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THE NITRATION OF SOME METHYL SUBSTITUTED INDOLE-3-ALDEHYDES*

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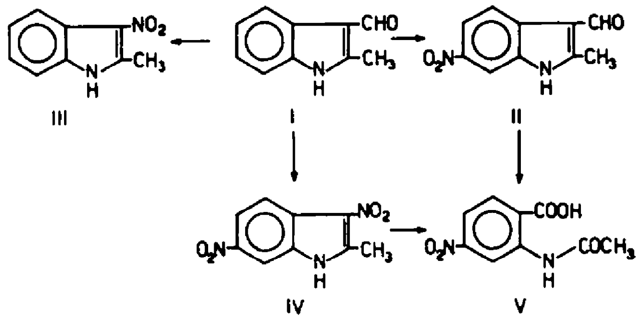
Abstract—The reactions of some methyl derivatives of indole-3-aldehyde with nitric acid in acetic acid medium have been investigated. 2-Methylindole-3-aldehyde gives the 6-nitro derivative, together with some 2-methyl-3-nitro- and 2-methyl-3,6-dinitroindole. 1-Methylindole-3-aldehyde gives 4- and 6-nitro derivatives, 1-methyl-3-nitroindole, 1-methyl-5-nitroisatin, N-formyl-N-methyl-5-nitroanthranilic acid and N-methyl-5-nitroanthranilic acid. 1,2-Dimethylindole-3-aldehyde gives 1,2-dimethyl-3-nitroindole, 1,2-dimethyl-3,6-dinitroindole, N-methyl-4-nitroanthranilic acid and 4- and 6-nitro-2-methylaminobenzonitrile.

Indole-3-aldehydes can readily be prepared in excellent yields by the Vilsmeier-Haack reaction,[1] and used as intermediates in the synthesis of some indole derivatives. Previous work[2,3] has shown that, on treatment with nitric acid, indole-3-aldehyde yields simple, easily separable nitro compounds, while indole and its alkyl derivatives polymerize into mixtures of unknown composition.[4] The present work was undertaken to see whether alkyl groups would render the indole ring less prone to oxidation and thus lead to better yields of nitro derivatives. In this study 1-methyl-, 2-methyl- and 1,2-dimethyl indole-3-aldehydes were treated with nitric acid in acetic acid medium.

CHART I



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* Taken in part from the doctoral thesis of O. Livi, University of Pisa, 1963.

[1] F. T. Tyson and J. T. Shaw, *J. Amer. Chem. Soc.* **74**, 2273 (1952); G. F. Smith, *J. Chem. Soc.* 3842 (1954).

[2] G. Berti and A. Da Settimo, *Gazz. Chim. Ital.* **91**, 728 (1961).

[3] W. E. Noland and R. D. Rieke, *J. Org. Chem.* **27**, 2250 (1962).

[4] G. Berti and A. Da Settimo, *Gazz. Chim. Ital.* **90**, 525 (1960).

Nitration of 2-methylindole-3-aldehyde (I) gives the 6-nitro derivative (II) in about 50% yield, as against the 16% yield reported earlier when indole-3-aldehyde is similarly treated.[2] Some 2-methyl-3-nitroindole (III) and 2-methyl-3,6-dinitroindole (IV) are also formed as subsidiary products which were identified by oxidation to N-acetyl-4-nitroanthranilic acid (V).

The nitration of 1-methylindole-3-aldehyde (VI) yields only about 20% of the 6-nitro (VII) and 4-nitro (VIII) derivatives, which were identified by methylation of the known compounds IX and X. In this case too, some replacement of the formyl by the nitro group takes place, with formation of 1-methyl-3-nitroindole (XI), the UV-spectrum of which is very similar to the spectra of other 3-nitroindoles (Fig. 1), and quite different from the spectra of indoles carrying a nitro group in other positions.[5] In the nitration mixture of VI substantial amounts of N-formyl-N-methyl-5-nitroanthranilic acid (XIII), N-methyl-5-nitroanthranilic acid (XIV) and N-methyl-5-nitroisatin (XII) were present. These compounds were obviously formed by oxidation of VI followed by nitration, and not *vice-versa*, since in the latter case 1-methyl-5-nitroindole-3-aldehyde would have been formed which would, moreover, be in contrast

