696. *Substituent Interactions in* ortho-*Substituted Nitrobenzenes. Part II.*[1]

By J. D. LOUDON and G. TENNANT.

Potassium cyanide reacts with 2-nitro-α-phenylcinnamonitrile (I) or with α-*o*-nitrophenylcinnamonitrile (VIII), forming 2-amino-4-cyano-3-3-phenylquinoline *N*-oxide (II) and 3-cyano-1-hydroxy-2-phenylindole (III). Derivatives of 1-hydroxyindole are also formed from α-benzyl-2-nitrobenzyl cyanides, *e.g.*, (IX), by treatment with alkali.

BY the action of potassium cyanide and ammonium chloride on 2-nitro-α-phenylcinnamonitrile (I) Brand and Loehr[2] obtained a compound to which they ascribed the formula, $C_{17}H_{13}ON_3$, but did not assign a structure. The more plausible formula, $C_{16}H_{11}ON_3$, is not inconsistent with the analyses recorded, and analogy with the formation of the 1-hydroxy-2-quinolone, described in Part I, suggested (II) as a possible structure. We have therefore re-examined the reaction and find that it leads to a mixture of products among which the base (II) and an acidic compound (III) predominate. By adjusting the reaction conditions either of these products can be obtained at will.

The base, a yellow crystalline solid, gave a blue-green colour with ferric chloride in ethanol. With concentrated hydrochloric acid it formed a rather unstable, colourless hydrochloride and with acetic anhydride yielded an *N*-acetyl derivative (ν 1670 and 1550 cm.$^{-1}$). With iron and hydrochloric acid it was reduced to a deoxy-compound which was likewise basic and acetylatable. The presence of a cyano-substituent in these compounds, as shown by their infrared spectra (ν 2220 cm.$^{-1}$), was confirmed for the deoxy-base by alkaline hydrolysis to the amide (IV). This amide resisted further hydrolysis, and with nitrous acid formed the carbostyril (V) which was obtained as the monohydrate and was identified by synthesis *via* the carboxylic acid prepared from isatin and phenylacetic acid.[3]

The colourless acidic compound (III) which accompanied the base (II) reacted with acetic anhydride to form an acetate whose infrared spectrum contained a strong absorption

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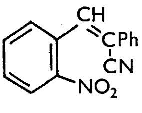
[1] Part I, preceding paper.

[2] Brand and Loehr, *J. prakt. Chem.*, 1925, **109**, 359.

[3] Hübner, *Ber.*, 1908, **41**, 482.

band at 1805 cm.$^{-1}$. This is indicative of a cyclic :N·OAc grouping (Part I) and, consistently, hydrogenolysis of the acetate afforded a non-acidic deoxy-compound (III; H for OH). A cyano-group, present in these compounds (ν 2210 cm.$^{-1}$), was again rather difficult to hydrolyse but forceful alkaline conditions converted compound (III) into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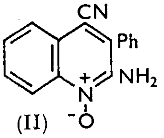
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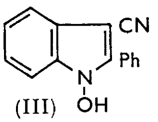
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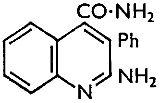
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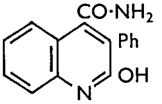
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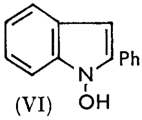
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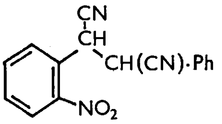
1-hydroxy-2-phenylindole (VI), apparently by hydrolysis and decarboxylation. The indole (VI) was originally prepared[4] by cyclodehydration of benzoin oxime and closely resembles the nitrile (III) in acidity and in ultraviolet and infrared spectra, but it differs markedly in imparting a deep red-brown colour to ferric chloride in ethanol, whereas the compound (III) is without effect. Although we were unable to prepare a crystalline acetate, the benzoate[5] from 1-hydroxy-2-phenylindole was found to have a carbonyl band at a significantly high frequency (ν 1760 cm.$^{-1}$), and to give 2-phenylindole on hydrogenation. Hydrogenation of 1-hydroxy-2-phenylindole (VI) likewise gave 2-phenylindole when conducted in acetic anhydride, but not in acetic acid wherein formation of the acetate is unlikely. As a further confirmation of the structure (III) the cyanoindole, identical with the deoxy-compound (III; H for OH), was synthesised by dehydrating 2-phenylindole-3-aldoxime.[6]

