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ELECTROPHILIC SUBSTITUTION IN ANTHRANILS*[1]

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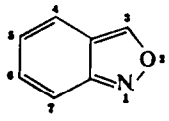
Abstract—Structures are assigned to the so-called "3-methylanthranil dichloride" and "x-chloro-3-methylanthranil". Nitration of anthranils gives mainly the 5-substituted derivatives.

THE anthranil (2,1-benzisoxazole, I) ring system has been known for many years, although at first its structure was the subject of controversy.[2] It is theorefore most

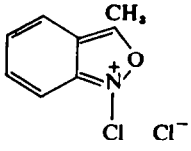


I

surprising that, apart from some inconclusive halogenations, electrophilic substitution reactions do not appear to have been studied. An interest in other heterocycles containing, formally at least, the *ortho*-quinonoid system led us to reinvestigate the chlorination of 3-methylanthranil and to look into the nitration of this compound and of anthranil itself.

By passing chlorine into a cooled solution of 3-methylanthranil in hydrochloric acid, Bamberger[3] found that a dichloride was precipitated, which he represented with both chlorine atoms attached to the nitrogen (II), a formulation which is unacceptable today, and in its modern equivalent (III) incompatible with the physical properties of the dichloride (it is easily soluble in petroleum ether, and has a pleasant, penetrating smell, and so is somewhat volatile).

II



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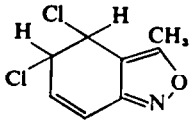


IV

* Dedicated to the memory of Professor H. Stephen.

[1] A preliminary account of some of these results has been published: K. H. Wünsch, H. Linke, A. J. Boulton and Altaf-ur-Rahman, *Chem. Comm.* 408 (1965).

[2] A. Quilico in Weissberger's *The Chemistry of Heterocyclic Compounds* (Edited by R. H. Wiley) Vol. 17; pp. 166–173 Interscience (1962) and G. Speroni *ibid.* pp. 177–222 have written brief reviews of the chemical and physical properties, respectively, of these compounds.

[3] E. Bamberger and F. Elger, *Ber. Dtsch. Chem. Ges.* **36**, 1611 (1903). The dichloride had earlier been made by R. Camps, *Arch. Pharm.* 240, 436 (1902) by a different method. Chlorination and bromination of anthranil have been reported by E. Bamberger and J. Lublin, *Ber. Dtsch. Chem. Ges.* **42**, 1676 (1909); a dichloride, a monobromo and a monochloro derivative different (m.p. 79–79·5°) from our 6-chloroanthranil (m.p. 61·5–62°), and now established to be the 5-halo derivative,[1] were obtained.

We have found that the dichloride gives an NMR spectrum (Fig. 1) which is compatible only with the addition product IV, or with its isomer with the chlorine atoms added across the 6,7-bond. This latter possibility can be rejected on chemical grounds (see later). Assignment of each group of absorptions to its proton, and of the coupling constants, follows logically from the starting assumption that the lowest-field doublet is due to H(7). The coupling constant between the protons adjacent to the chlorine atoms (2·1 c/s) is small enough to permit the assignment of a gauche configuration between them with a reasonable degree of confidence,[4] but it does not make a distinction between *cis*- and *trans*-relationships, and a decision must await the results of X-ray analysis.