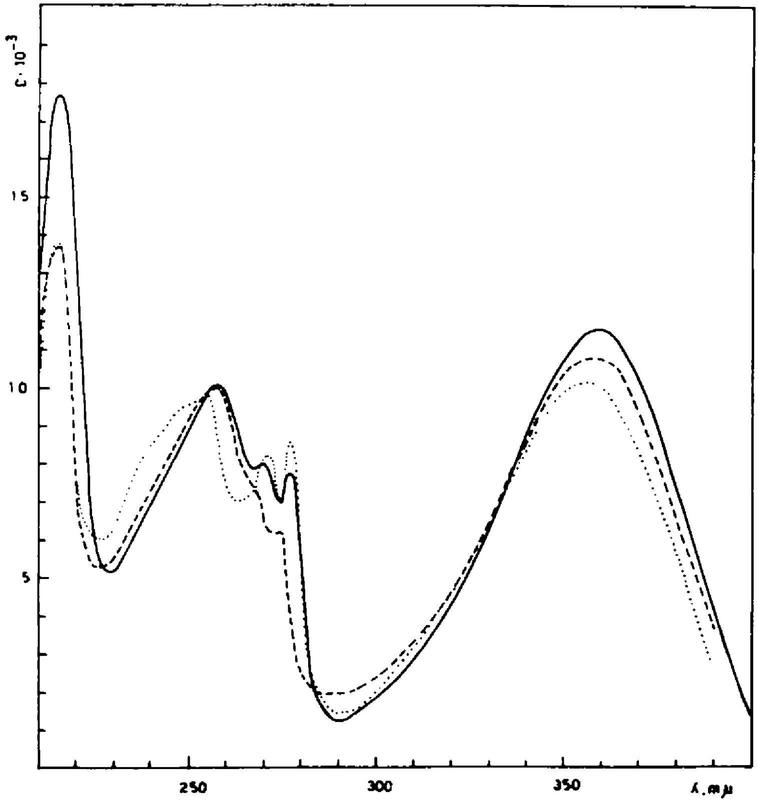

FIG. 1. UV Spectra (Ethanol solutions): ..... 2-methyl-3-nitroindole; – – – – 1-methyl-3-nitroindole; ——— 1,2-dimethyl-3-nitroindole.

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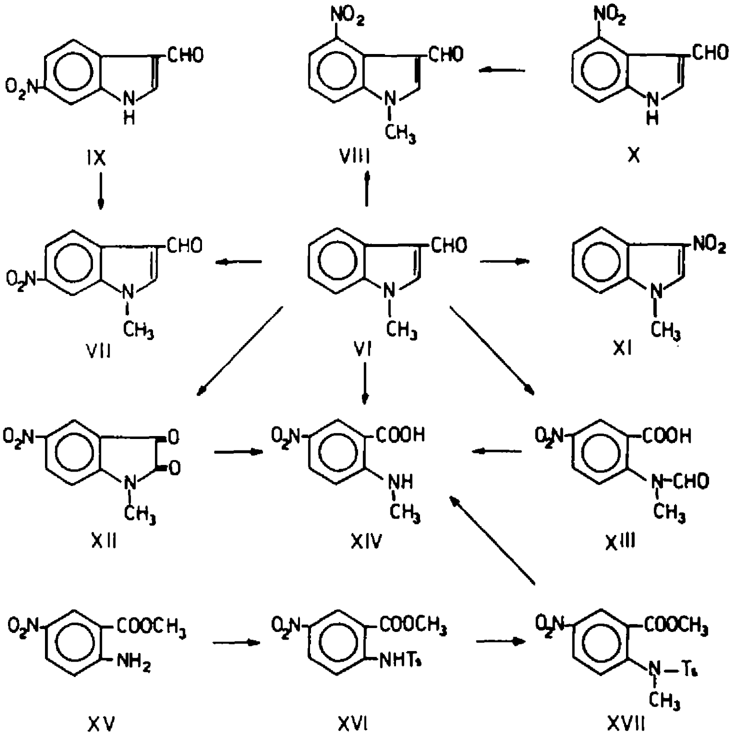
[5] G. Berti, A. Da Settimo and D. Segnini, *Gazz. Chim. Ital.* 90, 539 (1960).

with the orientations observed in all nitrations of indoles in acetic acid,[2,4,6] as well as with the formation of the nitro aldehydes VII and VIII observed in the present case. The acid XIV can be prepared from 5-nitroanthranilic acid, and also from XIII by acid or alkaline hydrolysis or by pyrolysis, and from XII by oxidation with hydrogen peroxide and alkali, as shown in Chart II.