From these results it is clear that the adduct (VII) is primarily formed by the action of potassium cyanide on the cinnamonitrile (I). The same intermediate should be formed by similar addition to the isomeric nitrile (VIII). This nitrile was prepared by condensing benzaldehyde with 2-nitrobenzyl cyanide and, as expected, also reacted with potassium cyanide to yield the products (II) and (III) under appropriate conditions. Therefore, although the adduct itself has not been isolated, the pattern of reactions is closely analogous to that described for ethyl 2-nitrobenzylidenemalonate (Part I). It is interesting also to note the commanding influence of cyanide ion on the course of the reaction. In its absence initially, *i.e.*, in aqueous-ethanolic alkali, the nitrile (I) is rapidly transformed into *N*-benzoylanthranilic acid,[7] perhaps through the intermediates (X)—(XI).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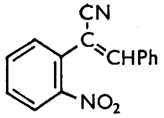
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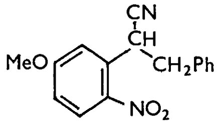
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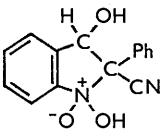
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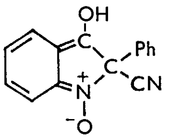

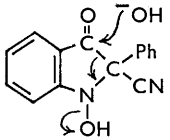

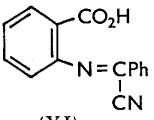
(XI)

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[4] Fischer and Hütz, *Ber.*, 1895, **28**, 585.

[5] Angeli and Angelico, *Atti Accad. naz. Lincei, Rend. Classe Sci. fis. mat. nat.*, 1906, **15**, II, 762.

[6] Blume and Lindwall, *J. Org. Chem.*, 1945, **10**, 255.

[7] Pschorr and Wolfes, *Ber.*, 1899, **32**, 3399.

Earlier in these laboratories Mr. J. McLean observed that, while the nitrile (IX) could be hydrolysed to the corresponding carboxylic acid (*via* the ethyl ester) by sulphuric acid in ethanol, it was converted by potassium hydroxide in aqueous ethanol into an unidentified acidic compound, $C_{16}H_{12}O_2N_2$. Renewed examination has now identified this compound as the 5-methoxy-derivative of the indole (III). Thus its infrared spectrum reveals an intact cyano-group (ν 2205 cm.$^{-1}$), and the spectrum of the derived acetate contains the band at 1805 cm.$^{-1}$ characteristic of this type of *N*-acetoxy-compound: hydrogenation of the acetate affords 3-cyano-5-methoxy-2-phenylindole. 5-Methoxy-2-nitro-α-(3,4,5-trimethoxybenzyl)benzyl cyanide[8] [as IX; $C_6H_2(OMe)_3$ for Ph] was similarly cyclised to, and identified by means of, a tetramethoxy-derivative of the indole (III).

EXPERIMENTAL

α-o-*Nitrophenylcinnamonitrile*, m. p. 115° (from ethanol), was prepared by adding a few drops of piperidine to a melt of 2-nitrobenzyl cyanide (1·5 g.) and benzaldehyde (1 g.) at 65°, cooling the resultant mixture and, after 48 hr., collecting the crystalline product (Found: C, 71·85; H, 3·8; N, 11·3. $C_{15}H_{10}O_2N_2$ requires C, 72·0; H, 4·0; N, 11·2%).