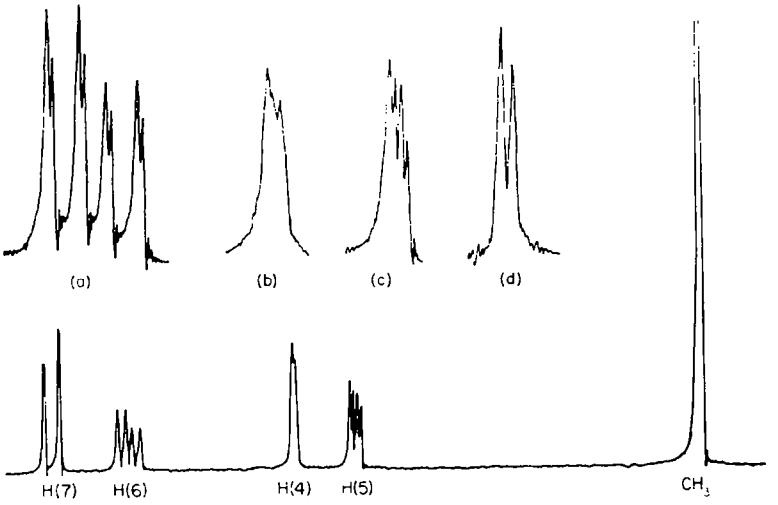
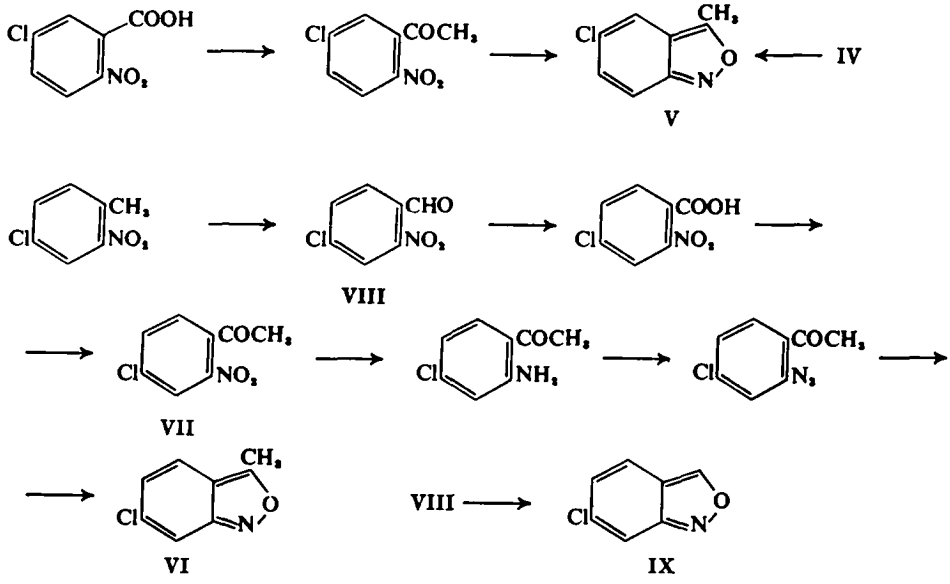


FIG. 1. The NMR spectrum of 3-methylanthranil dichloride (100 Mc/s). Assignments are indicated. Insets: (a) H(6) at high resolution: (b)–(d) H(4) at high resolution; (b) normal run, (c) spin-decoupled from the CH_3 protons, (d) spin-decoupled from H(6). Chemical shifts and coupling constants are as follows: τ (CH_3) 7·54, τ_4 4·82, τ_5 5·23, τ_6 3·71, τ_7 3·20; J_{Me-4} <0·5, $J_{4,6}$ 1·0, $J_{5,6}$ 5·4, $J_{6,7}$ 9·7 c/s.

Steam-distillation of 3-methylanthranil dichloride leads to decomposition and the formation of "x-chloro-3-methylanthranil".[3] The NMR spectrum of this compound revealed a methyl group and an ABC system of aromatic protons with one *ortho*-coupling constant (Table), requiring the chlorine atom to be at position 5 or 6. Both 5- (V) and 6-chloro-3-methyl-anthranil (VI) were synthesized by standard routes, from 5- and 4-chloro-2-nitrobenzoic acid, respectively, and the 5-chloro isomer was found to be the same as the product from the methylanthranil dichloride. The dichloride therefore is assumed to have a chlorine atom at the 5-position, and so to have structure IV.

The reduction of *ortho*-nitroaryl aldehydes or ketones directly to the anthranils is often difficult to accomplish in high yield, because the anthranils themselves are quite easily reduced to *ortho*-aminoaryl keto compounds. The reduction of the ketone VII with tin and acetic acid, for example, gave in one experiment a mixture of anthranil and amine containing ca. 70% of the amine. Therefore, more forcing conditions were

[4] M. Karplus, *J. Chem. Phys.* **30**, 11 (1959); M. Karplus, *J. Amer. Chem. Soc.* **85**, 2870 (1963) and Refs therein.



