The Chemistry of Nitro-compounds. Part III.[1] The Intramolecular Nucleophilic Displacement of Aromatic Nitro-groups by Carbanions

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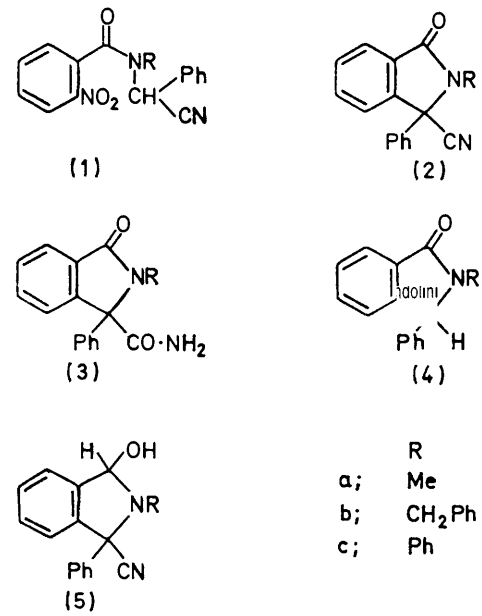
Heating α-(*N*-methyl-*N*-*o*-nitrobenzoylamino)phenylacetonitrile (1a) with sodium ethoxide in ethanol affords moderate yields of 2-methyl-3-oxo-1-phenylisoindoline-1-carboxamide (3a) and benzoic acid. Similar treatment of the *N*-benzyl and *N*-phenyl *o*-nitrobenzamide derivatives (1b and c) yields, in addition to benzoic acid, separable mixtures of the 3-oxoisoindoline-1-carbonitriles (2b and c), the derived amides (3b and c), and the 3-phenylisoindolin-1-ones (4b and c). Isoindolinone formation by direct intramolecular displacement of the *ortho*-nitro-group by the cyanobenzyl carbanion generated in the side-chain is indicated by the conversion of the amides (1a—c) in hot ethanolic sodium carbonate in high yield into the 3-oxoisoindoline-1-carbonitriles (2a—c). In addition to benzoic acid, the latter reactions respectively afford *o*-azidobenzoic acid (12), benzaldehyde *o*-carboxyphenylhydrazone (13), and azobenzene-2-carboxylic acid (14) as by-products. The substituted benzamides (6), (7a and b), and (8a and b) are unaffected by ethanolic sodium carbonate. In contrast, the 2-nitro-5-methyl compound (6) and the 2-chloro-5-nitro-derivative (8c) are respectively converted by heating with ethanolic sodium ethoxide and ethanolic sodium carbonate into the 5-methyl- and 5-nitro-3-oxo-1,2-diphenylisoindoline-1-carbonitriles (9a and b). The mechanisms of the reactions are discussed.

INTRAMOLECULAR nucleophilic displacements of aromatic nitro-groups by nitrogen,[2] oxygen,[3] and sulphur[4] nucleophiles are well known and include cyclisation reactions which provide practical methods for the synthesis of a variety of heterocycles. Recently Krohnke and his co-workers[5] described the first examples of similar displacements by a nucleophilic carbon atom. We now describe base-catalysed reactions of *NN*-disubstituted *o*-nitrobenzamides which involve the intramolecular displacement of aromatic nitro-groups by cyanobenzyl carbanions. These novel cyclisation reactions constitute a valuable method for the synthesis of otherwise inaccessible isoindolinone (phthalimidine) derivatives.

Our interest[1] in the base-catalysed transformations of *NN*-disubstituted *o*-nitrobenzamides prompted the study of the phenyl-substituted compounds (1a—c), which were readily available from the condensation of *o*-nitrobenzoyl chloride with the appropriate *N*-substituted α-aminophenylacetonitriles. The amides (1a—c) were chosen for study in the expectation that they would undergo base-catalysed cyclisation with loss[1] of the cyano-group to afford the corresponding 2-phenylquinazolin-4(3*H*)-one 1-oxides (18). In practice, heating the amide (1a) with ethanolic sodium ethoxide afforded, in addition to benzoic acid, a product which gave analytical data consistent with the molecular formula $C_{16}H_{14}N_2O_2$. It lacked i.r. absorption due to a nitro-group but showed bands at 3350 and 3200 cm^{-1} (NH_2) and 1680 cm^{-1} (CO) attributable to a primary amide group. These properties are consistent with the isoindolinone structure (3a), which was firmly established by forcing alkaline hydrolysis to the known[6] 2-methyl-3-phenylisoindolin-1-one (4a). The conversion of the amide (1a) into the isoindolinone derivative (3a) is readily accommodated by nucleophilic displacement of the *ortho*-nitro-group by the cyanobenzyl carbanion generated in the side-chain, followed by hydrolysis of the nitrile (2a) formed. This course for isoindolinone formation is substantiated by the transformation of the *N*-benzyl



amide (1b) in hot ethanolic sodium ethoxide into a mixture of the nitrile (2b), the derived amide (3b), and the known[7] 2-benzyl-3-phenylisoindolinone (4b). The structure of the nitrile (2b) was established by hydrolysis with ethanolic sodium carbonate to give a mixture of the amide (3b) and the isoindolinone (4b), which was also the product of forcing hydrolysis of the nitrile (2b) or of the amide (3b). 2-Benzyl-3-phenylisoindolinone (4b) was

[1] Part II, T. W. M. Spence and G. Tennant, *J.C.S. Perkin I*, 1972, 97.