2-*Amino*-4-*cyano*-3-*phenylquinoline* 1-*Oxide* (II).—(*a*) (Repetition of Brand and Loehr's experiment.) Solutions of *o*-nitro-α-phenylcinnamonitrile (8 g.) in ethanol (80 ml.), potassium cyanide (6 g.) in water (10 ml.), and ammonium chloride (5 g.) in water (10 ml.) were mixed, treated with piperidine (1 ml.), and heated at 100° for 15 hr. The mixture which contained suspended solid was then added to water and extracted with chloroform. The dark chloroform extract was washed with *dilute* sodium hydroxide solution (a rather insoluble sodium salt may be formed), then with water, and the washings were combined with the original aqueous layer and worked up for 3-cyano-1-hydroxy-2-phenylindole (30% yield; cf. below). Evaporation of the dried chloroform extract left a soft crystalline mass and this was rubbed with benzene (removing some highly coloured material and an oil which were not further examined). The solid residue gave yellow needles of 2-*amino*-4-*cyano*-3-*phenylquinoline* 1-*oxide*, m. p. 236° (3·4 g.; from ethanol), $\lambda_{max.}$ 227, 265, 335, 404 mμ (ε 21,000, 31,600, 7000, 8500), $\nu_{max.}$ 3250, 3400, 2220 cm.$^{-1}$ (Found: C, 73·5; H, 4·0; N, 15·9. $C_{16}H_{11}ON_3$ requires C, 73·6; H, 4·2; N, 16·1%). Treated with acetic anhydride and a trace of concentrated sulphuric acid, it formed the 2-*acetamido-derivative*, m. p. 238° (decomp.) (from dimethylformamide), $\nu_{max.}$ 1550, 1670, 2220 cm.$^{-1}$, giving a weak red colour with ferric chloride in ethanol (Found: C, 71·0; H, 4·6; N, 13·7. $C_{18}H_{13}O_2N_3$ requires C, 71·3; H, 4·3; N, 13·9%).

(*b*) The brown solution formed by warming *o*-nitro-α-phenylcinnamonitrile (2 g.) with aqueous potassium cyanide (3 ml; 50%) and ethanol (12 ml.) deposited the above-mentioned amine (0·6 g.) when cooled at 0°. From the filtered mother-liquor, after separation into acidic and non-acidic fractions as described in (*a*), more of this amine (0·31 g.) and some 3-cyano-1-hydroxy-2-phenylindole (0·44 g.; cf. below) were obtained. These products were identified by mixed m. p.s and infrared spectra.

(*c*) α-*o*-Nitrophenylcinnamonitrile (0·25 g.), 50% aqueous potassium cyanide (2 ml.), and ethanol (3 ml.), when treated as in (*b*), also gave the aminoquinoline (0·05 g.) and the hydroxyindole (0·14 g.).

3-*Cyano*-1-*hydroxy*-2-*phenylindole* (III).—Acidification of the alkaline solutions obtained as in (*a*), (*b*), and (*c*) of the foregoing section, gave a curdy yellow precipitate which afforded 3-*cyano*-1-*hydroxy*-2-*phenylindole* as almost colourless pointed slabs (from ethanol, after charcoal-treatment) or as long felted needles (from ethanol–water), m. p. 195°, $\lambda_{max.}$ 220, 245, 305 mμ (ε 25,300, 24,400, 17,700), $\nu_{max.}$ 2220 cm.$^{-1}$ (Found: C, 77·2; H, 4·7; N, 11·5. $C_{15}H_{10}ON_2$ requires C, 77·4; H, 4·8; N, 11·3%). With sodium hydroxide it formed a sparingly soluble salt and with warm acetic anhydride yielded 1-*acetoxy*-3-*cyano*-2-*phenylindole*, m. p. 111°, $\nu_{max.}$ 2220, 1805 cm.$^{-1}$ (Found: C, 74·2; H, 4·3; N, 10·0. $C_{17}H_{12}O_2N_2$ requires C, 73·9; H, 4·4; N, 10·1%).

When a suspension of *o*-nitro-α-phenylcinnamonitrile (I) (1 g.) in ethanol (6 ml.) was treated with 50% aqueous potassium cyanide (2 ml.), and the whole shaken at 18° for 7 hr., filtration gave unchanged nitrile (I) (0·81 g.) and a blue filtrate which by dilution with water (charcoal) and acidification afforded the indole (III) (0·13 g.).

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[8] Cook, Dickson, Ellis, and Loudon, *J.*, 1949, 1074.