used (Sn/AcOH/HCl) to obtain the amine exclusively; this was diazotized and converted into the azide, and the azide decomposed in refluxing acetic acid to give the anthranil (VI). The same technique was tried in order to prepare anthranil itself, since poor yields had been obtained on direct reduction with tin and acetic acid.[5] However, it is known that *o*-azidobenzaldehyde is rather difficult to decompose satisfactorily,[6] and we found also that the anthranil was difficult to separate from undecomposed azide. Recent experiments involving reductive cyclization of nitro-groups using trialkyl phosphites[7] led us to try this method, but in only one case (VII → VI) was the method really satisfactory. No anthranil was obtained from *o*-nitrobenzaldehyde by phosphite reduction, and the preparation which was consistently found to be most useful for this compound was by the reduction of the nitro-aldehyde with zinc dust and ammonium chloride solution, followed by steam-distillation of the mixture.[8] Tin and acetic acid gave good yields of 6-chloroanthranil (IX) from the aldehyde VIII, but no anthranil was obtained by phosphite reduction.

The nitration of anthranils was undertaken partly on account of another investigation, which had led to the preparation of 3-methyl-7-nitroanthranil.[9] Because it is known that in several similar ring systems, e.g., benzofuroxan[10] (X; Y = N^+–O^-, Z = 0), benzofurazan[10] (X; Y = N, Z = 0), piazthiole[11] (X; Y = N, Z = S), and

[5] P. Friedländer and R. Henriques, *Ber. Dtsch. Chem. Ges.* **15**, 2105 (1882).

[6] E. Bamberger and E. Demuth, *Ber. Dtsch. Chem. Ges.* **34**, 3874 (1901).

[7] J. I. G. Cadogan and R. J. G. Searle, *Chem. & Ind.* 1282 (1963).

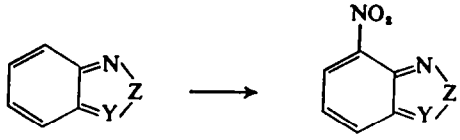
[8] Reduction of *o*-nitrobenzaldehyde in ether with Zn dust and NH_4Claq in the cold gives "agnotobenzaldehyde" [E. Bamberger, *Ber. Dtsch. Chem. Ges.* **39**, 4252 (1906)]. By using EtOH instead of ether, and allowing the reaction to warm, and then steam-distilling the whole, we obtained anthranil in fair yields (40–50%).

[9] A. J. Boulton, P. B. Ghosh and A. R. Katritzky, *Angew. Chem.* **76**, 816 (1964); *Angew. Chem.* (Int. Ed) **3**, 693 (1964); and unpublished work.

[10] P. Drost, *Liebigs Ann.* **307**, 49 (1899).

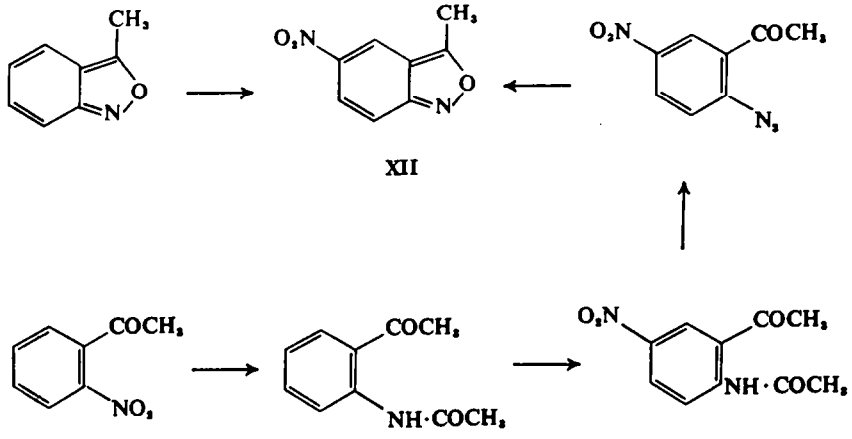
[11] L. S. Efros and R. N. Levit, *Zh. Obshch. Khim.* **23**, 1552 (1953); A. M. Khaletskii and V. G. Pesin, *Ibid.* **20**, 1914 (1950); A. M. Khaletskii and V. G. Pesin, *Ibid.* **24**, 133 (1954).

