) was obtained in yields up to 96.5% by a slight modification of the procedure of Lea and Robinson (5). On nitration in acetic acid with concentrated nitric acid this compound underwent considerable destruction with formation of tar. This side reaction could be decreased only slightly by holding the temperature between 25 and 30°.

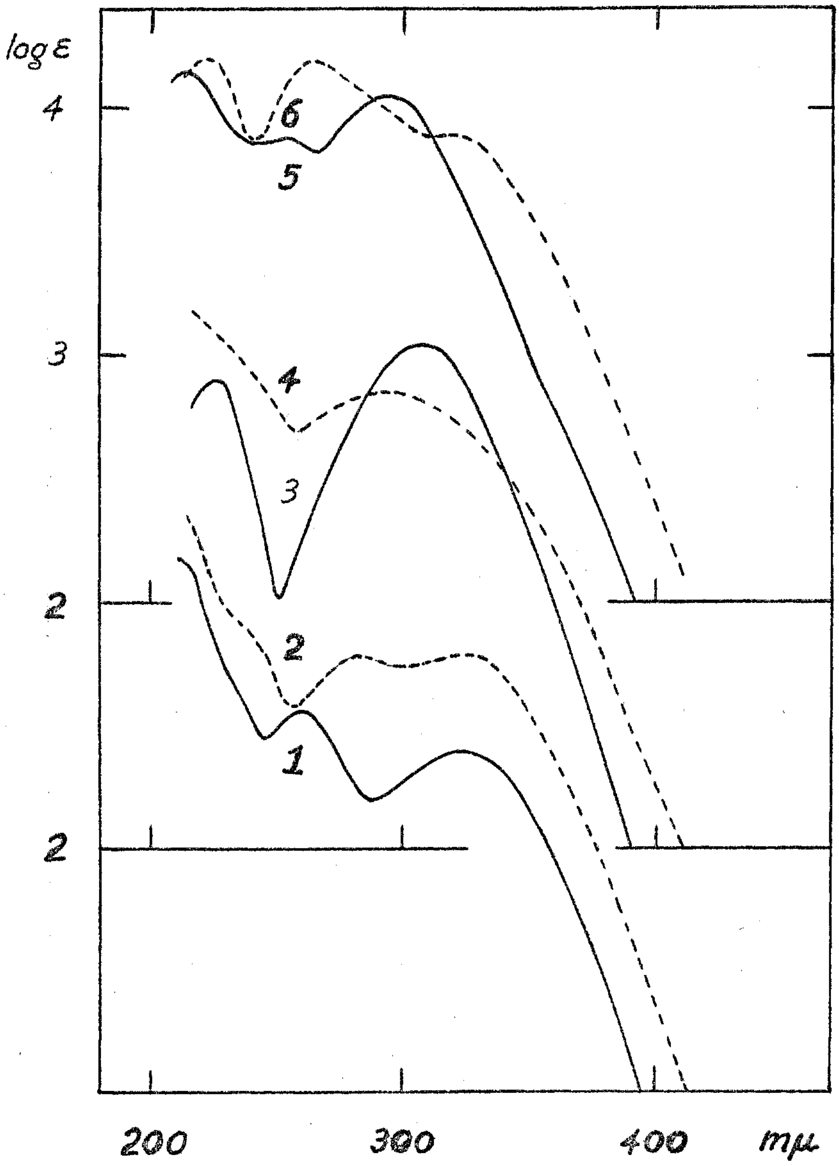


FIG. 2. 1, *o*-METHOXYNITROBENZENE; 2, 2-METHOXY-4-PHENOXYNITROBENZENE; 3, *p*-METHOXYNITROBENZENE; 4, 2-PHENOXY-4-METHOXYNITROBENZENE; 5, 2,4-DINITROANISOLE; 6, 2,4-DINITRO-5-PHENOXYANISOLE

Concentrated nitric acid (14.4 cc.) was added dropwise, with stirring, to a cooled solution of 16 g. of *m*-phenoxyanisole in 74.2 cc. of glacial acetic acid. The temperature was maintained at 25–30° by external cooling. Stirring was continued for 30 minutes after the addition was completed. The resultant green-blue mixture was poured onto 100 g. of ice and was allowed to stand for one hour. The mixture was extracted with benzene. The extract was filtered, washed with water, and distilled to remove the azeotrope and solvent. The residual oil (16.20 g.) distilled at 158–173° (0.1 mm.); yield, 3.21 g.