2-*Amino*-4-*cyano*-3-*phenylquinoline*.—A solution of the *N*-oxide (II) (0·5 g.) in acetic acid (4 ml.) was heated (10 min.) with iron powder (0·2 g.) and the cooled, filtered solution basified with ammonia. The precipitated *quinoline* formed yellow needles, m. p. 196° (from ethanol, after treatment with charcoal) (Found: C, 78·1; H, 4·9; N, 17·3. $C_{16}H_{11}N_3$ requires C, 78·35; H, 4·5; N, 17·1%). With acetic anhydride it afforded the 2-*acetamido-compound*, m. p. 247° (from ethanol), $\nu_{max.}$ 1660, 1550 cm.$^{-1}$ (Found: C, 75·3; H, 4·9; N, 14·4. $C_{18}H_{13}ON_3$ requires C, 75·3; H, 4·5; N, 14·6%). This compound was also prepared (m. p. and mixed m. p. 246°; identical infrared spectra), by hydrogenating 2-acetamido-4-cyano-3-phenylquinoline 1-oxide in acetic acid over palladium–charcoal.

2-*Amino*-3-*phenylquinoline*-4-*carboxyamide* (IV). The red flux, obtained by heating for 10 min. a mixture of the 4-cyano-compound (0·4 g.), potassium hydroxide (0·7 g.), water (0·5 ml.), and ethylene glycol (1·5 ml.), was cooled and treated with water, affording the *amide*, m. p. 346° (from dimethylformamide), $\nu_{max.}$ 3270, 3450, 1570, 1610 cm.$^{-1}$ (Found: C, 72·5; H, 4·95; N, 15·85. $C_{16}H_{13}ON_3$ requires C, 73·0; H, 4·9; N, 16·0%).

2-*Hydroxy*-3-*phenylquinoline*-4-*carboxyamide* (V).—Aqueous 0·5N-sodium nitrite (1·6 ml.) was gradually introduced below the surface of a solution of the amine (IV) (0·2 g.) in sulphuric acid (1·5 ml.; 90% w/v) with the temperature kept under 30°. The total volume was made up to 5 ml. with water and, after 1 hr., the suspended solid was collected, recovered from its filtered solution in aqueous sodium hydroxide, and washed with aqueous sodium carbonate to remove some carboxylic acid. The amide (V) was thus obtained as the *monohydrate*, m. p. 287° (from aqueous acetic acid) (Found: C, 67·8; H, 5·5; N, 9·7. $C_{16}H_{12}O_2N_2,H_2O$ requires C, 68·1; H, 5·0; N, 9·9%), which was dehydrated at 140° *in vacuo* (3 hr.). It then had m. p. 299° (Found: C, 72·4; H, 4·5; N, 10·5. Calc. for $C_{16}H_{12}O_2N_2$: C, 72·7; H, 4·6; N, 10·6%), and mixed m. p. 299—301° with a specimen prepared essentially by Hübner's method:[3] the infrared spectra of the two samples were identical.

3-*Cyano*-2-*phenylindole*, m. p. 243° (decomp.) (from ethanol), was obtained (*a*) by hydrogenating 1-acetoxy-3-cyano-2-phenylindole over 5% palladium–charcoal, and (*b*) by heating the oxime[6] of 2-phenylindole-3-aldehyde[9] with acetic anhydride (Found: C, 82·4; H, 4·8; N, 12·8. $C_{15}H_{10}N_2$ requires C, 82·5; H, 4·6; N, 12·8%).

Hydrolysis of 3-*Cyano*-1-*hydroxy*-2-*phenylindole*.—This indole (25 mg.) was heated for 10 min. with potassium hydroxide (0·2 g.) and ethylene glycol (0·2 ml.) until a deep red solution was obtained. Dilution with water, filtration through charcoal, and acidification then gave 1-hydroxy-2-phenylindole, m. p. and mixed m. p. 172° (from ethanol), further identified by comparison of infrared spectra. When the reaction time was extended to 20 min. the cooled solution deposited plates of 2-phenylindole, m. p. and mixed m. p. 186° (from ethanol) (identified by infrared spectra), and it was ascertained that this was formed from 1-hydroxy-2-phenylindole similarly treated.

Hydrogenolysis of 1-*Hydroxy*-2-*phenylindole*.—(*a*) 1-Benzoyloxy-2-phenylindole,[5] $\nu_{max.}$ 1760 cm.$^{-1}$, m. p. 101° (from ethanol), prepared by shaking with benzoyl chloride a solution of the 1-hydroxy-compound in 10% aqueous sodium hydroxide at 18°, was rapidly hydrogenolysed over palladium–charcoal, affording 2-phenylindole, m. p. 186° (from ethanol). (*b*) 1-Hydroxy-2-phenylindole (0·25 g.) in a mixture of acetic anhydride (25 ml.) and acetic acid (2 ml.) was likewise, but more slowly hydrogenolysed, 2-phenylindole being recovered from the filtered and concentrated reaction solution. (*c*) No absorption of hydrogen occurred when procedure (*b*) was attempted in acetic acid alone as solvent.