CHART II



The main product of nitration of 1,2-dimethylindole-3-aldehyde (XVIII) is 1,2-dimethyl-3-nitroindole (XIX) (yield 30%), which is oxidized to N-acetyl-N-methylanthranilic acid (XXI) with peroxyacetic acid. The same acid is obtained by similar oxidation of XVIII. The nitration product also contains the dinitro derivative XX, which can be oxidized to XXII, and the degradation product XXIII. Two unexpected subsidiary products are 2-methylamino-4-nitro- (XXIV) and 2-methylamino-6-nitrobenzonitrile (XXV), which were chromatographically isolated in small quantities from the crude neutral fraction, while somewhat larger quantities of the two nitriles were obtained from the alkaline washings on acidification, thus showing the presence of acidic precursors of XXIV and XXV in the nitration mixture.

The formation of the two nitriles can be explained by the reaction of nitrous acid (present in the nitration mixture) on the nitro aldehydes XXXII, followed by elimination of the formyl group from the intermediate nitroso compound XXXIV.

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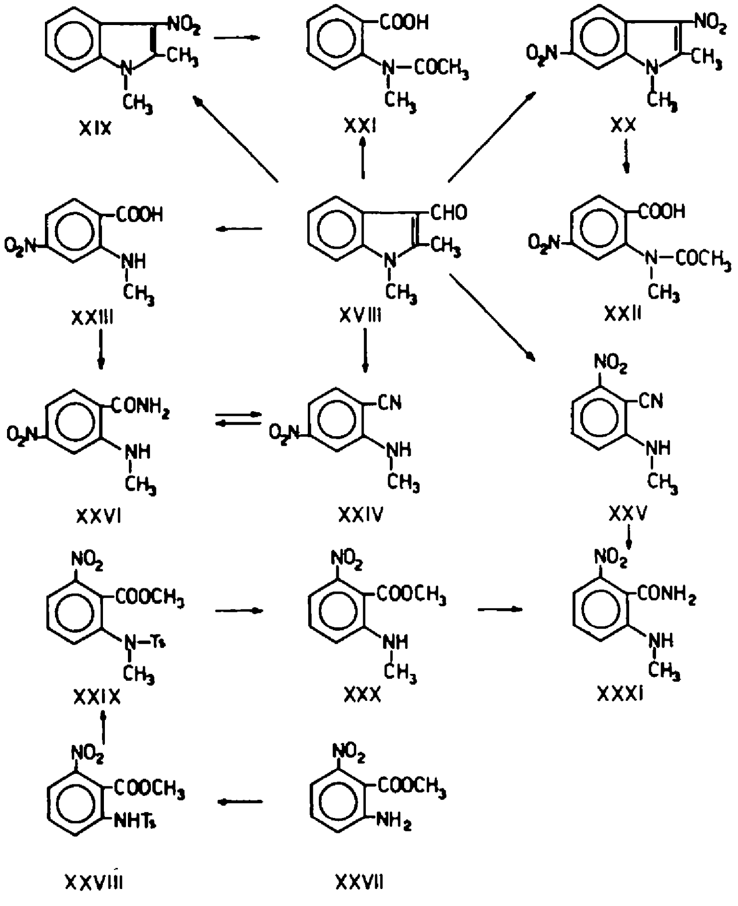
[6] R. de Fazi, G. Berti and A. Da Settimo, *Gazz. Chim. Ital.* **89**, 2238 (1959).

Oxidation of XXXIV would produce the isatin oximes XXXV, which could give the nitriles by elimination of carbon dioxide. The transformation of isatin oximes into amino nitriles is a known reaction,[7] which, however, takes place under conditions which are quite different from the present ones. A better explanation would be in a hydrolytic attack on the double bond of XXXIV, favoured by the electron-withdrawing properties of the nitroso group as observed in a similar facile hydrolytic ring-opening in the case of 3-nitrobenzofuran.[8] Compound XXXVII is tautomeric with XXXVIII and XXXIX, which could be the acidic precursors of the nitriles XXXVI.