[2] A. Werner and T. Herberger, *Ber.*, 1899, **32**, 2686; K. Schimmelschmidt and H. Hoffmann, *Annalen*, 1964, **677**, 157; F. Ullmann, *ibid.*, 1909, **366**, 79.

[3] K. B. L. Mathur and K. P. Sarbhai, *Tetrahedron Letters*, 1964, 1743; D. H. Hey, J. A. Leonard, and C. W. Rees, *J. Chem. Soc.*, 1962, 4579; D. M. Collington, D. H. Hey, J. A. Leonard, and C. W. Rees, *J. Chem. Soc.* (*C*), 1968, 1030; M. W. Partridge, J. M. Sprake, and H. J. Vipond, *ibid.*, 1966, 1245; G. S. Turpin, *J. Chem. Soc.*, 1891, **59**, 714.

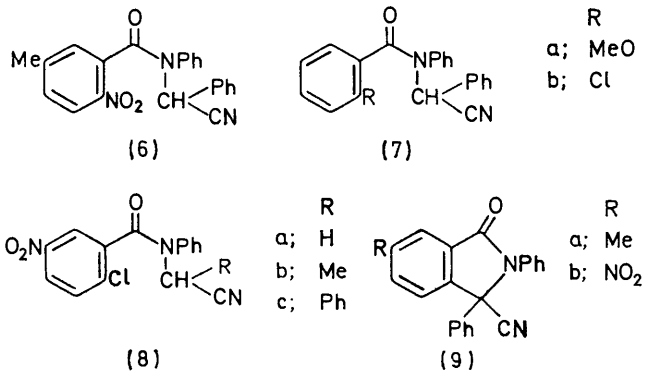
[4] F. Kehrmann and J. Steinberg, *Ber.*, 1911, **44**, 3011.

[5] W. Augstein and F. Krohnke, *Annalen*, 1966, **697**, 158; D. B. Reuschling and F. Krohnke, *Ber.*, 1971, **104**, 2103, 2110.

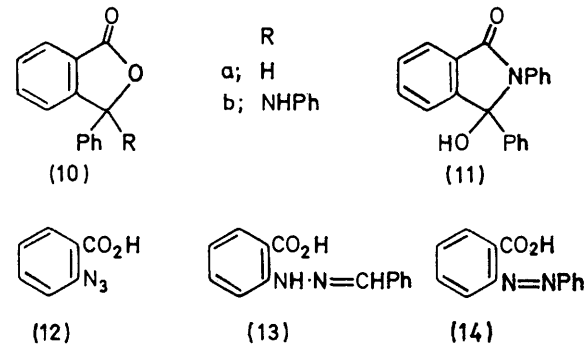
[6] W. Theilacker and W. Schmidt, *Annalen*, 1955, **597**, 95; D. M. Bailey and C. G. DeGrazia, *Tetrahedron Letters*, 1970, 633.

also formed in high yield by reduction of the nitrile (2b) at room temperature by lithium aluminium hydride. Conversion of the nitrile (2b) into the isoindolinone (4b) is explicable in terms of reduction to the hydroxyisoindoline (5b) and subsequent loss of hydrogen cyanide. Reduction of isoindolinones by lithium aluminium hydride at elevated temperature is reported [7,8] to afford the corresponding isoindoline derivatives. The stability of the isoindolinone (4b) to further reduction can be attributed in the present case to the milder conditions employed. As in the case [9] of the parent 2-benzylisoindolinone (4b), the ^{1}H n.m.r. absorption of the benzyl protons in the nitrile (2b) consists of a pair of doublets centred at τ 5·02 and 5·69. This splitting pattern is consistent with restricted rotation of the benzyl group about the C–N bond.[9]

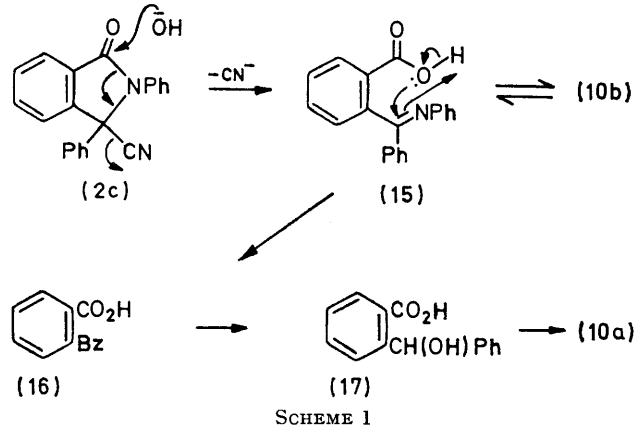
Heating the *N*-phenyl amide (1c) with ethanolic sodium ethoxide gave, in addition to the expected 3-oxo-1,2-diphenylisoindoline-1-carbonitrile (2c) and the known [8] isoindolinone (4c) and benzoic acid, a product (*A*), $C_{20}H_{15}NO_2$. The latter was also formed together with 2,3-diphenylisoindolinone (4c) when the nitrile (2c) was heated with potassium hydroxide in triethylene glycol. The structure of the nitrile (2c) was established by its conversion in concentrated sulphuric acid into the amide (3c), alkaline hydrolysis of which yielded 2,3-diphenylisoindolinone (4c). Reduction of the nitrile (2c) with lithium aluminium hydride afforded the compound (4c) directly (see before). The product (*A*) lacked i.r. absorption due to a nitro-group but showed i.r. bands



