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

THE NITRATION OF *m*-PHENOXYACETANILIDE

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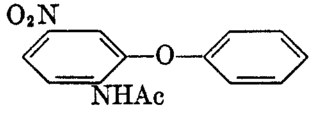
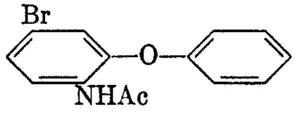
Investigations concerning electrophilic substitution reactions of aromatic acetamino compounds have established a strong directive influence for the acetamino group and a steric effect which tends to inhibit substitution *ortho* to this group (1–7). Thus, *o*-phenoxyacetanilide is nitrated and brominated to give 5-derivatives (I) and (II) (4, 5).

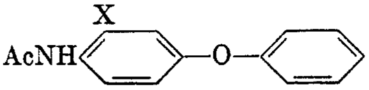


I

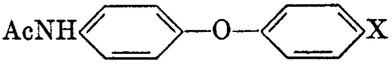


II

The orientation in the *p*-isomer depends, in addition, on the type of attacking ion since nitration and halogenation yield products (III) and (IV) which are substituted in different nuclei.

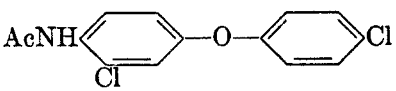


III



IV

While substitution *ortho* to an acetamino group is normally inhibited by the steric effect of the group, this effect can be overcome when the *para* position is blocked, as in the formation of (III, $X = NO_2$) (2, 3) and related compounds (7). Bromination and iodination of *p*-phenoxyacetanilide yield halides of structure (IV); chlorination, on the other hand, leads to a dichloro compound of unknown structure which contains one chlorine in the *p*′-position (5). In view of the ease of dichlorination, it appears likely that the dichloro compound will have structure (V) although no proof is available.



V

The relative sizes of the substituent groups involved are in the order: $Cl < NO_2 < Br < I$ and the corresponding attacking ions, Cl^+, NO_2^+, Br^+, and I^+, can be expected to possess the same order of sizes. The experimental data indicate that cationoid reagents larger than NO_2^+ attack the *para* position of the unsubstituted ring in *p*-phenoxyacetanilide while NO_2^+ and presumably smaller

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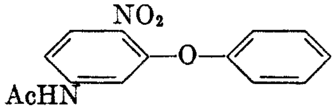
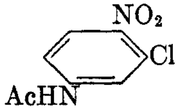
ions can cause substitution *ortho* to the acetamino group. An explanation on steric grounds appears quite attractive.[2, 3]

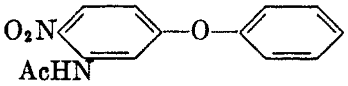
The orientation in *m*-phenoxyacetanilide (VI) has now been found to be *para* to the acetamino group even though each *ortho* position is activated by both groups and the *para* position is hindered to some extent by the phenoxy group. The structure of the single nitration product (VII) has been established by synthesis of the compound from 3-chloro-4-nitroacetanilide (VIII). For purposes of comparison two isomers (IX) and (X) of the nitration product (VII) have also been prepared by unambiguous syntheses.



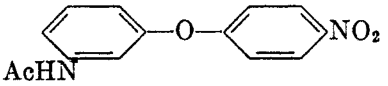
VII



VIII



IX



X

Evidence for steric hindrance in the positions adjacent to the ether oxygen is derived from the usual lack of reactivity of these positions and from the absorption spectra of the isomeric nitroacetanilides (Fig. 1). The main maximum for compound (VII) is at a lower wavelength and shows a lower molecular extinction than *p*-nitroacetanilide which is ascribed to steric interference between the nitro and phenoxy groups. The normal bathochromic (and hyperchromic) shift of the phenoxyl group is observed by comparison of the curves for *o*-nitroacetanilide and the phenoxy derivative (IX), presumably augmented in this case by an increased stability of the chelate ring in (IX).

EXPERIMENTAL

All temperatures uncorrected. Analyses by Ishmael Ortega.

m-Phenoxyacetanilide (VI). *m*-Phenoxyaniline, prepared from *m*-bromoaniline and potassium phenoxide (8), was converted to the acetyl derivative with acetic anhydride according to the procedure of McElvain (9). In view of an over-all yield of less than 10%, alternative procedures were investigated. *m*-Chloroacetanilide proved to be unreactive in the Ullmann reaction under ordinary conditions but *m*-bromoacetanilide (42.8 g.) reacted with potassium phenoxide (from 18.8 g. of phenol) and copper (0.3 g.) in phenol (50 g.) solution at 205–218°. The product was taken up in benzene and was filtered. The filtrate was washed free from phenol with 10% aqueous sodium hydroxide and with water until the washings were neutral. Removal of the solvent left 36.6 g. of crude viscous oil. Dis-

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[2] Recent evidence [Weisburger, Weisburger, and Day, *J. Org. Chem.*, **16**, 1698 (1951)] indicates that steric interference can occur between acetamino and iodo substituents in adjacent positions.