(With J. McLean) α-*Benzyl*-5-*methoxy*-2-*nitrobenzyl Cyanide* (IX).—Solutions in lime-dried ethanol containing (*a*) 5-methoxy-2-nitrobenzyl cyanide (1 g. in 13 ml.) and (*b*) sodium ethoxide (from 0·13 g. of sodium in 4 ml.) were mixed and treated with benzyl chloride (0·66 g.). After 48 hr. the *cyanide* (IX), m. p. 107° (from ethanol), was collected (Found: C, 68·2; H, 4·9; N, 9·9. $C_{16}H_{14}O_3N_2$ requires C, 68·1; H, 5·0; N, 9·9%). When heated with sulphuric acid in ethanol it afforded *ethyl* α-*benzyl*-5-*methoxy*-2-*nitrophenylacetate*, m. p. 68° (from ethanol) (Found: C, 65·6; H, 5·5; N, 4·5. $C_{18}H_{19}O_5N$ requires C, 65·6; H, 5·8; N, 4·25%), and this was hydrolysed, by potassium hydroxide in aqueous methanol, to the corresponding *acid*, m. p. 134° (from aqueous acetic acid) (Found: C, 63·8; H, 5·0; N, 4·8. $C_{16}H_{15}O_5N$ requires C, 63·8; H, 5·0; N, 4·65%).

3-*Cyano*-1-*hydroxy*-5-*methoxy*-2-*phenylindole*.—A solution of the nitrile (IX) (1 g.) in ethanol (6 ml.) and water (2 ml.) was treated with 20% aqueous potassium hydroxide (4 ml.), and the

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[9] Swaminathan and Ranganathan, *Chem. and Ind.*, 1955, 1774.

whole heated under reflux for 1 hr. Acidification of the cooled solution gave 3-*cyano*-1-*hydroxy*-5-*methoxy*-2-*phenylindole*, m. p. 173° (from ethanol–water) (Found: C, 72·5; H, 4·35; N, 10·8. $C_{16}H_{12}O_2N_2$ requires C, 72·7; H, 4·6; N, 10·6%). With acetic anhydride it formed the 1-*acetoxy-derivative*, m. p. 145° (from ethanol), $\nu_{max.}$ 1805 cm.$^{-1}$ (Found: C, 70·6; H, 4·8; N, 9·4. $C_{18}H_{14}O_3N_2$ requires C, 70·6; H, 4·6; N, 9·15%), which was hydrogenated in ethanol over palladium–charcoal, affording 3-*cyano*-5-*methoxy*-2-*phenylindole*, m. p. 250° (from ethanol) (Found: C, 77·2; H, 4·6; N, 11·1. $C_{16}H_{12}ON_2$ requires C, 77·4; H, 4·8; N, 11·3%).

3-*Cyano*-1-*hydroxy*-5-*methoxy*-2-(3,4,5-*trimethoxyphenyl*)*indole*, m. p. 205° (from ethanol–water), was obtained from 5-methoxy-2-nitro-α-(3,4,5-trimethoxybenzyl)benzyl cyanide as described for the cyanide (IX) (Found: C, 63·95; H, 5·1; N, 8·0. $C_{19}H_{18}O_5N_2$ requires C, 64·4; H, 5·1; N, 7·9%). It yielded with acetic anhydride, the 1-*acetoxy-derivative*, m. p. 132° (from ethyl acetate), $\nu_{max.}$ 1805 cm.$^{-1}$ (Found: C, 63·4; H, 4·9; N, 7·2. $C_{21}H_{20}O_6N_2$ requires C, 63·6; H, 5·1; N, 7·1%), which on hydrogenation gave 3-*cyano*-5-*methoxy*-2-(2,3,4-*trimethoxyphenyl*)-*indole*, m. p. 220° (from ethanol–water) (Found: C, 67·45; H, 5·4; N, 8·4. $C_{19}H_{18}O_4N_2$ requires C, 67·4; H, 5·4; N, 8·3%).

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