The oily distillate deposited two crops of needles (m.p. 65–69°, yield 0.26 g.) when diluted with ligroin. The remaining mother liquors failed to give any further crystalline material. Recrystallization of the solid material from ligroin yielded nearly colorless needles, m.p. 70–71°, which did not depress the melting point of synthetic 3-phenoxy-6-nitroanisole (VI).

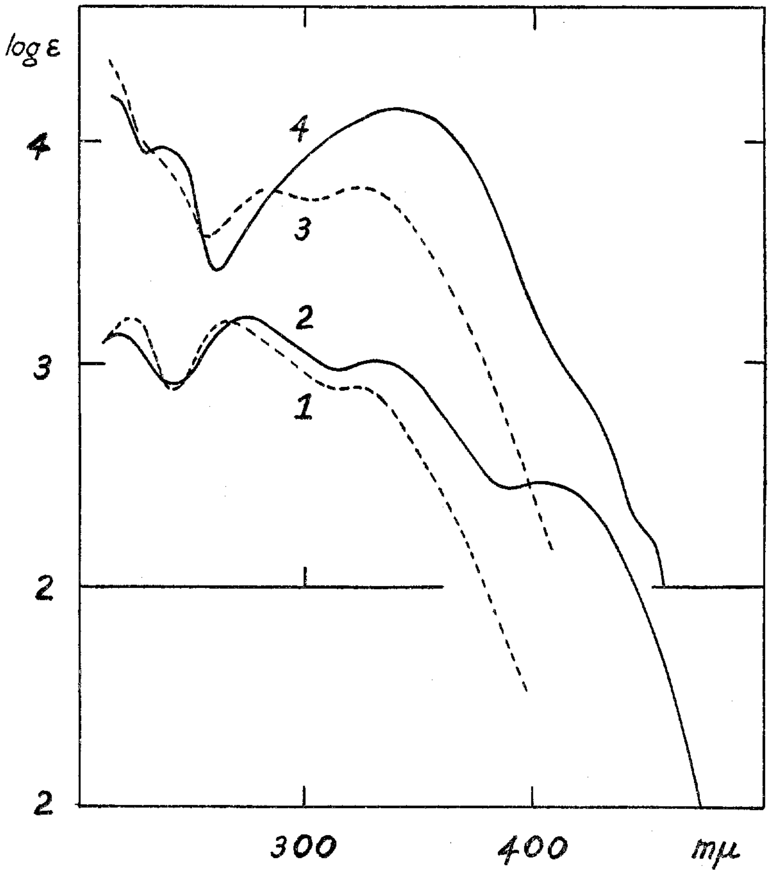


FIG. 3. 1, 2,4-DINITRO-5-PHENOXYANISOLE; 2, 2,4-DINITRO-5-PHENOXYPHENOL; 3, 2-NITRO-5-PHENOXYANISOLE; 4, 2-NITRO-5-PHENOXYPHENOL

Anal. Calc'd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52.

Found: C, 64.19; H, 4.97.

Chromatographic adsorption of the oil from the combined mother liquors on alumina with benzene as solvent and eluant provided six bands which were washed through the column. Most of the product was contained in the third band which furnished a brown oil. The ultraviolet absorption spectrum of this oil was indicative of a mixture of mono and dinitro compounds (λ_{max} 277 mμ, log ε 4.35, based on M.W. 231), the other bands gave only traces of oily material.

Demethylation of the nitration products. In view of the extensive destruction during the vacuum distillation of the above nitration products, the crude oily product (13.13 g.) was adsorbed on alumina from a benzene solution. The main band, eluted with benzene, contained 9.17 g. of a brown oil. A portion of this oil (5.79 g.) was demethylated by refluxing for 3½ hours in a copper flask with 47 g. of sodium hydroxide in 281.3 cc. of water in an atmosphere of nitrogen. The reaction mixture was acidified with concentrated hydrochloric acid and extracted with benzene. Acidic products were separated by washing the extract with 10% aqueous sodium hydroxide solution, acidification with concentrated hydrochloric acid, and extraction with benzene and ether. The combined benzene and ether extracts were washed with water and distilled. The residual oily product (0.23 g.) solidified partially on standing. Two recrystallizations from ligroin gave a yellow microcrystalline powder, m.p. 96–98°, mixture melting point with the lower-melting form of 3-phenoxy-6-nitrophenol, 96–98°.