at 3350 and 1735 cm^{-1} attributable to an NH group and the carbonyl group of a γ-lactone, respectively. Heated with potassium hydroxide in triethylene glycol it afforded a product subsequently identified as 3-phenylphthalide (10a). These properties are in accord with the 3-anilinophthalide structure (10b), which was firmly established by comparison with an authentic sample prepared by condensing *o*-benzoylbenzoic acid with aniline. This condensation [10] affords a product, m.p. 221°, which was identical with the product (*A*) and has been variously formulated as the anilinophthalide [10,11] (10b) and the 3-hydroxyisoindolinone [12] (11). The



latter structure has recently been reassigned [13] to the product, m.p. 195°, originally formulated [10] as 2-benzoylbenzanilide and in any case is excluded by the relatively high frequency of the carbonyl i.r. absorption, which is in the range expected [14] for a 3-aminophthalide rather than a 3-hydroxyisoindolinone.[15] Base-catalysed ring-opening to the imino-acid (15) and spontaneous lactonisation accounts for the formation of the anilinophthalide (10b) from the nitrile (2c) (Scheme 1). Conversely, the



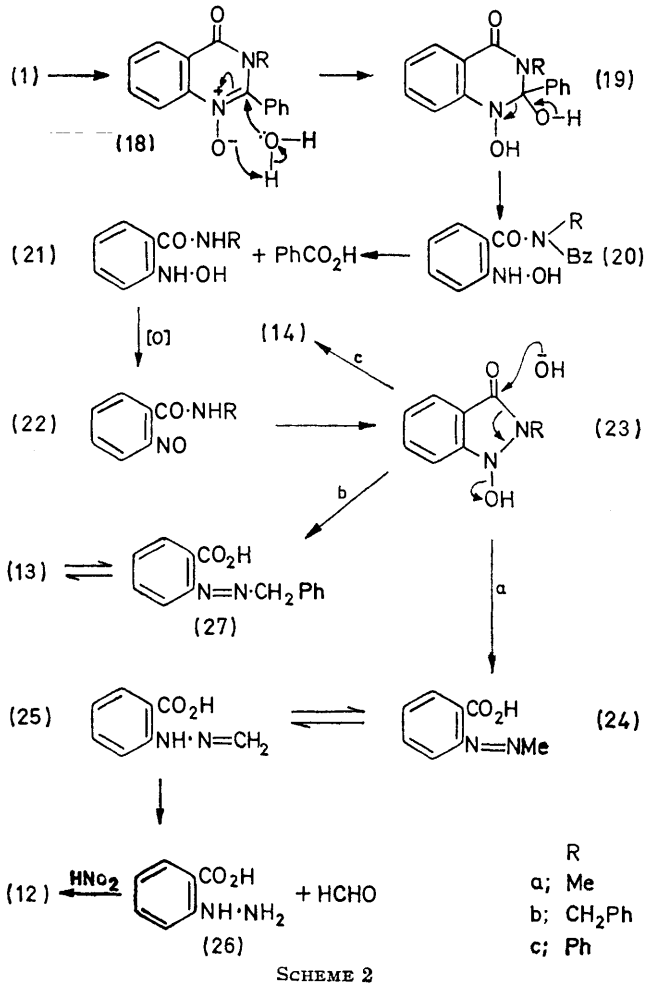
SCHEME 1

transformation of the anilinophthalide (10b) into 3-phenylphthalide (10a) under more vigorous conditions is explicable in terms of hydrolysis of the open-chain tautomer (15) to *o*-benzoylbenzoic acid (16) followed by reductive cyclisation [16] in the alcoholic alkaline medium (Scheme 1). This course is supported by the conversion of *o*-benzoylbenzoic acid in moderate yield into 3-phenylphthalide (10a) on heating with potassium hydroxide in triethylene glycol.

[7] T. Cohen, A. H. Dinwoodie, and C. D. McKeever, *J. Org. Chem.*, 1962, **27**, 3385.
[8] A. Pernot and A. Willemart, *Bull. Soc. chim. France*, 1953, 324.
[9] A. H. Lewin, J. Lipowitz, and T. Cohen, *Tetrahedron Letters*, 1965, 1241.
[10] H. Meyer, *Monatsh*, 1907, **28**, 1211.
[11] W. Graf, E. Girod, E. Schmid, and W. G. Stoll, *Helv. Chim. Acta*, 1959, **42**, 1085.
[12] S. Wawzonek, H. A. Laitinen, and S. J. Kwiatkowski, *J. Amer. Chem. Soc.*, 1944, **66**, 830; H. Watanabe, C. L. Mao, I. T. Barnish, and C. R. Hauser, *J. Org. Chem.*, 1969, **34**, 919.
[13] W. L. F. Armarego and S. C. Sharma. *J. Chem. Soc.* (*C*), 1970, 1600.
[14] D. D. Wheeler, D. C. Young, and D. S. [illegible]y, *J. Org. Chem.*, 1957, **22**, 547.
[15] H. R. Müller and M. Seefelder, *Annalen*, 1969, **728**, 88.
[16] F. Ullmann, *Annalen*, 1896, **291**, 17.

