Heterocyclic Imines and Amines. Part XV.[1] Reactions of Hydrazines with 1,3-Di-iminoisoindoline and Related Compounds

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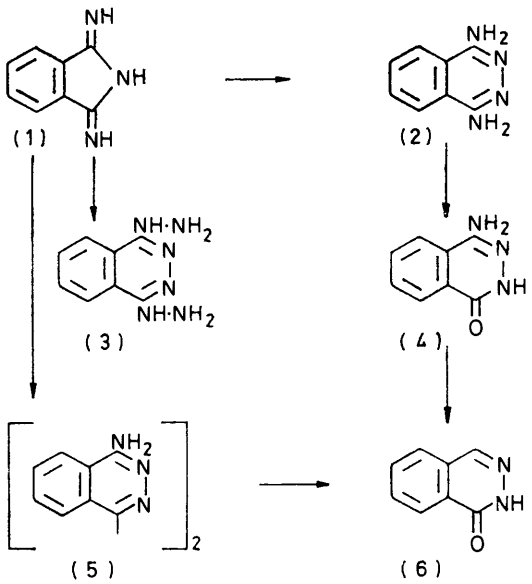
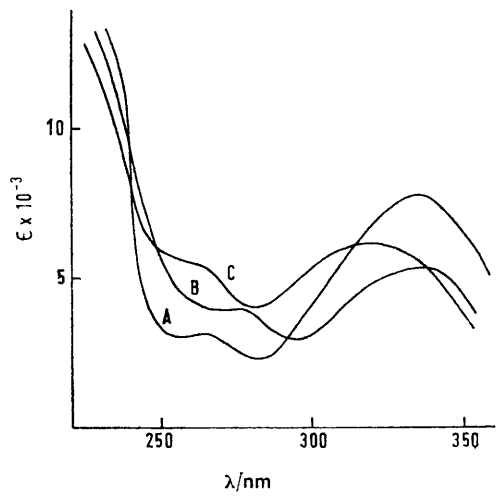
The ring-expansion reactions of 1,3-di-iminoisoindoline with hydrazine are detailed. In the cold, 1,4-diaminophthalazine is given; in boiling butanol, 1,4-dihydrazinophthalazine; and under reflux, bis-(4-aminophthalazin-1-yl) together with phthalazin-1(2*H*)-one, which is the major product at higher temperature. Methylhydrazine likewise effects ring expansion to give 4-amino-1,2-dihydro-1-imino-2-methylphthalazine, which is hydrolysed to 4-amino-2-methylphthalazin-1(2*H*)-one, also obtained from 3-iminoisoindolinone and methylhydrazine and by methylation of 4-aminophthalazin-1(2*H*)-one. Phenylhydrazine merely displaces an exocyclic imino-group of di-iminoisoindoline and of 3-iminoisoindolinone to yield phenylhydrazonoisoindolines or tautomers. Hydrazine adds to phthalonitrile in the presence of ethoxide, and reacts with monothiophthalimide, to give hydrazonoisoindolines which readily isomerise to aminophthalazines. The structures of the benzoyl derivatives of 4-aminophthalazinone have been established.

RING EXPANSION of 1,3-di-iminoisoindoline (1) with hydrazine was briefly reported (without detail) to yield 1,4-diaminophthalazine (2).[2] We now provide details of this reaction, which we were studying independently,[3]



and describe supporting evidence and some related reactions leading to phthalazines and hydrazonoisoindolines.

1,3-Di-iminoisoindoline (1) in ethanol with hydrazine hydrate rapidly gave ammonia and a crystalline base, $C_8H_{10}N_4O$, which was the hydrate of 1,4-diaminophthalazine (2). This was stable at 100° under high vacuum, but sublimed at a higher temperature to give the hygroscopic anhydrous base. A hydrochloride and a dihydrochloride were obtained which crystallised as hemihydrates, and also a solvent-free picrate, a phthalic acid salt, and a dibenzoyl derivative. The base was unaffected by boiling acetone, showing the absence of an NH_2·N function; it consumed 2 molecular proportions of nitrous acid to afford 2,3-dihydrophthalazine-1,4-dione, and it was identical with the product from ammonium acetate and 1,4-diphenoxyphthalazine.[3,4] That it existed in the 1,4-diaminophthalazine form (2) was indicated by the similarity of its u.v. absorption curve to that of 1,4-dimorpholinophthalazine[5] (see Figure). Under more vigorous conditions in boiling butanol, 1,3-di-iminoisoindoline (1) and hydrazine hydrate afforded traces of orange-red material and mainly 1,4-dihydrazinophthalazine (3), identical with authentic material[6a] from phthalonitrile and hydrazine in boiling acetic acid. Again, the tautomeric form (3) was supported by the similarity of the u.v. absorption curve to those already mentioned



U.v. absorption in ethanol of (A) 1,4-diaminophthalazine, (B) 1,4-dihydrazinophthalazine, and (C) 1,4-dimorpholinophthalazine