[3] An analogous situation exists in similarly constituted diphenyls. 4-Acetaminodiphenyl is nitrated in the 3-position but yields a 4′-bromo derivative. Here also steric effects may be operative though Bell [*J. Chem. Soc.*, 2339 (1931)] does not consider them very important.

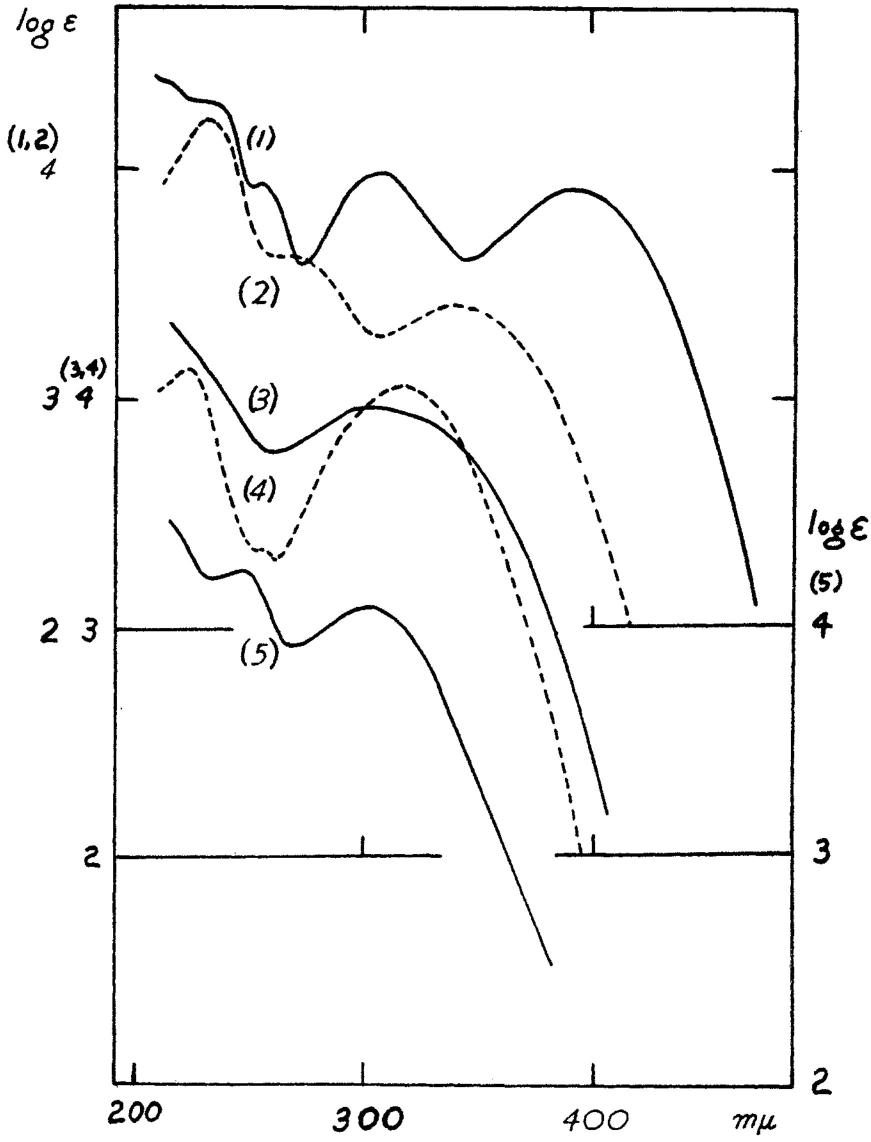

Fig. 1. Absorption Spectra: (1). 2-Nitro-5-phenoxyacetanilide (IX); (2). *o*-Nitroacetanilide; (3). 4-Nitro-3-phenoxyacetanilide (VII); (4). *p*-Nitroacetanilide; (5). *m*-(4-Nitrophenoxy)acetanilide (X).

tillation at 1 mm. gave 21.8 g. of viscous yellow oil (b.p. 180–220°) which proved difficult to crystallize. Adsorption on alumina from benzene solution and elution with the same solvent gave a viscous oil which was eventually crystallized from aqueous acetic acid, m.p. 83.5–84° [lit. m.p. 83° (2)].

Hydrolysis of this material with 20% aqueous hydrochloric acid furnished the known hydrochloride of *m*-phenoxyaniline, m.p. 130–132° [lit. m.p. 139° (2)].

3-Phenoxy-4-nitroacetanilide (VII). *m*-Phenoxyacetanilide (1.0 g.) was recovered unchanged on treating with concentrated nitric acid (1.11 cc.) in acetic acid (7.2 cc.) at 15–

20°. It was successfully nitrated by adding dropwise, with stirring, 4 cc. of concentrated nitric acid in 4 cc. of glacial acetic acid to a solution of 1.03 g. of the material in 4.0 cc. of glacial acetic acid at 80°. The red mixture was poured into 100 cc. of water containing chipped ice and the aqueous mixture was extracted with benzene. The extract was washed with 10% aqueous sodium hydroxide and with water. Solid material from the interphase, filtered and dried, weighed 0.13 g., m.p. 206° (dec.). Ether extraction of the alkaline washings gave an additional 0.065 g. of the same material. The benzene solution yielded 0.51 g. of crude product, m.p. 209–210°. The combined material (0.705 g.), dissolved in benzene containing a little acetone, was adsorbed on aluminum oxide. Development of the column with benzene yielded a single yellow band which was eluted with the same solvent. Further washing with acetone removed a narrow second band. Both of these gave substances with identical absorption spectra. Crystallization of the single product (0.54 g.) from benzene yielded yellow needles, m.p. 209–210°.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA

ACETANILIDE	$\frac{\text{Moles}}{1 \times 10^5}$	$\lambda_{\max_1}$[a]	log ϵ	$\lambda_{\max_2}$	log ϵ	$\lambda_{\max_3}$	log ϵ
Unsubstituted	7.7	—	—	242	4.11	—[b]	—
o-Nitro	4.3	233	4.23	270	3.72	340	3.40
p-Nitro	4.18	222	4.12	316	4.05	—	—
3-Phenoxy (VI)	1.15	—	—	277	3.75	—	—
3-Phenoxy-4-nitro (VII)	3.70	—	—	302	3.95	—	—
3-Phenoxy-6-nitro (IX)	2.13	254	3.96	306	3.98	395	3.92
m-(4-Nitrophenoxy) (X)	7.65	—	—	245	4.25	306	4.08

[a] The assignment of the absorption bands was made in accordance with the work of Doub and Vandenbelt (11); $\lambda_{\max_1}$ corresponds to the second primary band, $\lambda_{\max_2}$ to the first primary band, and $\lambda_{\max_3}$ to the secondary band of these authors.

[b] A shoulder was observed at 280 mμ (log ϵ 2.64 at 3.9×10^{-4} moles/l.) which represents the secondary band. In aqueous solution the shoulder was barely distinguishable and the curve showed only one broad band ($\lambda_{\max}$ 238, log ϵ 4.02). In cyclohexane, on the other hand, the main band ($\lambda_{\max}$ 238, log ϵ 4.13) was narrower and showed two submaxima at 274 and 282 mμ which are to be regarded as secondary bands in view of their smaller intensity (log ϵ 2.93 and 2.82). Acetanilide spectra by H. Sam Lee.

The substance was synthesized by heating 3-chloro-4-nitroacetanilide (VIII) (10) (1.07 g.) with potassium phenoxide (prepared from 0.47 g. of phenol), 0.1 g. of copper powder, and 10 g. of phenol for three hours at 180–204°. The reaction mixture was taken up in hot water and benzene and the benzene layer was washed with 10% aqueous sodium hydroxide and water. Solid material from the interphase was dried on clay plate; m.p. 195–204° (dec.). Recrystallization from ether furnished pure material, m.p. 210–211.5°, yield 0.10 g., which did not depress the melting point of the nitration product. Only traces of solid were contained in the benzene solution.

Anal. Calc'd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.41.

Found: C, 61.89; H, 4.62.

3-Phenoxy-6-nitroacetanilide (IX). A mixture of potassium phenoxide (0.01 mole), 2.0 g. of 3-chloro-6-nitroacetanilide, 0.1 g. of copper powder, and 7 cc. of phenol was heated for two hours at 180–204°. The reaction mixture, decomposed in the usual way, was taken up in benzene, washed free from phenol, and concentrated. A small amount (0.04 g.) of the product crystallized on addition of petroleum ether. The mother liquor was adsorbed on aluminum oxide and eluted with benzene. Dark impurities were strongly adsorbed in the top zone. The yellow eluate gave 1.20 g. of material which was crystallized from benzene. The first crop, m.p. 133–135°, weighed 0.15 g.

Anal. Calc'd for $C_{14}H_{12}N_2O_4 \cdot \frac{1}{2} H_2O$: C, 59.80; H, 4.60.

Found: C, 60.30; H, 4.72.

m-(4-Nitrophenoxy)acetanilide (X). Potassium 3-acetylaminophenoxide was prepared from 1.56 g. of potassium, 100 cc. of methanol, and 6.04 g. of *m*-hydroxyacetanilide (m.p. 143–144°). The solvent was removed, the last traces under reduced pressure. The residue was heated for four hours with 0.2 g. of copper powder, 6.3 g. of *p*-nitrochlorobenzene, and 50 cc. of β,β'-dihydroxydiethyl ether at 190–210°. The reaction mixture was taken up in hot water and benzene and the organic layer was washed with 10% aqueous sodium hydroxide and with water. The crystalline product was filtered from the interphase and dried, yield 1.76 g., m.p. 133–134°. Recrystallization from benzene gave yellow needles, m.p. 135–135.5°.

Anal. Calc'd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.41.

Found: C, 62.00; H, 4.60.

Absorption Spectra. Ultraviolet absorption spectra for the acetamino compounds were determined with a model DU Beckman spectrophotometer in alcoholic solution except as indicated. The results from the measurements in 1-cm. silica cells are summarized in Table I.

SUMMARY

The nitration of *m*-phenoxyacetanilide yields 4-nitro-3-phenoxyacetanilide under the conditions described. The nitration product and two of its isomers have been synthesized and characterized by their physical properties.

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