Isoindolinone formation by direct nucleophilic displacement of the nitro-group by the *ortho*-side-chain is further substantiated by the reactions of the amides (1a—c) in hot ethanolic sodium carbonate. The amide (1a) was smoothly converted in this medium in high yield into the nitrile (2a), together with benzoic acid and a product subsequently identified as *o*-azidobenzoic acid (12). The structure (2a) for the nitrile follows from its mild hydrolysis to the amide (3a) and its transformation by forcing hydrolysis or lithium aluminium hydride reduction into 2-methyl-3-phenylisoindolinone (2a). Ethanolic sodium carbonate similarly converted the amides (1b and c) into the corresponding 3-oxoisoindolinecarbonitriles (2b and c). In addition to benzoic acid, these reactions also yielded the known [17] hydrazone (13) and the azo-acid [18] (14), respectively. The acids (13) and (14) are also observed [1] as products in the base-catalysed transformations of other *NN*-disubstituted *o*-nitrobenzamides, and their formation from the amides (1b and c) is consistent with competing nucleophilic attack by the side-chain on the nitro-group.[1] This mode of interaction in the amides (1b and c) would lead initially to intermediate 2-phenylquinazolin-4(3*H*)-one 1-oxides (18), convertible (Scheme 2) by hydrolytic decomposition [1] in the alkaline medium into benzoic acid and the *o*-(hydroxyamino)benzamide derivatives (21b and c). Ring scission (Scheme 2) of 1-hydroxyindazolones (23b and c) derived by mild oxidation of the hydroxylamines (21b and c) to the nitroso-derivatives (22b and c) and subsequent cyclisation, then accounts for the observed products (13) and (14). A similar series of transformations in the case of the amide (1a) would afford the azo-compound (24). Hydrolysis of the tautomeric hydrazone (25) and reaction [19] of the resulting *o*-hydrazinobenzoic acid (26) with nitrous acid liberated in the isoindolinone-forming process then accounts for the formation of *o*-azidobenzoic acid (12).

Activation of the *ortho*-position by at least two strongly electron-withdrawing groups appears to be a prerequisite for successful cyclisation to phthalimidine derivatives. Thus the methoxy- and chloro-amides (7a and b) were unaffected by hot ethanolic sodium carbonate, demonstrating the deactivating effect of electron-donating *ortho*-substituents. In contrast, the nitro-derivative (8c), in which the electron-deficiency of the *ortho*-position is suitably enhanced, was smoothly cyclised under similar conditions to the nitroisoindolinone (9b). The degree of electron deficiency required is further demonstrated by the failure of the 5-methyl derivative (6) to cyclise on treatment with sodium carbonate in ethanol. However, cyclisation occurred smoothly in ethanolic sodium ethoxide to afford the expected isoindolinone derivative (9a). The resistance of the amide (6) to cyclisation is consistent with deactivation of the *ortho*-position by the electron-donating 5-methyl group. A high degree of electron deficiency at the *ortho*-position is not the only factor however. Thus, the amides (8a and b) did not cyclise on treatment with sodium carbonate in ethanol, demonstrating the



SCHEME 2

controlling influence of the stability of the side-chain carbanion.

EXPERIMENTAL

I.r. spectra were recorded for Nujol suspensions with a Unicam SP 200 instrument. N.m.r. spectra were measured at 60 MHz for solutions in deuteriochloroform at 28° with tetramethylsilane as internal standard (Perkin-Elmer R10 instrument).

Light petroleum had b.p. 60—80°. Alumina was Spence type H. Chloroform extracts were dried ($MgSO_4$) prior to evaporation under reduced pressure.

N-Substituted α-Aminophenylacetonitriles.—(*a*) Freshly distilled benzaldehyde (20·8 g, 0·2 mol) was added dropwise to a solution of sodium hydrogen sulphite (21·0 g, 0·2 mol) in water (200·0 ml) and the mixture was stirred until homogeneous. Aqueous 27·5% methylamine or benzylamine (0·2 mol) was added dropwise and the mixture was stirred at room temperature for 2 h. Solid potassium cyanide (13·0 g, 0·2 mol) was then added in one portion and stirring was continued for a further 1 h at room temperature. The oil which separated was recovered in chloroform to afford

[17] E. Fischer and R. Blochmann, *Ber.*, 1902, **35**, 2315.
[18] M. P. Freundler, *Bull. Soc. chim. France*, 1911, **9**, 657.
[19] J. H. Boyer and F. C. Canter, *Chem. Rev.*, 1954, **54**, 1.

the crude *N*-substituted α-aminophenylacetonitriles, which were used without further purification; α-(methylamino)-phenylacetonitrile [20] was obtained as an oil (54%) and was characterised as the hydrochloride, which formed needles, m.p. 118° (lit.,[21] 112°); α-(benzylamino)phenylacetonitrile was also obtained as an oil (78%), which slowly crystallised to afford plates, m.p. 32° (lit.,[22] 34°).

(*b*) A mixture of freshly distilled benzaldehyde (10·6 g) and sodium hydrogen sulphite (10·4 g) in water (100·0 ml) was treated as in (*a*) with freshly distilled aniline (9·3 g). The mixture was stirred at 40° for 2 h and was then treated in one portion with solid potassium cyanide (8·0 g). Stirring was continued at 60° for 2 h and the solid which separated was collected, washed with water, and crystallised to yield α-anilinophenylacetonitrile (25·0 g), m.p. 85° (from ethanol–water) (lit.,[23,24] 85°).