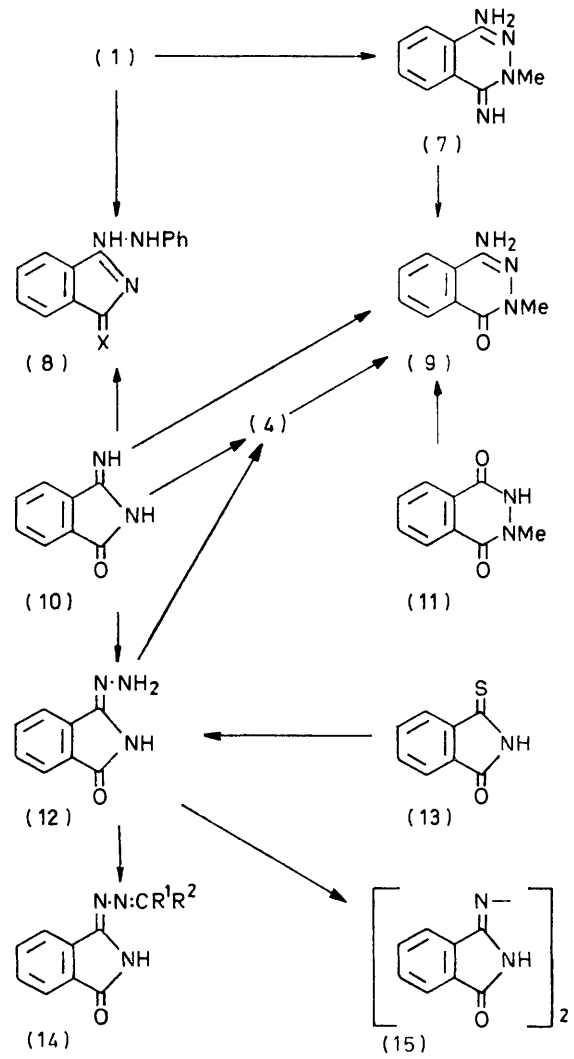
(Figure). At a higher temperature still (190°), di-iminoisoindoline and hydrazine hydrate gave phthalazin-1(2*H*)-one (6), evidently by hydrolytic and reductive deamination of intermediately formed 1,4-di-

[1] Part XIV, J. A. Elvidge and J. A. Pickett, *J.C.S. Perkin I*, 1972, 2346.
[2] F. Baumann, B. Bienert, G. Rösch, H. Vollman, and W. Wolf, *Angew. Chem.*, 1956, **68**, 133.
[3] A. P. Redman, Ph.D. Thesis, London, 1958.
[4] I. Satoda, T. Fukui, and K. Mori, *Yakugaku Zasshi*, 1962, **82**, 302.
[5] J. A. Elvidge and A. P. Redman, *J. Chem. Soc.*, 1960, 1710.
[6] (*a*) Ciba Ltd., B.P. 743,204/1956; (*b*) *cf.* J. Druey and B. H. Ringier, *Helv. Chim. Acta*, 1951, **34**, 195.

aminophthalazine (2), as indicated by separate experiments. Thus water at 190° hydrolysed 1,4-diaminophthalazine (2) to 4-aminophthalazin-1(2*H*)-one (4), which in hydrazine hydrate at 190° was deaminated to phthalazin-1(2*H*)-one (6). When 1,3-di-iminoisoindoline was heated with hydrazine hydrate under reflux, phthalazin-1(2*H*)-one (6) was formed together with a moderate yield of the orange compound, $C_{16}H_{12}N_6$. The latter showed NH_2 absorption in the i.r. spectrum, had maximum absorption at 398 nm in the u.v., did not condense with acetone, and gave phthalazin-1(2*H*)-one (6) on reductive hydrolysis with hydrazine hydrate at 195°, behaviour suggestive of the bis-aminophthalazinyl structure (5). Confirmation came from the mass spectrum which showed M^+ and $(M + 1)^+$ peaks at *m/e* 288 and 289, the latter having an intensity of 19·2% as compared with the former. The base peak had *m/e* 272 ($M - NH_2$) and other significant fragment ions were at *m/e* 144 ($M/2$), 103 ($C_7H_5N^+$), 89 ($C_7H_5^+$), and 76 ($C_6H_4^+$). Attempted synthesis of compound (5) through Ullmann coupling [7] of 1-chloro-4-phenoxyphthalazine followed by amination failed, as also did an approach from *o*-cyanobenzaldehyde,[8] in that the corresponding benzil could not be derived [9] for reaction with hydrazine.

Methylhydrazine effected ring expansion of 1,3-di-iminoisoindoline to 4-amino-1,2-dihydro-1-imino-2-methylphthalazine (7), which was isolated as the picrate and the hydrochloride hemihydrate. This imino-compound was readily hydrolysed to the *N*-methylphthalazinone (9), also obtained directly from 1,3-di-iminoisoindoline (1) and boiling aqueous methylhydrazine, and from 3-iminoisoindolinone (10). The orientation in these products (7) and (9) was substantiated by an unambiguous synthesis of the latter from 2,3-dihydro-2-methylphthalazine-1,4-dione (11) by reaction with phosphoryl chloride and then ammonia. Methylation of 4-aminophthalazin-1(2*H*)-one (4) gave the same product (9).