CHART III



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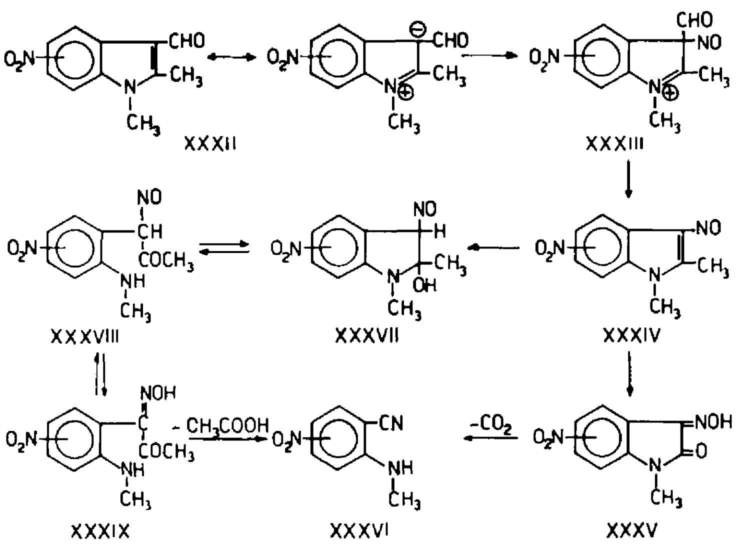
[7] W. Borsche, H. Weussmann and A. Frizsche, *Ber. Dtsch. Chem. Ges.* **57**, 1149 (1924); G. Bargellini and C. Jacobelli Turi, *Gazz. Chim. Ital.* **84**, 157 (1954); G. R. Bedford and M. W. Partridge, *J. Chem. Soc.* 1633 (1959).

[8] F. Kaluza and G. Perold, *Chem. Ber.* **88**, 597 (1955).

CHART IV



The transformation of XXXIX into XXXVI would be a case of the reaction of diketone and ketol oximes, known as "second order Beckman rearrangement".[9] Work is in progress to test this mechanistic hypothesis.

It will be observed from the results described above that a methyl group in position 2 stabilizes the indole system towards oxidation and causes a better yield of nitro derivative. On the other hand a methyl substituent in position 1 decreases the stability of the aldehyde group, probably because it prevents the equilibrium between the indole-3-aldehyde and the 3-(hydroxymethylene)indolenine forms. Side-reactions predominate, particularly the one involving exchange between the formyl and nitro groups. Such reactions could take place by a mechanism similar to that indicated for the transformation XXXII → XXXIV, through an attack of the nitronium ion on carbon 3, followed by elimination of the formyl group. Several cases of similar exchange reactions are known in pyrrole chemistry.[10]

EXPERIMENTAL

M.ps were determined on a Kofler apparatus and are uncorrected. IR spectra were taken on a Perkin-Elmer Infracord 137 in Nujol mulls, UV spectra on a Beckman DU in ethanol solutions. All comparisons between compounds described in this paper and those prepared according to the literature are on the basis of IR spectra and mixed m.ps.

Nitration of 2-methylindole-3-aldehyde (I)

To a suspension of 1 g I[11] in 8 ml acetic acid, 0·96 ml HNO_3 (*d* 1·37) was added drop-wise and the mixture was heated on a steam-bath. When an exothermic reaction started at about 80°, heating

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[9] L. G. Donaruma and W. Z. Heldt, *Org. Reactions* **11**, 38 (1960).

[10] G. Ciamician and P. Silber, *Ber. Dtsch. Chem. Ges.* **18**, 1456 (1885); H. Fischer and W. Zerweck, *Ibid.* **55**, 1942, 1949 (1922).

[11] E. Leete, *J. Amer. Chem. Soc.* **81**, 6023 (1959).

was discontinued and the precipitate formed on cooling (0·6 g) was crystallized from dimethylformamide–water to give 2-*methyl-6-nitroindole-3-aldehyde* (II), which decomposes slowly without melting, above 260°, λ_{max} (log ε) 284 (4·35), 346 mμ (3·97, infl), λ_{NH} 3·20, λ_{CO} 6·10, λ_{NO_2} 6·62, 7·55 μ. (Found: N, 13·81. $C_{10}H_8N_2O_3$ requires: N, 13·72%).

The acetic acid filtrate deposited on standing 0·25 g of a residue, which was dissolved in benzene–acetone (9:1) and chromatographed on a column of neutral Al_2O_3 (act. II) of 37 × 1·1 cm. Elution with the same mixture of solvents gave 10 mg 2-*methyl*-3-*nitroindole*, m.p. 247°, λ_{NH} 3·10, λ_{NO_2} 6·50, 7·38 μ (UV spectrum, see Fig. 1), identical with a sample prepared according to Angeli and Angelico.[12] Further elution gave a series of fractions, which were crystallized from benzene–ethanol to give 75 mg 2-*methyl*-3,6-*dinitroindole* (IV), yellow needles, m.p. 300–302°, λ_{max} (log ε) 207 (4·23), 222 (4·00, infl.), 308 (4·15), 347 mμ (4·16), λ_{NH} 3·10, λ_{NO_2} 6·61, 7·51 μ. (Found: C, 49·03; H, 3·48; N, 18·87. $C_9H_7N_3O_4$ requires: C, 48·87; H, 3·19; N, 19·00%). Further elution yielded mixtures, from which a small amount of an unidentified compound, m.p. 268–271°, was obtained.