NN-*Disubstituted* o-*Nitrobenzamides*.—(*a*) α-(Methylamino)phenylacetonitrile or α-(benzylamino)phenylacetonitrile (0·02 mol) was cooled to 0° and treated dropwise with stirring with *o*-nitrobenzoyl chloride (1·9 g, 0·01 mol). The mixture was heated (exclusion of atmospheric moisture) at 100° for 30 min, giving a deep red solution which was cooled and treated with chloroform and water. The solid obtained by evaporating the washed (aqueous sodium hydrogen carbonate and water) extract was crystallised to afford α-(N-*methyl*-N-o-*nitrobenzoylamino*)*phenylacetonitrile* (1a), needles (75%), m.p. 112° (from ethanol), $\nu_{max.}$ 1650 (CO) and 1530 and 1350 (NO_2) cm^{-1}, τ 1·70—2·60 (9H, m, Ar–H), 2·80 (1H, s, CH), and 7·32 (1H, s, Me) (Found: C, 64·6; H, 4·4; N, 14·1. $C_{16}H_{13}N_3O_3$ requires C, 65·1; H, 4·4; N, 14·2%) or α-(N-*benzyl*-N-o-*nitrobenzoylamino*)*phenylacetonitrile* (1b), needles (91%), m.p. 181° (from benzene), $\nu_{max.}$ 1650 (CO) and 1535 and 1355 (NO_2) cm^{-1}, τ 1·70—3·30 (15H, m, CH + Ar–H), and 5·73 (5H, s, CH_2) (Found: C, 71·2; H, 4·6; N, 11·2. $C_{22}H_{17}N_3O_3$ requires C, 71·2; H, 4·6; N, 11·3%).

(*b*) A solution of anilinoacetonitrile,[24] α-anilinopropiononitrile,[25] or α-anilinophenylacetonitrile (0·02 mol) in anhydrous benzene (100·0 ml) was treated dropwise with stirring with a solution of *o*-nitrobenzoyl chloride, 2-chloro-5-nitrobenzoyl chloride, 5-methyl-2-nitrobenzoyl chloride, *o*-methoxybenzoyl chloride, or *o*-chlorobenzoyl chloride (0·01 mol) in anhydrous benzene (60·0 ml), and the mixture was stirred at room temperature for 24 h. After filtration to remove the insoluble amine hydrochloride the mixture was evaporated, and the solid was crystallised to yield α-(N-o-*nitrobenzoylanilino*)*phenylacetonitrile* (1c), prisms (76%), m.p. 182° (from methanol), $\nu_{max.}$ 1655 (CO) and 1535 and 1350 (NO_2) cm^{-1}, τ 1·95—3·30 (15H, m, CH + Ar–H) (Found: C, 70·8; H, 3·9; N, 11·9. $C_{21}H_{15}N_3O_3$ requires C, 70·6; H, 4·2; N, 11·8%), α-(N-2-*chloro*-5-*nitrobenzoylanilino*)*phenylacetonitrile* (8c), needles (80%), m.p. 191° (from glacial acetic acid), $\nu_{max.}$ 1665 (CO) and 1540 and 1360 (NO_2) cm^{-1} (Found: C, 64·3; H, 3·9; N, 11·1. $C_{21}H_{14}ClN_3O_3$ requires C, 64·3; H, 3·6; N, 10·7%), *N*-(2-*chloro*-5-*nitrobenzoyl*)*anilinoacetonitrile* (8a), needles (95%), m.p. 172° (from glacial acetic acid), $\nu_{max.}$ 1655 (CO) and 1530 and 1345 (NO_2) cm^{-1}, τ 1·92—2·71 (8H, m, Ar–H) and 5·18 (2H, s, CH_2) (Found: C, 56·6; H, 3·4; N, 13·3. $C_{15}H_{10}ClN_3O_3$ requires C, 56·9; H, 3·2; N, 13·3%), α-(N-2-*chloro*-5-*nitrobenzoylanilino*)*propiononitrile* (8b), prisms (66%), m.p. 178° (from ethanol), $\nu_{max.}$ 1660 (CO) and 1540 and 1365 (NO_2) cm^{-1}, τ 1·98—2·70 (8H, m, Ar–H), 4·05 (1H, q, CH), and 8·45 (3H, d, Me) (Found: C, 57·9; H, 3·7; N, 13·1. $C_{16}H_{12}ClN_3O_3$ requires C, 58·2; H, 3·6; N, 12·7%), α-(N-5-*methyl*-2-*nitrobenzoylanilino*)*phenylacetonitrile* (6), needles (51%), m.p. 155° (from ethanol), $\nu_{max.}$ 1660 (CO) and 1535 and 1350 (NO_2) cm^{-1} (Found: C, 70·6; H, 4·6; N, 11·1. $C_{22}H_{17}N_3O_3$ requires C, 71·2; H, 4·6; N, 11·3%), α-(N-o-*methoxybenzoylanilino*)*phenylacetonitrile* (7a), needles (61%), m.p. 124° (from ethanol–light petroleum), $\nu_{max.}$ 1660 (CO) cm^{-1} (Found: C, 77·1; H, 5·4; N, 8·1. $C_{22}H_{18}N_2O_2$ requires C, 77·2; H, 5·3; N, 8·2%), or α-(*N*-o-*chlorobenzoylanilino*)*phenylacetonitrile* (7b), prisms (60%), m.p. 146° (from ethanol), $\nu_{max.}$ 1660 (CO) cm^{-1} (Found: C, 73·2; H, 4·6; N, 8·1. $C_{21}H_{15}ClN_2O$ requires C, 72·6; H, 4·3; N, 8·1%).