Phenylhydrazine and 1,3-di-iminoisoindoline gave a base, which was characterised as the picrate and the hydrochloride hemihydrate, but it had not resulted from ring expansion and was a mono(phenylhydrazono)-isoindoline or tautomer (8; X = NH), as shown by the composition, and ready hydrolysis with aqueous acid to phthalimide. The base itself was sensitive to the air and was not obtained crystalline. With 3-iminoisoindolinone (10), phenylhydrazine gave the isoindolenine analogue (8; X = O) as already described: [10] we confirmed that hydrolysis yields phthalimide, as the constitution requires. The intense u.v. maximum at 386 nm (together with a carbonyl band in the i.r. at 1695 cm^{-1}) provided a clear indication of the tautomeric form (8; X = O) (see later). Reinvestigation of the reaction of 3-iminoisoindolinone (10) with hydrazine showed that the previous formulation [10] of the product as 3-hydrazonoisoindolinone was incorrect. We agree that the product had undergone ring-expansion [11]



and was 4-aminophthalazin-1(2*H*)-one (4). This was characterised further as the hydrochloride and by treatment with nitrous acid to give 2,3-dihydrophthalazine-1,4-dione. The hydrolysis with aqueous hydrochloric acid, previously thought [10] to give phthalimide, in fact gives the hydrochloride of the aminophthalazinone, which happens not to depress the m.p. of phthalimide; this accounts for the misidentification. Flitsch and Peters [11] later showed that 3-hydrazonoisoindolinone (12) was formed by treatment of 3-iminoisoindolinone (10) with hydrazine hydrochloride. An alternative route (*cf.* ref. 12) involved treatment of

[7] P. E. Fanta, *Chem. Rev.*, 1946, **38**, 139; E. C. Kleiderer and R. Adams, *J. Amer. Chem. Soc.*, 1933, **55**, 4219; N. Kornblum and D. L. Kendall, *J. Amer. Chem. Soc.*, 1952, **74**, 5782.

[8] F. F. Blicke and R. A. Patelski, *J. Amer. Chem. Soc.*, 1936, **58**, 559.

[9] W. S. Ide and J. S. Buck, *Org. Reactions*, 1948, **4**, 269; A. L. Morrison and R. F. Long, *J. Chem. Soc.*, 1958, 211.

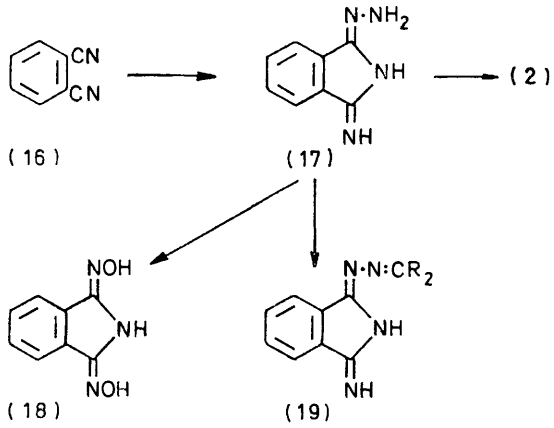
[10] J. A. Elvidge and R. P. Linstead, *J. Chem. Soc.*, 1952, 5000.

[11] W. Flitsch and H. Peters, *Angew. Chem. Internat. Edn.*, 1967, **6**, 173.

[12] W. Köhler, M. Bubner, and G. Ulbricht, *Chem. Ber.*, 1967, **100**, 1073.

monothiophthalimide (13) with hydrazine, which we found gave the base (12) more cleanly. The base (12) was characterised by u.v. and i.r. spectra, conversion into the known benzaldehyde derivative (14; $R^1 = H$, $R^2 = Ph$), and hydrolysis with pyridine hydrochloride in methanol to phthalimide; treatment with aqueous hydrochloric acid gave the known *NN'*-bis-(3-oxoisoindolin-1-ylidene)hydrazine [12] (15). The last reaction is yet another example of the propensity of hydrazones and mixed azines to give the symmetrical azine.

Phthalonitrile (16) appeared not to react with 1 molecular proportion of hydrazine hydrate in boiling ethanol. However, on addition of sodium ethoxide as catalyst a vigorous reaction ensued with separation



of a base, isomeric with diaminophthalazine, for which the 3-hydrazono-1-iminoisoindoline structure (17) was indicated by further results. This base crystallised as a solvate from ethanol but anhydrous from water, gave a picrate, and condensed with acetone to form an isopropylidene derivative (19; R = Me). Treatment with hydroxylamine hydrochloride yielded the known 1,3-bis(hydroxyimino)isoindoline (18), and the action of mixed nitrous and hydrochloric acids on the compound (17) gave phthalimide. The new base (17) showed maximum light absorption at 338 nm and so is best represented in this hydrazono-imino-isoindoline form. The parent imidine (1) absorbs at 303 nm,[13] and simple *N*-substituted derivatives in which this bond structure is fixed absorb in the 305—316 nm region,[14] whereas the bathochromic effect of an additional amino-group is often about 30 nm and sometimes much more.[15] Simple fixed-bond amino-imino-isoindolenines absorb at higher wavelengths in the region 348 to *ca.* 380 nm,[13,14] and so a hydrazino-isoindolenine structure in place of (17) is excluded. The isopropylidene derivatives (14; $R^1 = R^2 = Me$) and (19; R = Me), which absorb in the 310—317 nm region, are likewise best represented as di-iminoisoindolines, as shown.