Degradation of II *and* IV

A mixture of 0·15 g II, 1·7 ml 36% H_2O_2 and 6 ml acetic acid was heated on a steam bath for 90 min, the solvent eliminated under red. press. and the residue crystallized from ethanol–water to yield 70 mg N-acetyl-4-nitroanthranilic acid (V), m.p. 218–219°, identical with a sample prepared according to Seidel and Bittner.[13]

Similarly, 60 mg IV, on heating for 50 min with 3 ml acetic acid and 0·6 ml 36% H_2O_2, followed by evaporation, extraction with 2N Na_2CO_3 and acidification with HCl, gave 20 mg V.

Nitration of 1-*methylindole*-3-*aldehyde* (VI)

Since the yields of the different products of this reaction varied considerably and depended on the conditions of heating, a typical run is described here. A solution of 2 g VI[14] in 16 ml acetic acid was treated with 2 ml HNO_3 (*d* 1·37) and heated on a steam-bath. As soon as the thermometer used as a stirrer indicated the beginning of an exothermic reaction, the flask was cooled with cold water (to avoid formation of larger amounts of the degradation products XIII and XIV), then heated again on the steam-bath for 20 min. The acetic acid was eliminated under red. press. (the last traces in a vacuum dessiccator over KOH) and the residue taken up in 12 ml ethyl acetate, from which a mixture of compounds (0·55 g) crystallized, which on the basis of its IR spectrum was composed of VIII, XIII and a little XI and XII (Fraction A). XIII was eliminated by treatment with cold 2N Na_2CO_3, XII with 2N NaOH and the residue was crystallized from ethanol to give 0·10 g 1-*methyl-4-nitroindole-3-aldehyde* (VIII), orange needles, m.p. 233–234·5°.

The Na_2CO_3 washings on acidification yielded 0·37 g 5-*nitro*-N-*formyl*-N-*methylanthranilic acid* (XIII), yellow prisms (from acetone), m.p. 200°, resolidifying and melting again at 262–264° (transformation into XIV), λ_{CO} 5·88, 6·10, λ_{NO_2} 6·60, 7·48 μ. (Found: C, 48·50; H, 3·62; N, 12·38. $C_9H_8O_5N_2$ requires: C, 48·22; H, 3·60; N, 12·50%).

The mother liquor of fraction A was concentrated, and the 0·4 g residue (fraction B) obtained was extracted with hot 2N Na_2CO_3. The insoluble part consisted mainly of VII, in admixture with VIII and XI. The alkaline extract was acidified to yield almost pure 1-*methyl-5-nitroisatin* (XII; 0·1 g) which crystallized from ethanol in oranges needles, m.p. 204–206° (lit., m.p. 203°[15]); λ_{CO} 5·77, 6·21, λ_{NO_2} 6·60, 7·50 μ. (Found: C, 52·40; H, 2·73; N, 13·35. $C_9H_6O_4N_2$ requires: C, 52·43; H, 2·93; N, 13·59%).

The filtrate from fraction B was evaporated to dryness and the residue extracted with 2N NaOH. The alkaline extracts were acidified to yield 0·65 g of a semi-crystalline material, which on the basis of its IR spectrum contained about 50% XIV, and some XII. The alkali-insoluble part (0·45 g) consisted of VII and XI in about equal amounts, which could not be separated by fractional crystallization, but their presence was confirmed by the IR spectrum and by thin-layer chromatography over silica, using 9:1 benzene–acetone mixture: VII has R_f 0·21 (yellow fluorescence in the UV), XI 0·68 (violet fluorescence). The mixture on chromatography through a 25 × 1·1 cm column of

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[12] A. Angeli and F. Angelico, *Gazz. Chim. Ital.* **30**, II, 268 (1900).

[13] H. Siedel and J. C. Bittner, *Monatsh.* **23**, 431 (1902).

[14] V. M. Rodionov and T. K. Veselovskaya, *Zh. Obshch Khim.* **20**, 2202 (1950).

[15] W. Borsche, H. Weussmann and A. Fritzsche, *Ber. Dtsch. Chem. Ges.* **57**, 1151 (1924).