2-substituted benzotriazoles[12] (e.g. X; Y = N, Z = N·$C_6H_4NO_2$-*p*), nitration occurs at the 4-position (XI), it was thought that direct nitration of 3-methylanthranil (X; Y = CMe, Z = O) might provide an independent route to the 7-nitro-derivative. However, the nitration product was not the same as the compound earlier obtained,

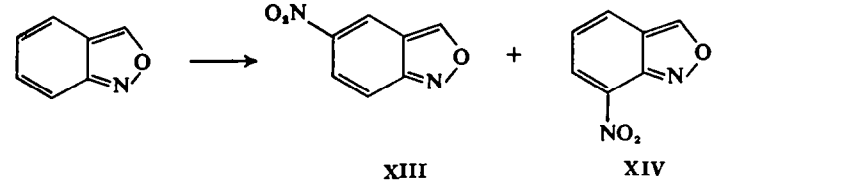


X XI

and NMR evidence suggested that the substituent has entered at the 5- or the 6-position. The UV spectrum was not very different from that of 6-nitroanthranil[13] (Fig. 2), but sufficiently so to suggest that the product was the 5-nitro compound (XII), which was confirmed by an independent synthesis, as outlined in the reaction scheme.



XII



XIII XIV

No other product was isolated from the nitration of 3-methylanthranil; however, when anthranil itself was nitrated, two mono-nitro-derivatives were obtained. The major product (32% yield) showed, like the 3-methyl-5-nitroanthranil, only one ortho-coupling constant in the NMR spectrum, and, since it was not the same as Joshi and Gambhir's 6-nitroanthranil,[13] it was the 5-nitro compound (XIII); this conclusion was confirmed by alkaline degradation. The minor product (5%) showed two

[12] K. Fries, W. Francke and W. Bruns, *Liebigs Ann.* **511**, 213 (1934).
[13] S. S. Joshi and I. R. Gambhir, *J. Amer. Chem. Soc.* **78**, 2222 (1956).

ortho-coupling constants, and so was either the 4- or the 7-nitro derivative. Alkaline degradation[2] of this compound gave 3-nitroanthranilic acid, which requires that it be assigned the 7-nitro structure (XIV). It is remarkable that the introduction of a methyl group at the 3-position leads to a considerable bathochromic shift (20 mμ) in the longest-wavelength UV absorption band (Fig. 2). This effect is also shown by 5-nitroanthranil (14 mμ). It is also rather surprising that no 7-nitro isomer was isolated from the nitration of 3-methylanthranil, but its formation in small yield ($<$ ca. 2%) cannot altogether be ruled out.

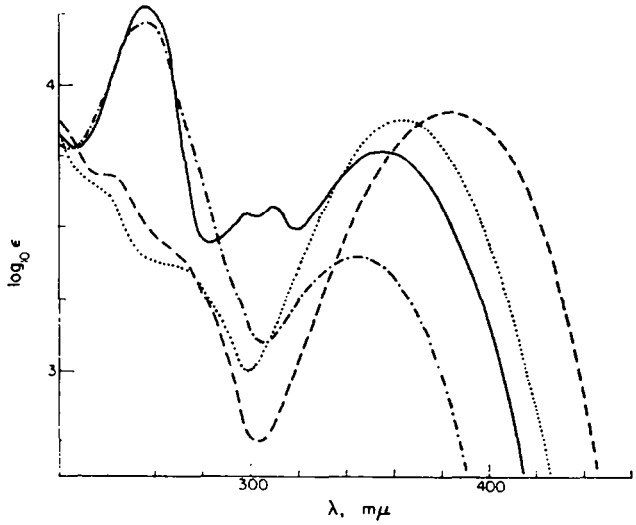


FIG. 2. The UV spectra of nitroanthranils.
——— 3-Methyl-5-nitroanthranil
-·-·-·-·- 6-Nitroanthranil
····· 7-Nitroanthranil
– – – – – 3-Methyl-7-nitroanthranil

NMR chemical shifts and coupling constants of the anthranils investigated are listed in the Table. Noteworthy is the low-field absorption found when the 3-position is unsubstituted, and particularly when a nitro group is present: it is coupled to the proton at the 7-position, when one is present.

This work has established the preference of two anthranils for attack by certain electrophiles at the 5-position. While, as pointed out earlier, this represents a departure from the behaviour of other formally analogous compounds, we would not feel justified in elaborating an explanation for these results on the basis of the few data presented here. Recent calculations by Berthier and Del Re, using a semi-empirical HMO method, indicate that it is the 7-position which carries the highest electron-density in the isolated molecule.[14] However, their figures are not likely to be applicable to the solvated, and possibly also protonated, species which undergoes reaction. In any case, it would be rash to assume that ground-state electron densities are a reliable guide in making a choice between transition states.