[13] P. F. Clark, J. A. Elvidge, and R. P. Linstead, *J. Chem. Soc.* 1953, 3593.
[14] P. F. Clark, J. A. Elvidge, and J. H. Golden, *J. Chem. Soc.*, 1956, 4135.

Although condensation of the hydrazono-iminoisoindoline (17) with acetone had been successful, yielding (19; R = Me), an attempted condensation with benzophenone was not. However, the benzophenone product (19; R = Ph) was formed by condensing benzophenone hydrazone with 1,3-di-iminoisoindoline, and the structure (19; R = Ph) was confirmed by acid hydrolysis to phthalimide. Acetone hydrazone evidently disproportionates readily: from a reaction between it and 1,3-di-iminoisoindoline (1) under similar conditions, 3-hydrazono-1-iminoisoindoline (17) and 1,4-diaminophthalazine (2) were isolated. It was not then surprising to find that with 3-iminoisoindolinone (10), acetone hydrazone afforded 4-aminophthalazinone (4).

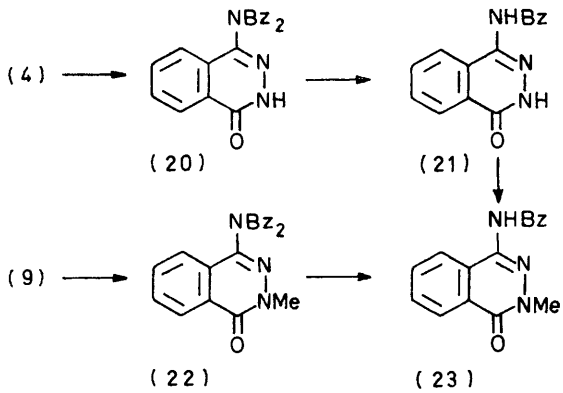
The isomerisation of 3-hydrazono-1-iminoisoindoline (17) in ethanol solution to 1,4-diaminophthalazine (2) occurred rapidly with warm hydrazine hydrate, but not in the boiling solvent alone or with ethanolic sodium ethoxide or ammonia. 3-Isopropylidenehydrazonoisoindolinone (14; $R^1 = R^2 = Me$) resisted boiling water, at least for a short time, but when dissolved in warm hydrazine hydrate soon gave a precipitate of 4-aminophthalazin-1(2*H*)-one (4), as a result of disproportionation and then isomerisation. When 1-imino-3-isopropylidenehydrazonoisoindoline (19; R = Me) was dissolved in the minimum of ethanol and treated with hydrazine hydrate, disproportionation ensued and the sparingly soluble 3-hydrazono-1-iminoisoindoline (17) precipitated as the ethanolate. Thus ring expansion had no chance to occur as it did with the soluble isoindolinone analogue or when the compound (17) was held in dilute solution.

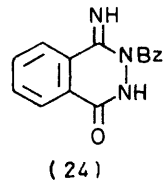
It is apparent from previous work in this series that amines react with imidines by addition.[14,16] This is usually followed by an elimination, which can take the form of ring opening to a diamidine derivative. Reclosure with elimination of ammonia or an amine can then follow, the various stages being potentially reversible. Loss of a volatile amine or separation of a sparingly soluble product may bring the reactions to an end. In the conversion of di-iminoisoindoline (1) into 1,4-diaminophthalazine (2) with hydrazine, 2-amidinobenzamide hydrazone would be the open-chain intermediate. In the analogous reaction with compound (17), the intermediate must be phthalamide dihydrazone. Under the more vigorous conditions which convert di-iminoisoisoindoline (1) into 1,4-dihydrazinophthalazine (3), phthalohydrazidine is presumably the intermediate.

Benzoyl Derivatives of 4-Aminophthalazin-1(2H)-one.—Treatment of 4-aminophthalazin-1(2*H*)-one (4) with benzoyl chloride in pyridine was known [17] to give a dibenzoyl derivative, but the structure, for which there are three possibilities, had not been settled. We found that 4-amino-2-methylphthalazin-1(2*H*)-one (9) likewise afforded a dibenzoyl derivative, for which of

[15] E. A. Braude, *Ann. Reports*, 1945, **42**, 105.
[16] J. A. Elvidge and J. H. Golden, *J. Chem. Soc.*, 1957, 700.
[17] E. F. M. Stephenson, *J. Chem. Soc.*, 1944, 678.

course an *ON*-dibenzoyl structure was excluded. The two dibenzoyl derivatives had closely similar i.r. absorption in the 1710—1000 cm^{-1} region, indicating analogous structures. The following results show that these were (20) and (22).