Al_2O_3, using benzene as eluant gave, as first eluted product, 0·22 g 1-*methyl*-3-*nitroindole* (XI), m.p. 156–157°, after crystallization from benzene–hexane or sublimation at 140°/2 mm; λ_{NO_2} 6·53, 7·34 μ (UV spectrum, see Fig. 1). (Found: C, 61·70; H, 4·71; N, 15·92. $C_9H_8N_2O_2$ requires: C, 61·36; H, 4·58; N, 15·90%). Further elution with benzene produced a few mg of an unidentified product, m.p. 241–243° (no CO band in the IR). On continuing the elution with 9:1 benzene–acetone, 0·14 g of a compound was obtained, m.p. 242–244° (from acetone), λ_{CO} 5·98, λ_{NO_2} 6·65, 7·49 μ, which was not present before the chromatography and was derived from a transformation of the aldehyde VII, as shown by subjecting pure VII to chromatography under the same conditions. It is probably 4-(1-*methyl*-6-*nitro*-3-*indolyl*)-3-*buten*-2-*one*, formed by condensation of VII with the acetone used as eluant (Found: C, 64·42; H, 5·06; N, 11·87. $C_{13}H_{12}N_2O_3$ requires: C, 63·92; H, 4·95; N, 11·47%).

1-*Methyl*-4-*nitroindole*-3-*aldehyde* (VIII)

A solution of 0·1 g X[16] in 3 ml 7% NaOH was treated with 0·4 ml dimethyl sulphate, stirred 3 hr, treated again with 0·3 ml dimethyl sulphate and enough NaOH to keep the solution alkaline, while stirring for two more hr. The resulting precipitate was taken up in 3 ml 2N NaOH, washed with hot water and crystallized from ethanol to give 80 mg orange needles, m.p. 233–234·5°, identical with those obtained in the nitration of VI; λ_{max} (log ε) 227 (4·31), 292 (3·89), 362 (3·61) mμ; λ_{CO} 6·08, λ_{NO_2} 6·60, 7·52 μ. (Found C, 59·16; H, 4·12; N, 14·08. $C_{10}H_8N_2O_3$ requires: C, 58·82; H, 3·95; N, 13·72%).

1-*Methyl*-6-*nitroindole*-3-*aldehyde* (VII)

Compound IX[2] (0·2 g), treated as described above for the preparation of VIII, gave 0·17 g VII, m.p. 203–205° (from ethanol), λ_{max} (log ε) 284 (4·47), 330 (3·84, infl.) mμ; λ_{CO} 6·07, λ_{NO_2} 6·68, 7·49 μ. (Found: N, 13·97. $C_{10}H_8N_2O_3$ requires: N, 13·72%).

2-*Methylamino*-5-*nitroanthranilic acid* (XIV)

(a) *From* XV. A solution of 1 g of the ester XV[17] and 1·5 g tosyl chloride in 10 ml pyridine was left 2 days at room temp, then diluted with 70 ml water, heated to boiling and filtered to give 0·47 g insoluble material, which after two crystallizations from benzene-hexane (charcoal), produced *methyl* N-*tosyl*-4-*nitroanthranilate* (XVI), m.p. 168–170°. (Found: N, 8·07. $C_{15}H_{14}O_6N_2S$ requires: N, 8·01%). A solution of 0·28 g crude XVI in 3 ml ethanol was treated with 2·7 ml 0·3N NaOH, the solvent was evaporated and the dry residue refluxed 4 hr with 1·3 ml methyl iodide in 6 ml acetone. On evaporation of acetone crude XVII was left as residue. It was heated 30 min at 100° with 3 ml conc. H_2SO_4, poured into water, and the precipitate formed was refluxed 30 min with 6 ml 2N NaOH, filtered and acidified with HCl aq. The resulting precipitate was sublimed at 210°/2 mm to yield XIV, m.p. 271–273° (lit. m.p. 258°).[18] (Found: C, 49·36; H, 4·20. $C_8H_8N_2O_4$ requires: C, 48·98; H, 4·11%).

(b) *From* XIII. Compound XIII was transformed into XIV by heating with 2N NaOH or conc. HCl for a short period, by heating at 190° in quinoline, or by sublimation at 200°/2 mm.

(c) *From* XII. A solution of 25 mg XII in 2·5 ml 10% NaOH and 1 ml 3% H_2O_2, left 30 min at room temp, then acidified with HCl aq, gave 15 mg XIV, m.p. 272–273°.