Base-catalysed Reactions of NN-*Disubstituted* o-*Nitrobenzamides* (1a—c).—The amides (1a—c) (0·01 mol) were heated under reflux with aqueous N-sodium carbonate (40·0 ml) in ethanol (200·0 ml) for 3 h, or with a solution of sodium (0·9 g) in absolute ethanol (50·0 ml) for 0·5 h. The ethanol was removed by distillation under reduced pressure and the residual solid was treated with water and chloroform. The organic layer was separated [extract (*A*)] and the aqueous layer was acidified (aqueous 2N-sulphuric acid) and extracted with chloroform. The chloroform layer was washed with saturated aqueous sodium hydrogen carbonate and dried to give extract (*B*). The aqueous acid layer was adjusted to neutral pH and re-extracted with chloroform [extract (*C*)]. The sodium hydrogen carbonate washings were acidified (aqueous 2N-sulphuric acid) and extracted with chloroform [extract (*D*)].

(a) *Reactions with ethanolic sodium ethoxide*. (i) α-(N-*Methyl*-N-o-*nitrobenzoylamino*)*phenylacetonitrile*. Extract (*A*) afforded a gum which gave the solid 2-*methyl*-3-*oxo*-1-*phenylisoindoline*-1-*carboxamide* (3a) (0·11 g) on contact with ether. It formed needles, m.p. 297° (from glacial acetic acid), $\nu_{max.}$ 3350 and 3200 (NH) and 1680br (CO) cm^{-1} (Found: C, 72·0; H, 5·4; N, 10·4. $C_{16}H_{14}N_2O_2$ requires C, 72·2; H, 5·3; N, 10·5%). Extract (*B*) gave an intractable gum. Extract (*D*) yielded benzoic acid (0·45 g), which was identified by comparison (m.p. and i.r. spectrum) with an authentic sample.

(ii) α-(N-*Benzyl*-N-o-*nitrobenzoylamino*)*phenylacetonitrile*. Extract (*A*) gave a gum which was chromatographed over alumina. Elution with benzene gave 2-*benzyl*-3-*oxo*-1-*phenylisoindoline*-1-*carbonitrile* (2b) (0·05 g), needles, m.p. 115° (from ethanol), $\nu_{max.}$ 1710 (CO) cm^{-1}, τ 1·90—2·90 (14H, m, Ar–H) and 5·35 (2H, q, CH_2) (Found: C, 81·2; H, 5·0; N, 8·9. $C_{22}H_{16}N_2O$ requires C, 81·5; H, 4·9; N, 8·6%). Further elution, with 3 : 1 benzene–ether gave 2-benzyl-3-phenylisoindolinone (4b) (0·7 g), needles, m.p. 124° (from benzene–light petroleum) (lit.,[7] 124°), $\nu_{max.}$ 1690br (CO) cm^{-1}, 2·00—3·05 (14H, m, Ar–H), 4·08 (1H, s, CH), 4·65 (1H, d, CH), and 6·30 (1H, d, CH) (Found: C, 84·5; H, 5·9; N, 4·6. Calc. for $C_{21}H_{17}NO$: C, 84·3; H, 5·7; N, 4·7%), identical (mixed m.p. and i.r. spectrum) with a sample prepared later. Finally, elution with 1 : 3 ether–chloroform yielded 2-*benzyl*-3-*oxo*-1-*phenylisoindoline*-1-*carboxamide* (3b) (0·2 g), needles, m.p. 202° (from ethanol–water), $\nu_{max.}$ 3350 and 3200 (NH) and 1675br (CO) cm^{-1} (Found: C, 77·4; H, 5·2; N, 8·2. $C_{22}H_{18}N_2O_2$ requires C, 77·2; H, 5·3; N, 8·2%), identical (mixed m.p. and i.r. spectrum) with a

[20] F. Tiemann and R. Piest, *Ber.*, 1881, **14**, 1982.
[21] D. F. Ewing and D. G. Neilson, *J. Chem. Soc.* (*C*), 1966, 390.
[22] J. C. Jochims, *Ber.*, 1963, **96**, 990.
[23] H. Bucherer and A. Schwalbe, *Ber.*, 1906, **39**, 2796.
[24] E. Knoevenagel, *Ber.*, 1904, **37**, 4073.
[25] F. Tiemann and R. Stephan, *Ber.*, 1882, **15**, 2034.

sample prepared later. Extract (*B*) gave an unidentified gum (0·08 g). Extract (*D*) afforded benzoic acid (0·3 g), identical (mixed m.p. and i.r. spectrum) with an authentic specimen.