Each compound was monodebenzoylated by aqueous ammonia in ethanol, and the monobenzoyl derivative of 4-aminophthalazinone was converted on methylation into the other monobenzoyl compound; thus each had the benzoyl group in the same position. The i.r. and ^1H n.m.r. spectra indicated the 4-benzamido-structures (21) and (23). These compounds (in Nujol) had amide absorption near 3250 cm^{-1}, and carbonyl bands at 1678 and near 1662 cm^{-1} from the benzoyl group and ring carbonyl. In addition, the unmethylated compound (21) showed NH absorption at 3165 cm^{-1}; it also showed two low-field signals in its ^1H n.m.r. spectrum at τ −2·63 and −0·68 from the ring NH and benzamido NH, respectively, whereas the 2-methyl compound (23) showed only a benzamido NH signal at τ −0·80. The last two τ values are much too low for an imino-group [18] as present in the alternative structure (24). Moreover, phthalazin-1(2*H*)-one (6) showed a ring NH signal at τ −2·67 and i.r. absorption at 3130 cm^{-1}. As the dibenzoyl derivative of 4-aminophthalazinone showed a ring NH signal at τ −2·66 and i.r. NH stretching absorption at 3145 cm^{-1}, it too was derived from the 4-aminophthalazin-1(2*H*)-one structure and so was the compound (20) as already mentioned; assignment of the structure (22) then followed.

EXPERIMENTAL

M.p.s designated ' inst.' were taken on a Kofler Hotbench and are instantaneous decomposition points. I.r. results (3500—1400 cm^{-1} region) were obtained with a Grubb-Parsons S4 spectrometer with sodium chloride prism, and u.v. results with a Unicam SP 500 spectrophotometer for solutions in ethanol. N.m.r. spectra were recorded with a Perkin-Elmer R10 instrument at 60 MHz and mass spectra with an A.E.I. MS12 spectrometer.

Reactions of 1,3-*Di-iminoisoindoline with Hydrazine.*—(a) 1,4-*Diaminophthalazine* (2). Hydrazine hydrate (0·7 ml) was added in drops to a solution of 1,3-di-iminoisoindoline [19] (2 g) in warm ethanol (40 ml). Ammonia was evolved and yellow solid (1·6 g) separated. From water (charcoal), the colourless *hydrate* crystallised as needles, m.p. 255° (decomp.) (Found: C, 53·6; H, 5·7; N, 31·1. $C_8H_8N_4,H_2O$ requires C, 53·8; H, 5·6; N, 31·4%), $\lambda_{max.}$ 335, 262, and 217 nm (ε 7750, 3100, and 56,100), $\nu_{max.}$ (KBr) 3242s and 3165 (NH_2, bonded), 3081br (H_2O bonded), 1623s (NH def.), 1564, and 1415s cm^{-1}. This hydrate was stable at 100° and 10^{-4} mmHg but at 130—150° and 10^{-4} mmHg the *anhydrous base* sublimed, m. p.255° (decomp.) (lit.,[2] 256°) (Found: C, 60·0; H, 5·1; N, 35·6. $C_8H_8N_4$ requires C, 60·0; H, 5·0; N, 35·0%), which was rehydrated on exposure to atmospheric moisture (Found: C, 54·2; H, 5·4%).

The *hydrochloride hemihydrate*, prepared in hot aqueous acid, formed cubes, m.p. 220° (inst.) [from ethanol–light petroleum (b.p. 60—80°)] [Found: C, 47·0; H, 5·0; Cl(ionic), 17·4; N, 27·3. $C_8H_9ClN_4,0{\cdot}5H_2O$ requires C, 46·7; H, 4·9; Cl, 17·2; N, 27·2%]. The *dihydrochloride hemihydrate* had m.p. *ca.* 226° (from concentrated hydrochloric acid) (Found: Cl, 29·6; N, 23·0. $C_8H_{10}Cl_2N,0{\cdot}5H_2O$ requires Cl, 29·3; N, 23·1%).

The *picrate* formed yellow needles, m.p. 302—303° (decomp.) (from dimethylformamide) (Found: C, 43·4; H, 3·1; N, 24·9. $C_{14}H_{11}N_7O_7$ requires C, 43·2; H, 2·8; N, 25·2%). The *phthalate*, prepared in acetic acid from the base hydrate and phthalic acid, had m.p. 225° with resolidification and then m.p. 299—301° (from water) (Found: C, 59·0; H, 4·5; N, 17·1. $C_{16}H_{14}N_4O_4$ requires C, 58·9; H, 4·3; N, 17·2%).