[14] G. Berthier and G. Del Re, *J. Chem. Soc.*, 3109 (1965).

TABLE 1. THE NMR PARAMETERS OF ANTHRANILS[a]

Substituents	Solvent	τ_3	τ_4	τ_5	τ_6	τ_7	$J_{4,5}$	$J_{5,6}$	$J_{6,7}$	Other J values
6-Cl	Me_2CO	0·84	2·54	3·06	(Cl)	2·47	9·5	—	—	$J_{3,7} = 1·0$; $J_{4,7} = 0·8$; $J_{5,7} = 1·6$
5-Cl-3-Me	Me_2CO	7·27[b]	2·59	(Cl)	2·85	2·53	—	—	8·9	$J_{4,6} = 0·9$; $J_{4,7} = 1·0$
6-Cl-3-Me	Me_2CO	7·28[b]	2·52	3·18	(Cl)	2·44	10·6	—	—	$J_{4,7} = 0·6$; $J_{5,7} = 1·2$
5-NO_2	Me_2CO	−0·03	1·10	(NO_2)	1·88	2·17	—	—	10·8	$J_{3,7} = 1·0$; $J_{4,6} = 1·9$; $J_{4,7} = 1·3$
6-NO_2	Me_2CO	0·13	1·95	2·23	(NO_2)	1·84	9·6	—	—	$J_{3,7} = 0·9$; $J_{4,7} = 1·2$; $J_{5,7} = 1·4$
7-NO_2	Me_2CO	−0·06	1·62	2·60	1·44	(NO_2)	9·0	7·6	—	$J_{4,6} = 1·0$
3-Me-5-NO_2	Me_2CO	7·20[b]	1·10	(NO_2)	1·90	2·27	—	—	9·7	$J_{4,6} = 2·2$; $J_{4,7} = 0·8$
3-Me-7-NO_2[c]	Me_2SO	—[d]	1·62	2·75	1·45	(NO_2)	9·0	7·5	—	$J_{4,6} = 0·8$

[a] τ values in ppm (tetramethylsilane $\tau = 10$). J values in c/s; [b] Me group (spectrum in CCl_4); [c] Ref. 8; [d] obscured by solvent peak.

EXPERIMENTAL

4,5-*Dichloro*-3-*methyl*-4,5-*dihydroanthranil*, IV ("3-methylanthranil dichloride"), was prepared following Bamberger's method,[8] and had m.p. 99–100° (lit.[8] m.p. 101–102°). It was converted into "x-chloro-3-methylanthranil", m.p. 97° (lit.[8] m.p. 97·5–98°) by steam-distillation.

5-*Chloro*-3-*methylanthranil* (V). 5-Chloro-2-nitroacetophenone[15] (1·0 g) was reduced by tin foil (2·0 g) in acetic acid (15 ml). The mixture was then poured into water (250 ml) and steam-distilled. The distillate was ether-extracted, the extracts dried ($MgSO_4$) and the ether distilled, leaving 5-*chloro*-3-*methylanthranil* (0·69 g, 82%) as colourless plates, m.p. 97–98°. (Found: C, 57·1; H, 3·3; N, 8·1. C_8H_6ClNO requires: C, 57·3; H, 3·6; N, 8·4%), identical (IR and mixed m.p.) with the product obtained from the dichloride.

4-*Chloro*-2-*nitrobenzaldehyde* (VIII). 4-Chloro-2-nitrotoluene (50 g) was oxidized in a mixture of acetic anhydride (500 ml), acetic acid (500 ml), and H_2SO_4 (150 ml), by slow addition of powdered CrO_3 (80 g), with stirring and external cooling, to maintain a temp of 0–5°. After addition was complete the mixture was stirred for 5 hr more, and then poured into ice. The precipitated solids were filtered off, washed, first with water, then with cold 5% Na_2CO_3aq, and then crystallized from pet. ether, giving 4-*chloro*-2-*nitrobenzal diacetate* as needles, (36 g, 42%) m.p. 110–111°. (Found: C, 46·2; H, 3·5. $C_{11}H_{10}ClNO_6$ requires: C, 45·9; H, 3·5%.) The diacetate (28·6 g) was boiled with a mixture of conc HCl (200 ml), water (225 ml) and EtOH (40 ml) for 45 min. The mixture was cooled to 0°, and the aldehyde separated by filtration and crystallized from pet. ether as plates (13·2 g, 71%), m.p. 63° (lit.[17] m.p. 64°).