(iii) α-(N-o-*Nitrobenzoylanilino*)*phenylacetonitrile*. Extract (*A*) gave a gum which solidified when triturated with methanol. Chromatography of the crude solid in benzene over alumina gave 3-*oxo*-1,2-*diphenylisoindoline*-1-*carbonitrile* (2c) (0·8 g), needles, m.p. 188° (from ethanol), $\nu_{max.}$ 1715 (CO) cm^{-1} (Found: C, 81·1; H, 4·5; N, 8·9. $C_{21}H_{14}N_2O$ requires C, 81·3; H, 4·5; N, 9·0%), followed by 2,3-diphenylisoindolinone (4c) (0·5 g), m.p. 199° (from ethanol) (lit.,[8] 195°), $\nu_{max.}$ 1690br (CO) cm^{-1}, τ 1·95—3·00 (14H, m, Ar–H) and 3·92 (1H, s, CH) (Found: C, 84·0; H, 5·3; N, 5·3. Calc. for $C_{20}H_{15}NO$: C, 84·2; H, 5·3; N, 4·9%), identical (mixed m.p. and i.r. spectrum) with a sample prepared later. Evaporation of the methanolic mother liquors gave a gum which solidified in contact with light petroleum to afford the anilinophthalide (10b), more of which was obtained similarly from extract (*B*) (total 0·9 g); m.p. 218° (from methanol) (lit.,[10] 220°), $\nu_{max.}$ 3350 (NH) and 1735 (CO) cm^{-1} (Found: C, 80·1; H, 5·3; N, 5·0. Calc. for $C_{20}H_{15}NO_2$: C, 79·7; H, 5·0; N, 4·7%), identical (mixed m.p. 218° and i.r. spectrum) with an authentic sample.[10] Extract (*C*) afforded some unidentified gum. Extract (*D*) yielded benzoic acid (0·16 g), m.p. and mixed m.p. 122° with an authentic sample.

(b) *Reactions with aqueous ethanolic sodium carbonate*. (i) α-(N-*Methyl*-N-o-*nitrobenzoylamino*)*phenylacetonitrile*. Extract (*A*) gave an oil which was triturated with ethanol to afford the amide (3a) (0·1 g), m.p. 297° (from glacial acetic acid), identical (mixed m.p. and i.r. spectrum) with a sample prepared later. The ethanol mother liquor was worked up to yield 2-*methyl*-3-*oxo*-1-*phenylisoindoline*-1-*carbonitrile* (2a), plates (1·1 g), m.p. 103° (from ethanol–water), $\nu_{max.}$ 1710 (CO) cm^{-1}, τ 1·95—2·80 (9H, m, Ar–H) and 6·99 (3H, s, Me) (Found: C, 77·4; H, 4·9; N, 11·3. $C_{16}H_{12}N_2O$ requires C, 77·4; H, 4·8; N, 11·3%). Extract (*D*) gave a red solid which was extracted with hot light petroleum to remove benzoic acid (0·3 g) and crystallised to yield *o*-azidobenzoic acid (12) (0·25 g), m.p. 140° (from water) (lit.,[26] 144·5°), identified by comparison (mixed m.p. and i.r. spectrum) with an authentic sample.[26]

(ii) α-(N-*Benzyl*-N-o-*nitrobenzoylamino*)*phenylacetonitrile*. Extract (*A*) yielded an oil which solidified in contact with ethanol to afford 2-benzyl-3-oxo-1-phenylisoindoline-1-carbonitrile (2b), needles (2·2 g), m.p. 115° (from ethanol), identical (mixed m.p. and i.r. spectrum) with a sample prepared before. Extract (*B*) yielded an unidentified solid (0·1 g). Extract (*D*) gave a semi-solid (0·35 g) which was extracted with hot light petroleum to remove benzoic acid (0·1 g). Crystallisation of the insoluble solid yielded the hydrazone (13) as platelets (0·2 g), m.p. 230° (from benzene), identical (mixed m.p. and i.r. spectrum) with an authentic sample.[17]

(iii) α-(N-o-*Nitrobenzoylanilino*)*phenylacetonitrile*. Extract (*A*) afforded a solid which was crystallised to yield 3-oxo-1,2-diphenylisoindoline-1-carbonitrile (2c) as needles (2·2 g), m.p. 188° (from ethanol), identical (mixed m.p. and i.r. spectrum) with a sample prepared before. Extract (*B*) gave a brown solid which was combined with solid material obtained by evaporating extract (*D*) to yield azobenzene-2-carboxylic acid (1·0 g), m.p. 91° (from light petroleum), identical (mixed m.p. and i.r. spectrum) with an authentic sample.[18]

3-*Oxo*-1-*phenylisoindoline*-1-*carboxamides* (3a—c).—(*a*) The nitriles (2a and b) (0·2 g) in ethanol (10·0 ml) were heated under reflux with aqueous N-sodium carbonate (4·0 ml) for 3—6 h. Removal of the ethanol under reduced pressure gave a solid, which was treated with water and combined with solid material obtained by chloroform extraction of the aqueous mother liquor to afford the amides (80—90%): (3a), needles, m.p. 297° (from glacial acetic acid); (3b), needles, m.p. 202° (from ethanol–water), identical (mixed m.p. and i.r. spectrum) with samples prepared before.

(*b*) The cyanophthalimidine (2c) (0·15 g) was stirred at room temperature in concentrated sulphuric acid (6·0 ml) for 30 min. The mixture was poured on ice and the solid was collected, washed with water, and crystallised to yield the *amide* (3c), plates (0·1 g), m.p. 248° (from ethanol), $\nu_{max.}$ 3350 and 3200 (NH) and 1690br (CO) cm^{-1} (Found: C, 76·9; H, 5·1; N, 8·8. $C_{21}H_{16}N_2O_2$ requires C, 76·8; H, 4·9; N, 8·5%).