TABLE I

ABSORPTION SPECTRA OF NITRO COMPOUNDS IN ETHANOL

SUBSTITUTED NITROBENZENE	$\lambda_{\max}$[e]	log ϵ	$\lambda_{\max}$[f]	log ϵ	$\lambda_{\max}$[g]	log ϵ
—	—	—	260	3.90	—	—
2-Hydroxy	—	—	272–273[b]	3.78	345–347[b]	3.49
2-Methoxy	—	—	260	3.52	320	3.38
2-Phenoxy	—	—	260[a]	3.62	315	3.33
2-Hydroxy-4-phenoxy	238	3.95	350[c]	4.15	—	—
2-Methoxy-4-phenoxy	—[a]	—	279	3.77	323	3.79
4-Hydroxy	224–226[b]	3.85	311–313[b]	4.02	—	—
4-Methoxy	226	3.90	305[d]	4.04	—	—
4-Phenoxy	213[a]	4.24	302	4.18	—	—
4-Methoxy-2-phenoxy	—[a]	—	295	3.83	—	—
2-Hydroxy-5-nitro	—	—	291–294[b]	3.96	—	—
2-Methoxy-5-nitro	214	4.13	290	4.04	—	—
2-Methoxy-4-phenoxy-5-nitro	222	4.20	265	4.20	322	3.90
2-Hydroxy-4-phenoxy-5-nitro	218	4.13	274	4.20	332	4.02[h]

[a] Shoulder. [b] Schroeder, *et al.*, *Anal. Chem.*, **23,** 1743 (1951). [c] Fused band. [d] These observations do not agree well with the results of Anderson, *et al.*, *J. Am. Chem. Soc.*, **54,** 3064 (1932), in ether, probably because in alcohol the two bands are completely fused. [e] Second primary bands. [f] First primary bands. [g] Secondary bands; the assignment of bands, in accordance with the work of Doub and Vandenbelt, *J. Am. Chem. Soc.*, **69,** 2714 (1947); **71,** 2414 (1949); is subject to some uncertainty. [h] An additional secondary band appears at 404 mμ (log 3.73).

Numerous attempts to separate the non-acidic reaction products failed to furnish identifiable compounds.

3-Chloro-6-nitroanisole. m-Chlorophenol was prepared from *m*-chloroaniline in 63.5% yield according to the procedure in Organic Syntheses (13). Nitration of *m*-chlorophenol (30 g.), dissolved in 30 cc. of glacial acetic acid, with a solution of 32.1 cc. of concentrated nitric acid in 90 cc. of glacial acetic acid at −15° yielded 5.89 g. of 3-chloro-6-nitrophenol, m.p. 39.5–40° [lit. m.p. 41° (14)], which was filtered from the steam-distillate after cooling in an ice-bath. The non-volatile portion was decolorized with Norit and crystallized from water, m.p. 120–120.5° [lit. m.p. for 3-chloro-4-nitrophenol 121–122° (13)]; yield, 19.42 g.

The sodium salt of 3-chloro-6-nitrophenol (5.85 g.) was prepared by stirring the phenol with 2.67 g. of sodium hydroxide in 13 cc. of water. The brick-red platelets were filtered and washed on the funnel with 95% alcohol. The washed precipitate was dried over sulfuric acid in a vacuum desiccator. The dry salt (5.45 g.) was refluxed with 6.87 cc. of methyl sulfate for 4 hours. The mixture was steam-distilled and the distillate was extracted with benzene. The extract was washed with 10% aqueous sodium hydroxide and with water. The benzene solution was distilled from a water-bath. The residual oil crystallized immediately on cooling leaving nearly colorless plates of 3-chloro-6-nitroanisole, m.p. 70.5–71.5° [lit. m.p. 71° (15)]; yield, 3.27 g.

3-Phenoxy-6-nitroanisole (VI). Potassium phenoxide (from 6.48 g. of phenol) was heated with 0.1 g. of copper powder, 7.0 g. of 3-chloro-6-nitroanisole, and a few drops of phenol at 200–205° for 2 hours. The mixture was steam-distilled. The benzene extract of the distillate was washed with 10% aqueous sodium hydroxide and with water and was distilled to remove the solvent. The residual oil boiled at 150–160° (7 mm.), yield 4.32 g. Crystallization from ligroin yielded 1.91 g. of pale yellow platelets which gave the constant m.p. 100–100.5° after decolorization and recrystallization from ligroin.

Anal. Calc'd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71.

Found: C, 63.70; H, 4.70; N, 5.80.

A second modification of the compound melted at 70–71° and was occasionally deposited in nearly colorless needles from ligroin. A mixture of the two forms gave both melting points and each form could be seeded out from the melt.

3-Phenoxy-6-nitrophenol. 3-Phenoxy-6-nitroanisole (1.64 g.) was refluxed for 72 hours with 13.14 g. of sodium hydroxide in 8.2 cc. of water in an atmosphere of nitrogen. The reaction mixture was acidified with hydrochloric acid and extracted with benzene.