Nitration of 1,2-*dimethylindole*-3-*aldehyde* (XVIII)

To a solution of 2 g XVIII[14] in 16 ml acetic acid 1·8 ml HNO_3 (*d* 1·37) was added dropwise and the reaction mixture heated 1 hr on a steam-bath. The solvent was eliminated under red. press. and the residue obtained was extracted with 15 ml 2N Na_2CO_3. The insoluble part (1·7 g) was extracted with 200 ml boiling benzene (0·3 g tar remaining insoluble) and the solution was chromatographed over a 29 × 1·8-cm column of Al_2O_3 (act. I). The first fractions eluted by benzene (0·7 g) were crystallized from benzene–hexane to give needles of 1,2-*dimethyl*-3-*nitroindole* (XIX) m.p. 190–191°; λ_{NO_2} 6·54 7·35 μ. (UV spectrum see Fig. 1). (Found: C 62·81; H 5·25; N 14·69.

[16] A. Da Settimo, *Gazz. Chim. Ital.* **92**, 150 (1962).

[17] M. T. Bogert and G. Scatchard, *J. Amer. Chem. Soc.* **41**, 2066 (1919).

[18] J. J. Blanksma, *Rec. Trav. Chim.* **21**, 275 (1902).

$C_{10}H_{10}N_2O_2$ requires: C 63·15; H 5·30; N 14·73%). Further elution with benzene gave mixed fractions, containing compounds XIX, XX, XXIV and XXV which were extracted with cold acetone. There remained undissolved 60 mg 1,2-*dimethyl*-3,6-*dinitroindole* (XX), which was crystallized from benzene: m.p. 293–295°, with decomposition; λ_{max} (log ε) 212 (4·17), 220 (4·02, infl.), 308 (4·18), 344 mμ (4·19); λ_{NO_2} 6·62, 7·60 μ. (Found: 51·48; H, 4·23; N, 17·52. $C_{10}H_9N_3O_4$ requires: C, 51·06; H, 3·86; N, 17·87%). The acetone solution was evaporated to dryness and the product sublimed at 150°/2 mm, 15 mg XX remaining as residue. The sublimate (70 mg) was chromatographed over a 32 × 1·1-cm column of neutral Al_2O_3 (act. II). Elution with benzene led to the separation of three orange bands of which the first one yielded 15 mg of the nitrile XXIV, the second one 30 mg XIX and the third one 15 mg of the nitrile XXV.

The Na_2CO_3 solution from the washing of the initial crude product gave on acidification with 2N HCl a tarry precipitate, containing some of the acid XXIII. The filtrate deposited very slowly on standing an orange solid, which after about one month amounted to 0·25 g. Treatment with 2N Na_2CO_3 dissolved only about 30 mg XXIII,[19] m.p. 259–260°, while 0·2 g of a mixture of about equal parts of the nitrile XXIV and XXV remained undissolved and was easily separated into its components by chromatography over Al_2O_3 as described above.

2-*Methylamino*-4-*nitrobenzonitrile* (XXIV)

The compound crystallized from benzene as orange needles, m.p. 200–202°, λ_{NH} 2·98, λ_{CN} 4·51, λ_{NO_2} 6·49, 7·42 μ. (Found: C, 54·04; H, 4·10; N, 23·71. $C_8H_7N_3O_2$ requires: C, 54·23; H, 3·98; N, 23·72%).

2-*Methylamino*-6-*nitrobenzonitrile* (XXV)

The compound crystallized from benzene in orange plates, m.p. 209–209·5°, λ_{NH} 2·97, λ_{CN} 4·50, λ_{NO_2} 6·58, 7·47 μ. (Found: C, 54·36; H, 4·28. $C_8H_7N_3O_2$ requires: C, 54·23; H, 3·98%).

N-*Acetyl*-N-*methylanthranilic acid* (XXI)

(a) *From* XIX. A mixture of 0·13 g XIX, 1·3 ml 35% H_2O_2 and 5 ml acetic acid was heated on a steam-bath for 90 min, then evaporated under red. press. The residue was crystallized from benzene (charcoal) to yield 60 mg XXI, m.p. 191–193°. identical with an authentic sample.[20]

(b) *From* XVIII. The aldehyde XVIII, treated as described under (a), gave XXI, m.p. 191–193°.