Treatment of the diamine hydrate (1 g) in pyridine (40 ml) with benzoyl chloride (1·3 ml) at 50—60° for 5 h, evaporation, and trituration of the residue with ethanol gave 1,4-dibenzamidophthalazine (0·9 g), m.p. 303° (from dimethylformamide–water) (Found: C, 71·7; H, 4·4; N, 15·1. $C_{22}H_{16}N_4O_2$ requires C, 71·7; H, 4·4; N, 15·2%), $\nu_{max.}$ (Nujol) 3268 and 3145 (NH bonded *trans* and *cis*), 1697s (CO), 1587s, 1560s, and 1525s cm^{-1}.

A solution of 1,4-diaminophthalazine hydrate (230 mg) in water (10 ml) was cooled to 0° and concentrated hydrochloric acid (0·5 ml) was added, followed by sodium nitrite solution in drops, with stirring, until an excess was present (starch–iodide paper, blue); *ca.* 2 molecular proportions had been added. 2,3-Dihydrophthalazine-1,4-dione separated (180 mg) (Found: C, 59·3; H, 3·9; N, 17·6. Calc. for $C_8H_6N_2O_2$: C, 59·3; H, 3·7; N, 17·3%), m.p. and mixed m.p.[19] 326—327°.

The diaminophthalazine hydrate was identical (mixed m.p., i.r. spectrum) with material synthesised [4] by fusing 1,4-diphenoxyphthalazine (0·7 g) with ammonium acetate (15 g) at 170° for 2 h and crystallising the product from water.

(b) 1,4-*Dihydrazinophthalazine* (3). 1,3-Di-iminoisoindoline (3 g) in n-butanol (35 ml) was heated under reflux

[18] N. R. Barot and J. A. Elvidge, *J.C.S. Perkin I*, 1972, 1009.
[19] H. D. K. Drew and H. H. Hatt, *J. Chem. Soc.*, 1937, 16.

with hydrazine hydrate (3 ml) for 13 h. Orange material (0·4 g), m.p. *ca.* 225°, was rejected and the filtrate cooled. Buff needles of 1,4-*dihydrazinophthalazine sesquihydrate* separated (2·3 g), m.p. 189° (inst.) (from ethanol–water), stable at 25° and 10^{-5} mmHg (Found: C, 44·5; H, 6·1; N, 38·5. $C_8H_{10}N_6,1{\cdot}5H_2O$ requires C, 44·2; H, 6·0; N, 38·6%). The anhydrous base was obtained by drying at 50° and 10^{-5} mmHg (Found: C, 50·6; H, 5·3; N, 43·8. Calc. for $C_8H_{10}N_6$: C, 50·5; H, 5·3; N, 44·2%), m.p. and mixed m.p. [6] 187°, $\lambda_{max.}$ 335 and 275 nm (ε 5140 and 4000), $\nu_{max.}$ (KBr) 3241s and 3150s (NH_2, bonded), 3190s (NH), 3017w (CH), 1646, 1626, 1592w, 1499s, and 1431 cm^{-1}.

(c) *More vigorous reactions with hydrazine and with water.* 1,3-Di-iminoisoindoline (1 g) and hydrazine hydrate (10 ml) were kept together for 3 days and then heated at 190° in a Carius tube for 20 h. The solid (0·71 g) obtained was phthalazin-1(2*H*)-one (6), m.p. 183° (from water), identical (mixed m.p., i.r. spectrum) with authentic material (see later).

1,4-Diaminophthalazine hydrate (200 mg) was heated with water (10 ml) in a Carius tube at 190° for 20 h. 4-Aminophthalazin-1(2*H*)-one (4) (150 mg) was collected, m.p. 268—269° (from ethanol) (lit.,[11] 265°) (Found: C, 59·4; H, 4·4. Calc. for $C_8H_7N_3O$: C, 59·7; H, 4·4%), $\lambda_{max.}$ 314, 263, 228infl, and 211 nm (ε 6050, 1800, 11,050, and 46,800), $\nu_{max.}$ (Nujol) 3279s, 3247s, and 3165s (NH_2, NH), 1656s,br (CO, NH def.), 1600s, 1557w, and 1490 cm^{-1} (lit.,[11] ν_{CO} 1670 cm^{-1}). When 4-aminophthalazinone was heated with an excess of hydrazine hydrate at 190° for 20 h phthalazin-1(2*H*)-one (6) was obtained, identical (mixed m.p.) with authentic material (see next).