3-*Phenylisoindolinones* (4a—c).—(*a*) The amides (3a—c) (0·001 mol) were heated under reflux with aqueous 20% w/v potassium hydroxide (15·0 ml) for 2·5 h. Alternatively (*b*) the nitriles (2a—c) (0·002 mol) were heated under reflux (10 min) with potassium hydroxide (0·5 g) in triethylene glycol (5·0 ml). The cooled solutions were diluted with water and extracted with chloroform to afford the 3-phenylisoindolinones (50—80%): (4a), needles, m.p. 107° (from ethanol–light petroleum) (lit.,[6] 105°), $\nu_{max.}$ 1685 (CO) cm^{-1} (Found: C, 81·2; H, 6·0; N, 5·9. Calc. for $C_{15}H_{13}NO$: C, 80·7; H, 5·8; N, 6·3%); (4b), m.p. 124° (from benzene–light petroleum) (lit.,[7] 124°); and (4c), m.p. 199° (from ethanol) (lit.,[8] 195°), which were further identified by comparison (mixed m.p. and i.r. spectrum) with authentic samples.[6–8] In the case of the nitrile (2c) acidification of the aqueous acidic mother liquors yielded 3-anilino-3-phenylphthalide (10b) (43%), needles, m.p. 218° (from methanol) (lit.,[10] 221°), identical (mixed m.p. and i.r. spectrum) with an authentic sample.[10]

(*c*) A solution of the nitrile (2a, b, or c) (0·001 mol) in anhydrous ether (70·0 ml) was added in one portion with stirring to a suspension of lithium aluminium hydride (0·15 g) in anhydrous ether (15·0 ml). The mixture was stirred at room temperature for 15 min and was then treated with water (8·0 ml) and aqueous 20% w/v potassium hydroxide (10·0 ml). Evaporation of the dried ($MgSO_4$) ether layer gave an oil which crystallised to afford the corresponding isoindolinone (4a, b, or c) (60%), identical (mixed m.p. and i.r. spectrum) with an authentic sample.[6–8]

3-*Phenylphthalide* (10a).—(*a*) 3-Anilino-3-phenylphthalide (10b) (0·2 g) was heated under reflux (1 h) with solid potassium hydroxide (0·1 g) in triethylene glycol (2 ml). Dilution with water and acidification (aqueous 2N-sulphuric acid) afforded 3-phenylphthalide (10a) (0·1 g), m.p. 114° (from ethanol–water) (lit.,[27] 115°), identical (mixed m.p. and i.r. spectrum)with an authentic sample.[27]

(*b*) *o*-Benzoylbenzoic acid (1·5 g) was heated under reflux (1 h) with solid potassium hydroxide (1·0 g) in triethylene glycol (10 ml). The cooled solution was diluted with water and acidified (aqueous 2N-sulphuric acid) and extracted with chloroform. The chloroform extract was washed with saturated aqueous sodium hydrogen carbonate to remove unchanged *o*-benzoylbenzoic acid (0·8 g) and evaporated to

[26] E. Bamberger and E. Demuth, *Ber.*, 1901, **34**, 1309.
[27] F. Rotering and T. Zincke, *Ber.*, 1876, **9**, 631; A. Pernot and A. Willemart, *Bull. Soc. chim. France*, 1953, 321.

yield 3-phenylphthalide (10a), needles (0·5 g), m.p. and mixed m.p. 114° with an authentic sample.[27]

(*c*) *o*-Benzoylbenzoic acid (1·5 g) treated as in (*b*) with solid potassium hydroxide (10·0 g) in triethylene glycol (10·0 ml) afforded 3-phenylphthalide (1·1 g), m.p. 114° (from ethanol), identical (mixed m.p. and i.r. spectrum) with an authentic sample.[27] Acidification of the bicarbonate washings yielded benzoic acid (0·4 g), m.p. 122°, identified by comparison with an authentic sample.

5-Methyl-3-oxo-1,2-diphenylisoindoline-1-carbonitrile (9a).—The amide (6) (0·37 g) in absolute ethanol (50·0 ml) was heated under reflux with a solution of sodium (0·09 g) in absolute ethanol (10·0 ml) for 1 h. The mixture was evaporated under reduced pressure, treated with water, and extracted with chloroform. The gum obtained by evaporating the chloroform extract was chromatographed in benzene over alumina to afford the *nitrile* (9a), needles (0·1 g), m.p. 151° (from ethanol), $\nu_{max.}$ 1710 (CO) cm^{-1} (Found: C, 81·8; H, 4·7; N, 8·7. $C_{22}H_{16}N_2O$ requires C, 81·5; H, 4·9; N, 8·6%). Acidification of the aqueous mother liquors and extraction with chloroform gave benzoic acid (0·07 g).

5-Nitro-3-oxo-1,2-diphenylisoindoline-1-carbonitrile (9b).—The amide (8c) (0·39 g) was heated under reflux with aqueous N-sodium carbonate (4·0 ml) in ethanol (60·0 ml) for 1 h. The red colour which developed initially was quickly discharged on heating. The mixture was evaporated under reduced pressure; the residue was treated with water and the solid obtained was crystallised to yield the *nitro-nitrile* (9b), needles (0·37 g), m.p. 225° (from glacial acetic acid), $\nu_{max.}$ 1710 (CO) and 1540 and 1360 (NO_2) cm^{-1} (Found: C, 70·8; H, 3·8; N, 11·9. $C_{21}H_{13}N_3O_3$ requires C, 71·0; H, 3·7; N, 11·8%).

Treatment of the Amides (6), (7a and b), *and* (8a and b) *with Aqueous Ethanolic Sodium Carbonate.*—These amides were recovered (>90%) after being heated under reflux (1 h) with aqueous N-sodium carbonate in ethanol as described before.

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