The benzene solution was extracted with 10% aqueous sodium hydroxide. Acidification of the alkaline solution with concentrated hydrochloric acid yielded 0.38 g. of yellow prisms, m.p. 111–113°. Recrystallization from benzene-petroleum ether raised the melting point to 118–119°.

Anal. Calc'd for $C_7H_7NO_4$: C, 49.67; H, 4.17.

Found: C, 49.00; H, 4.00.

The benzene layer contained 0.63 g. of starting material.

The combined aqueous solutions were extracted continuously with benzene for 24 hours. This extract furnished 0.45 g. of oil which solidified on cooling. Crystallization from ligroin gave 0.160 g. of minute yellow prisms, m.p. 107–109° or 96–97°. Either one of the dimorphic forms could be seeded from the melt. The compound formed a red sodium salt with 20% aqueous sodium hydroxide.

Anal. Calc'd for $C_{12}H_9NO_4$: C, 62.34; H, 3.92; N, 6.06.

Found: C, 62.90; H, 4.60; N, 6.11.

3-Chloro-4-nitroanisole. Dry sodium 3-chloro-4-nitrophenoxide (4.56 g.) was heated for 5 hours at 120–130° with 8.26 cc. of methyl sulfate. The steam-distillate from the reaction mixture crystallized on cooling. The colorless needles of 3-chloro-4-nitroanisole were filtered and dried; yield 4.14 g., m.p. 53–55°.

Anal. Calc'd for $C_7H_6ClNO_3$: C, 44.82; H, 3.23.

Found: C, 44.79; H, 3.35.

3-Phenoxy-4-nitroanisole (VII). The Ullmann reaction with potassium phenoxide (from 2.04 g. of phenol) and 2.0 g. of 3-chloro-4-nitroanisole gave a red oil (1.0 g.) which crystallized partially on cooling. It was dissolved in benzene and adsorbed on aluminum oxide. The single yellow band was eluted with benzene and furnished 0.95 g. of brown oil. Decolorization and crystallization from ligroin yielded 0.95 g. of tan prisms of 3-phenoxy-4-nitroanisole (VII), m.p. 87–88°.

Anal. Calc'd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71.

Found: C, 63.99; H, 4.53; N, 5.82.

Demethylation of 3-phenoxy-4-nitroanisole. 3-Phenoxy-4-nitroanisole (0.50 g.) was refluxed for 8 hours with 4.10 g. of potassium hydroxide in 25.6 cc. of water in an atmosphere of nitrogen. The reaction mixture was acidified with concentrated hydrochloric acid and then was extracted with hot benzene. The extracts were washed with water and were distilled. The residual oil crystallized on cooling. It was dissolved in benzene and the solution was adsorbed on aluminum oxide. One yellow band was developed and eluted with benzene. The eluate was concentrated to about 20 cc. and decolorized with charcoal. Yellow needles separated after addition of petroleum ether and cooling of the resultant solution. Recrystallization from carbon tetrachloride yielded yellow plates of 4-nitroresorcinol, m.p. 121–122° [lit. m.p. 122° (16)]; yield, 0.112 g.

Anal. Calc'd for $C_6H_5NO_4$: C, 46.46; H, 3.25; N, 9.03.
Found: C, 46.33; H, 3.25; N, 9.00.

3-Chloro-4,6-dinitroanisole. 3-Chloro-6-nitroanisole (3.0 g.), dissolved in 15 cc. of glacial acetic acid, was treated with stirring with 75 cc. of fuming nitric acid (*d.* 1.52) in 15 cc. of glacial acetic acid. The mixture was heated at 110–120° for 2½ hours. The hot reaction mixture was poured into a 400-cc. beaker of crushed ice. After 30 minutes the crystalline precipitate was filtered and washed with ice-water till neutral. The yellow needles melted at 97–98°, yield 3.18 g. Recrystallization from ethanol gave 2.85 g. of colorless needles, m.p. 102.8–103° [lit. m.p. 105° (17)].

3-Phenoxy-4,6-dinitroanisole (VIII). Potassium metal (0.68 g.) was added to 30 cc. of anhydrous methanol. To the resulting solution were added 1.64 g. of phenol and 2 g. of 3-chloro-4,6-dinitroanisole. The mixture was refluxed for 1 hour. A crystalline precipitate separated on cooling and was removed. Both the filtrate and the precipitate were extracted with hot benzene. The extract was concentrated to a small volume. 3-Phenoxy-4,6-dinitroanisole crystallized on cooling and was filtered with suction and dried; yield, 1.32 g., m.p. 154–156°. Decolorization with charcoal and recrystallization from benzene gave nearly colorless needles, m.p. 153.5–154°; yield, 1.04 g.