1,3-Di-iminoisoindoline (8 g) was mixed with hydrazine hydrate (30 ml) and heated under reflux for 20 h. Orange material was collected (2·2 g), m.p. 275—280°. Cooling of the filtrate then afforded a buff solid (5·2 g), m.p. 145—155°, of which a portion (1 g) in ethanol was chromatographed on a column (4 × 80 cm) of alumina (Spence grade 2) [20] to yield phthalazin-1(2*H*)-one [21] (6) (0·8 g) as needles (from water), m.p. 183—184° (Found: C, 65·5; H, 4·2; N, 18·8. Calc. for $C_8H_6N_2O$: C, 65·75; H, 4·1; N, 19·2%), $\nu_{max.}$ (KBr) 3130 (NH), 1652s (CO), 1607, 1595, 1570, 1475, and 1435w cm^{-1}, $\lambda_{max.}$ 280, 250, and 226 nm (ε 6040, 7510, and 16,100), τ(Me_2SO) 2·03 (m, 5-, 6-, 7-H), 1·80 (dd, 8-H), 1·60 (s, 4-H), and −2·65br (s, NH). The preceding orange material was extractively crystallised from pyridine to give dark orange prisms of *bis*-(4-*aminophthalazin*-1-*yl*) (5), m.p. 289° (decomp.) [Found: C, 66·4; H, 4·2; N, 29·1%; *M* (ebullioscopic in nitrobenzene), 350. $C_{16}H_{12}N_6$ requires C, 66·7; H, 4·2; N, 29·2%; *M*, 288], *m/e* 288 (61·9), 289 (11·9), 273 (19·5), 272 (100), 259 (16·2), 258 (19·1), 229 (9·0), 144 (11·4), 129·5 (2·4), 129 (17·2), 103 (57·1), 89 (28·6), and 76 (33·8%), $\lambda_{max.}$ 398 and 286 nm (ε 10,300 and 19,900), $\nu_{max.}$ (KBr) 3311s and 3226 (NH_2), 1605s, 1585s, 1550, 1474, and 1456s cm^{-1}.

Reactions Involving Methylhydrazine.—(a) 4-*Amino*-1,2-*dihydro*-1-*imino*-2-*methylphthalazine* (7). To a solution of 1,3-di-iminoisoindoline (1 g) in methanol (15 ml), methylhydrazine [5] (42%; 1 ml) was added. After 3 days, the solution was evaporated under high vacuum and the residue in methanol converted into the *picrate* (2 g) which crystallised from dimethylformamide–water (charcoal) as pale orange laths, m.p. 252° (inst.) (Found: C, 44·4; H, 3·5; N, 24·6. $C_{15}H_{13}N_7O_7$ requires C, 44·7; H, 3·3; N, 24·3%). The picrate (700 mg) was suspended in a mixture of ethanol (20 ml) and water (10 ml), and stirred with Amberlite IRA-400 resin (OH^- form). Evaporation of the filtrate, dissolution of the base (7) in 2N-hydrochloric acid and then cooling afforded the *hydrochloride hemihydrate* (140 mg), m.p. 312° (decomp.) (from 2N-hydrochloric acid) (Found: C, 49·5; H, 5·7; N, 25·6. $C_9H_{11}ClN_4,0{\cdot}5H_2O$ requires C, 49·2; H, 5·5; N, 25·5%).

(b) 4-*Amino*-2-*methylphthalazin*-1(2H)-*one* (9). A sample of the preceding base (7) (200 mg; from the picrate) was dissolved in hot water. Concentration of the solution under reduced pressure afforded 4-amino-2-methylphthalazin-1(2*H*)-one (9), identical (mixed m.p. 160°) with authentic material.

1,3-Di-iminoisoindoline (200 mg) was heated under reflux with aqueous methylhydrazine (42%; 5 ml) for 20 h. Concentration under reduced pressure yielded 4-amino-2-methylphthalazin-1(2*H*)-one, identical (mixed m.p.) with authentic material.

3-Iminoisoindolinone [10] (2 g) in methanol (30 ml) was heated with methylhydrazine solution (42%; 2 ml) under reflux for 20 min. Evaporation and crystallisation of the residue from water gave 4-amino-2-methylphthalazin-1(2*H*)-one (1·3 g) as needles, m.p. and mixed m.p. 160°.

2,3-Dihydro-2-methylphthalazine-1,4-dione [5] (5 g) was heated with phosphoryl chloride (30 ml) under reflux for 2 h, the excess of reagent was removed under reduced pressure, and the residue sublimed at 70—110° and 0·2 mmHg and then at 80—100° and 10^{-5} mmHg to give 4-*chloro*-2-*methylphthalazin*-1(2*H*)-*one*, m.p. 127—128° (Found: C, 55·5; H, 3·6; Cl, 18·1. $C_9H_7ClN_2O$ requires C, 55·6; H, 3·6; Cl, 18·2%). This chloro-compound (400 mg) was heated with ammonium carbonate (400 mg) and aqueous ammonia (10 ml; *d* 0·88) in a sealed tube at 213° for 20 h. The solution was evaporated and the residue extracted with a little hot water: on cooling, the product separated. Sublimation at 100—130° and 10^{-4} mmHg provided 4-*amino*-2-*methylphthalazin*-1(2H)-*one*, m.p. 160° (Found: C, 61·2; H, 4·9; N, 23·9; NMe, 8·6. $C_9H_9N_3O$ requires C, 61·7; H, 5·2; N, 24·0; NMe, 8·9%), $\lambda_{max.}$ 317, 263, 228infl, 215infl, and 209 nm (ε 6140, 1840, 9030, 46,500, and 52,500), $\nu_{max.}$ (Nujol) 3378s, 3306s and 3173s (NH_2 free and bonded), 3030 (CH), 1653 (CO), 1620s, 1571s, 1560sh, 1490s, and 1429 cm^{-1}.