6-*Chloroanthranil* (IX). 4-Chloro-2-nitrobenzaldehyde (2·0 g) in acetic acid (25 ml) was reduced with tin foil (2·5 g). The mixture was steam-distilled, and the distillate extracted with ether. The extracts were dried and the ether removed and replaced by benzene–light petroleum (1:1), and the solution run through a short (5 cm) column of alumina, eluting with the same solvent. The solution collected was evaporated and the residue of 6-*chloroanthranil* crystallized from light petroleum as plates (1·15 g, 70%), m.p. 61·5–62°. (Found: C, 54·8; H, 2·3; N, 9·0. C_7H_4ClNO requires: C, 54·7; H, 2·6; N, 9·1%.)

Oxidation of 4-chloro-2-nitrobenzaldehyde to the acid using $KMnO_4$ in acetic acid under various conditions of temp and added H_2SO_4 was successful, but yields were consistently poor, and it was most economical to resort to commercial sources for the supply of 4-chloro-2-nitrobenzoic acid required for the preparation of 4-chloro-2-nitroacetophenone.

6-*Chloro*-3-*methylanthranil* (VI). 4-Chloro-2-nitroacetophenone[15] (4·1 g) in 10N HCl (15 ml) and acetic acid (15 ml) was treated with tin foil (4 g). After the reaction was complete, the mixture was

[15] The *o*-nitroketones were prepared by Bowman's method [*J. Chem. Soc.* 322 (1950)]; their properties were in accord with earlier data.[16]

[16] N. J. Leonard and S. N. Boyd, *J. Org. Chem.* **11**, 405 (1946).

[17] F. Sachs and R. Kempf, *Ber. Dtsch. Chem. Ges.* **36**, 3299 (1903).

cooled, diluted with water and neutralized with Na_2CO_3aq. The amino-ketone was extracted from the resulting suspension with ether, isolated by evaporation of the ether and diazotized at 0° in a mixture of H_2SO_4 (3 ml) and acetic acid (10 ml) by addition of $NaNO_2$ (3·0 g) in water (10 ml). After 1 hr, to complete the diazotization, sodium azide (5·0 g) in water (10 ml) was added, and when the rapid evolution of N_2 had subsided the precipitated azide was extracted with ether and steam-distilled. Extraction of the distillate with ether, drying ($MgSO_4$) the extracts, evaporation of solvent, and crystallization of the residue from pet ether, gave the 6-*chloro*-3-*methylanthranil* as plates (2·5 g, 73%), m.p. 56–57°. (Found: C, 57·4; H, 3·9; N, 8·3%.)

Reductions with trialkyl phosphites. The method generally applied was as follows: The *o*-nitro-aldehyde or ketone (1–2 g) was heated to reflux 5–6 hr with trimethyl phosphite (7 ml) in EtOH (10 ml). It was then poured onto ice and allowed to stand 1 hr, to hydrolyse the excess of ester, and then the whole mixture was steam-distilled to isolate the anthranil formed. Yields of anthranil obtained from the following nitro compounds are given in parentheses: 4-chloro-2-nitroacetophenone (71%); 5-chloro-2-nitroacetophenone (27%); 2-nitroacetophenone (29%); 4-chloro-2-nitrobenzaldehyde and 2-nitrobenzaldehyde (0%). Shorter reaction times did not improve the yield in any case. More forcing conditions (reflux with triethyl phosphite for 3 hr) gave only a trace of chloroanthranil from 5-chloro-2-nitroacetophenone.

5-*Nitro*-3-*methylanthranil* (XII)

(a) *By nitration of* 3-*methylanthranil.* 3-Methylanthranil[9] (5·15 g) was slowly dissolved in H_2SO_4 (30 ml) at 0°, with shaking to minimize local overheating. A solution of KNO_3 (4·1 g) in H_2SO_4 (20 ml) was added dropwise, the temp being held below 5°. After addition was complete, the solution was warmed to 40° for 10 min, then poured into ice. The precipitated solid was collected and crystallized from benzene–pet. ether (1:1), or from EtOH, giving short, pale yellow, needles (5·5 g, 80%) of the 5-*nitro compound*, m.p. 145–146°. (Found: C, 53·9; H, 3·2; N, 15·95. $C_8H_6N_2O_3$ requires: C, 53·9; H, 3·4; N, 15·7%.) The crude precipitated solid, and the purified material, and the material remaining after evaporation of the mother liquors of the first crystallization, all showed virtually the same IR spectrum, and no evidence for the presence of any other isomer could be found.