Anal. Calc'd for $C_{13}H_{10}N_2O_6$: C, 53.79; H, 3.47; N, 9.65.
Found: C, 53.90; H, 3.49; N, 9.60.

3-Phenoxy-4,6-dinitrophenol. A mixture of 3-phenoxy-4,6-dinitroanisole (0.27 g.) and 2.19 g. of potassium hydroxide in 13.81 cc. of water was refluxed in an atmosphere of nitrogen for about 40 minutes (until the anisole went into solution). The hot solution was acidified with concentrated hydrochloric acid. A yellow crystalline precipitate was filtered off and washed with water. The dry material weighed 0.22 g., m.p. 99–148°. Repeated recrystallization from ligroin gave pale yellow needles with m.p. 99–100°. Crystals always remained in the melt which did not liquefy until the temperature was raised considerably higher. A second crystalline form melted at about 168–172°. The compound gave a yellow sodium salt with 20% aqueous sodium hydroxide.

Anal. Calc'd for $C_{12}H_8N_2O_6$: C, 52.18; H, 2.92; N, 10.15.
Found: C, 52.21; H, 2.93; N, 10.21.

3-Phenoxy-6-cyanoanisole (IX). Bromine (6.56 g.) was added dropwise with stirring to 3-phenoxyanisole (8.0 g.) dissolved in 3.28 g. of fused sodium acetate in 8 cc. of glacial acetic acid. The reaction mixture was poured on 100 g. of crushed ice. The heavy oil was extracted with chloroform and the extract was washed with 10% aqueous sodium hydroxide and water and distilled from a water-bath. The residual brown oil (9.12 g.) was dissolved in benzene and adsorbed on alumina. The main band, eluted with benzene, yielded 8.35 g. of brown oil which was further purified by distillation. The distillate [7.80 g., b.p. 180–182° (2 mm.)] was heated for 8 hours with 8.52 g. of cuprous cyanide and a few crystals of anhydrous copper sulfate at 250–255°. The cooled reaction mixture was ground and extracted continuously with acetone. The extract left 3.66 g. of brown oil. Adsorption of its benzene solution on aluminum oxide gave a single band containing 3.64 g. of halogen-free brown oil which was used for the following reactions.

4-Phenoxysalicylic acid (Xa). The oily cyanide (IX) (1.99 g.) was refluxed for 2 hours with 32.7 cc. of 47% hydriodic acid and an equal volume of glacial acetic acid. The mixture was poured on ice and extracted with hot benzene. The extract was distilled to remove water and solvents. The oily residue was taken up in benzene and extracted with 10% aqueous sodium carbonate. Decolorization and acidification of the carbonate solution yielded 0.02 g. of 4-phenoxysalicylic acid which melted at 180–183° after crystallization from benzene-petroleum ether [lit. m.p. 182–183° (11)].

The acid was also obtained by demethylation of the crude cyanide (3.64 g.) with 29.8 g. of potassium hydroxide dissolved in 18.6 cc. of water. The mixture was refluxed in an atmosphere of nitrogen until it became homogeneous and heating was continued for one additional hour. The acidic products were liberated by acidification with concentrated hydrochloric acid. The resulting oily suspension was extracted with benzene and ether and the combined organic layers were extracted with 10% sodium carbonate. The organic layer contained the hydroxy acid as indicated by a positive Folin test. The carbonate extract was Folin-negative. Distillation of the benzene-ether solution furnished a brown oil which was decolorized with Norit and crystallized from benzene-ligroin, yield 1.23 g., m.p. 176–179°. Recrystallization gave m.p. 178–180°. The mixture melting point with authentic 4-phenoxysalicylic acid showed no depression and the compounds gave identical absorption spectra.

2-Methoxy-4-phenoxybenzoic acid (Xb). The carbonate extract from the above demethylation was acidified with concentrated hydrochloric acid. The methoxy acid separated on cooling, yield 0.038 g., melting point and mixture melting point with authentic 2-methoxy-4-phenoxybenzoic acid, 78–80° (11).

Anal. Calc'd for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95.
Found: C, 68.77; H, 4.89.

Absorption spectra. Ultraviolet absorption spectra were determined in 95% ethyl alcohol in concentrations of 5×10^{-5} to 5×10^{-4} moles per liter as described previously (18). The results are given in Table I and in Fig. 1–3.

SUMMARY

Evidence is presented which shows that bromination and nitration of *m*-phenoxyanisole occur to some extent in the 6-position. The significance of the results is discussed.

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