N-*Acetyl*-N-*methyl*-4-*nitroanthranilic acid* (XXII)

A mixture of 30 mg XX, 2 ml acetic acid and 0·5 ml 35% H_2O_2 was refluxed 2 hr, treated again with 0·5 ml H_2O_2, refluxed 3 hr, some unchanged XX was removed by filtration and the acetic acid evaporated *in vacuo* over KOH. The residue was extracted with 2N Na_2CO_3, the solution filtered, acidified with 2N HCl and extracted with ether. Evaporation of the ether left 10 mg XXII, m.p. 177–178°, identical with an authentic sample.[4]

Structure proof of 2-*methylamino*-4-*nitrobenzonitrile* (XXIV)

A solution of 0·2 g methyl N-methyl-4-nitroanthranilate[19] in 20 ml methanol and 20 ml water was saturated in a 200-ml autoclave with gaseous ammonia and heated 5 hr at 80°. The resulting solution was evaporated to dryness and the residue sublimed at 200°/3 mm and crystallized from benzene–hexane to yield 0·11 g 2-*methylamino*-4-*nitrobenzamide* (XXVI), m.p. 189–191°. (Found: N, 21·79. $C_8H_9O_3N_3$ requires: N, 21·53%).

A mixture of 25 mg XXVI and 2 g P_2O_5 was heated 2 hr at 200°, then treated with water, the precipitate was washed with 2N NaOH, extracted with benzene, the benzene eliminated and the residue sublimed at 200°/2 mm to give orange needles of the nitrile XXIV, m.p. 200–202°.

A solution of 25 mg of the nitrile XXIV in 1·5 ml ethanol, 0·2 ml 30% H_2O_2 and one drop 25% NaOH was heated 50 min on a steam-bath, then evaporated. The residue, washed with water and sublimed, yielded 20 mg of the amide XXVI, m.p. 189–191°.

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[19] J. S. Morley and J. C. E. Simpson, *J. Chem. Soc.* 360 (1948).

[20] J. Houben and Th. Arendt, *Ber. Dtsch. Chem. Ges.* **43**, 3539 (1910).

Structure proof of 2-*methylamino-6-nitrobenzonitrile* (XXV)

A solution of 1·3 g methyl 6-nitroanthranilate[31] (XXVII) and 1·85 g tosyl chloride in 13 ml pyridine was left 3 days at room temp, then treated with 60 ml water and heated to the b.p. The solvent was decanted off and the residue crystallized from ethanol to yield 0·85 g *methyl* N-*tosyl-6-nitroanthranilate* (XXVIII), m.p. 91–92°. (Found: N, 7·90. $C_{15}H_{14}N_2O_6S$ requires: N, 8·01%). A solution of 0·6 g XXVIII in 5 ml ethanol, treated with an equivalent amount of NaOH, was evaporated to dryness and the residue boiled 6 hr with 2·6 ml methyl iodide in 25 ml anhydrous acetone. The solvent was evaporated, the residue washed with 2N NaOH, dried and heated 30 min on a steam-bath with 5 ml conc. H_2SO_4. Dilution with water and crystallization from aqueous methanol led to 0·29 g *mehtyl* N-*methyl-6-nitroanthranilate* (XXX), m.p. 74–75°. (Found: C, 51·48 H, 4·74. $C_9H_{10}O_4N_2$ requires: C, 51·42; H, 4·80%). Saponification of 0·10 g XXX by 30-min reflux with 5 ml 2N NaOH gave 70 mg N-*methyl-6-nitroanthranilic acid*, yellow crystals (from benzene), m.p. 205–206° (dec). (Found: C, 49·05; H, 4·13. $C_8H_8N_2O_4$ requires: C, 48·98; H, 4·11%).

A solution of 0·11 g of the ester XXX in 12 ml methanol and 12 ml water was saturated with gaseous NH_3 in a 200-ml autoclave, heated 1 hr at 130° and 3 hr at 80°. The resulting solution was evaporated to dryness and the residue sublimed at 200°/3 mm and crystallized from benzene–hexane to give 40 mg 2-*methylamino-6-nitrobenzamide* (XXXI), orange crystals, m.p. 184–186°. (Found: C, 49·08; H, 4·78. $C_8H_9N_3O_3$ requires: C, 49·23; H, 4·65%).

A solution of 20 mg of the nitrile XXV in 1 ml ethanol, 0·2 ml 30% H_2O_2 and 1 drop 25% NaOH was heated on a steam-bath for 30 min, diluted with 2 ml water and extracted with ether to give 12 mg of the amide XXXI, m.p. 184–186°.

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[31] E. H. Huntress, E. R. Atkinson, E. A. Ham and M. S. Tibbets, *J. Amer. Chem. Soc.* **75**, 743 (1953).