(b) *From* 5-*nitro*-2-*aminoacetophenone.* The acetophenone (2·7 g) (from 2-nitroacetophenone, by reduction, acetylation, nitration and deacetylation[16]) in H_2SO_4 (2 ml) and acetic acid (10 ml) was diazotized at 0–5° by addition of $NaNO_2$ (2·5 g) in water (10 ml), stirring until the solution became clear. Then sodium azide (5 g) in water (20 ml) were added, producing a vigorous effervescence and a pale yellow precipitate of the azide (0·87 g, 28%), which was not purified, but converted directly into the anthranil by refluxing for 20 min in acetic acid. Cooling, pouring into water and crystallization of the precipitate from EtOH gave a product (0·61 g, 81%) identical (m.p., mixed m.p. and IR spectrum) with the nitration product prepared as above, λ_{max} 256, 298, 309 and 356 mμ (ε_{max} 18,800, 3600, 3800 and 5800).

Nitration of anthranil. Anthranil[9] (3·87 g) was carefully dissolved in ice-cold H_2SO_4 (25 ml), and the mixture was well stirred while KNO_3 (3·0 g) in H_2SO_4 (20 ml) was added over 10 min. After a further 10 min at 0° the mixture was warmed to 40° for 10 min, then poured into ice and filtered. The precipitated solids were washed and dried, and dissolved in benzene–light petroleum (1:1), to separate the required compounds from a quantity of insoluble tarry matter. The dissolved material was chromatographed on alumina, eluting first with benzene–light petroleum (1:1), then with benzene, into a faster-running orange–red band, containing 5-*nitroanthranil* (XIII) [1·70 g, 32%, yellow needles, m.p. 120–121°, from pet. ether. (Found: C, 51·2; H, 2·3; N, 17·25. $C_7H_4N_2O_3$ requires: C, 51·2; H, 2·5; N, 17·1%) λ_{max} 252·5, 292, 304 and 343 mμ (ε_{max} 16,000, 2600, 2700 and 3650)], and a slower, purple band, which yielded 7-*nitroanthranil* (XIV) [0·29 g, 5%, yellow needles, m.p. 144–145°, from pet. ether. (Found: C, 51·3; H, 2·6; N, 16·7%), λ_{max} 364 mμ (ε_{max} 7550), with inflections at 237 and 267 mμ].

7-Nitroanthranil (ca. 3 mg) was dissolved in EtOH (0·5 ml) and water (0·5 ml), and 3N NaOH (0·2 ml) was added. The mixture instantly turned a deep red colour, fading to yellow on boiling 5 min. Dilution with water (1 ml) and cooling gave 3-nitroanthranilic acid (ca. 3 mg) m.p. 201° (dec), identical with a sample prepared by the action of ammonia on 2-bromo-3-nitrobenzoic acid.[18] A similar degradation of the 5-nitroanthranil (3·0 mg) gave 5-nitroanthranilic acid (2·2 mg, 65%), m.p.

[18] P. J. Culhane, *Organic Syntheses* Coll. I, 2nd Ed., p. 125 (1941).

259–260°, identical by comparison with a sample prepared by acetylation, nitration and deacetylation of anthranilic acid.[19]

UV spectra were measured on a Perkin–Elmer model 137 UV recording spectrophotometer, checking peak intensities on a Unicam SP 500 instrument. The NMR spectrum of the 3-methylanthranil dichloride was measured on a Varian Associates HA-100 spectrometer; the spectra of the rest of the compounds were taken on a Perkin–Elmer 40 Mc/s instrument.

Acknowledgements—We are grateful to Dr. J. Feeney, of Varian Associates, Russell House, Walton-on-Thames, for the 100 Mc/s spectrum, and to Messrs B. Ternai and G. J. T. Tiddy for the computer refinement of spectral data.

[19] H. Rupe, *Ber. Dtsch. Chem. Ges.* **30**, 1097 (1897).