4-Aminophthalazin-1(2*H*)-one (450 mg), dimethyl sulphate (700 mg), methanol (35 ml) and aqueous 20% potassium hydroxide (1·6 ml) were heated together under reflux for 1 h. Cooling afforded the 2-methyl derivative (6) (120 mg) as needles (from water), m.p. and mixed m.p. 160°.

1-*Imino*-3-*phenylhydrazino*-1H-*isoindole* (8; X = NH).—1,3-Di-iminoisoindoline (1 g) in methanol (15 ml) was treated with phenylhydrazine (0·7 ml). After 2 days, the solution was evaporated under reduced pressure, the residue was dissolved in the minimum of methanol, and the solution poured into ice-cold 2N-hydrochloric acid. From ethanol, the *hydrochloride hemihydrate* separated as orange crystals, m.p. 263° (decomp.) (Found: C, 59·7; H, 5·0; N, 19·0. $C_{14}H_{13}ClN_4,0{\cdot}5H_2O$ requires C, 59·8; H, 5·0; N, 19·9%). The *picrate* formed red needles, m.p. 253° (decomp.) (from dimethylformamide) (Found: C, 51·5; H, 3·4; N, 21·0. $C_{20}H_{15}N_7O_7$ requires C, 51·6; H, 3·3; N, 21·1%).

[20] H. Brockmann and H. Schodder, *Ber.*, 1941, **74**, 43.
[21] S. Gabriel and A. Neumann, *Ber.*, 1893, **26**, 521; S. F. Mason, *J. Chem. Soc.*, 1957, 4874.

Hydrolysis of the hydrochloride (130 mg) in ethanol (5 ml) by heating with concentrated hydrochloric acid (4 ml) and glacial acetic acid (4 ml) on a steam-bath for 7 min, and cooling of the solution, afforded phthalimide (30 mg), m.p. and mixed m.p. 234°.

3-*Phenylhydrazino*-1H-*isoindol*-1-*one* (8; X = O).—3-Iminoisoindolinone (3 g) in methanol (60 ml) was kept with phenylhydrazine (4·8 ml) for 3 days. Recrystallisation of the product from dimethylformamide–water gave yellow needles, m.p. 233° (lit.,[10] 234°; lit.,[12] 222°) (Found: C, 70·7; H, 5·4. Calc. for $C_{14}H_{11}N_3O$: C, 70·9; H, 4·7%), $\lambda_{max.}$ 386, 300, and 251 nm (ε 22,600, 5900, and 12,600), $\nu_{max.}$ (KBr) 3274 (NH of 3-substituent), and 3135 (ring NH), 3030w (CH), 1696 (CO), 1653w, 1616, 1600s, 1543, 1494, 1477, 1442w, and 1417 cm^{-1}. Hydrolysis of a portion (300 mg) in boiling 6N-hydrochloric acid for 5 min, filtration, and cooling of the filtrate afforded phthalimide (50 mg), m.p. and mixed m.p. 234°. The filtrate was made alkaline (NaOH) and extracted with ether. On addition to the extract of ethereal hydrogen chloride, phenylhydrazine hydrochloride was precipitated (40 mg), identified by mixed m.p.

Reaction of 3-*Iminoisoindolinone with Hydrazine* (cf. *refs.* 10 *and* 11).—Hydrazine hydrate (1 ml) was added to 3-iminoisoindolinone (0·5 g) in methanol (15 ml). During 3 days, 4-aminophthalazin-1(2*H*)-one (4) separated (0·6 g) as needles, m.p. 268—269° (from ethanol) (lit.,[11] 265°) (Found: C, 59·4; H, 4·6%), identical (i.r.) with the material already described. Recrystallisation from 4N-hydrochloric acid afforded the hydrochloride, m.p. *ca.* 250° (decomp.) (lit.,[22] 240°) (Found: C, 48·3; H, 4·2; Cl, 18·3; N, 20·8. Calc. for $C_8H_8ClN_3O$: C, 48·6; H, 4·1; Cl, 18·0; N, 21·3%), which did not depress the m.p. of phthalimide (*cf.* ref. 10). When the 4-aminophthalazinone (160 mg) in a mixture of water (10 ml) and concentrated hydrochloric acid (1 ml) was treated at 0° with aqueous sodium nitrite until an excess was present (starch–iodide paper), a solid separated (150 mg), m.p. *ca.* 320° undepressed by authentic 2,3-dihydrophthalazine-1,4-dione [19] and with the same i.r. spectrum.[5]

3-*Hydrazonoisoindolinone* (12).—Hydrazine hydrate (0·08 ml) was added to monothiophthalimide [23] (250 mg) in ethanol (5 ml). Hydrogen sulphide was evolved and 3-hydrazonoisoindolinone separated (212 mg); m.p. 230° (inst.) raised to 238° (inst.) by crystallisation from ethanol [lit.,[11] 195—205° (decomp.)] (Found: C, 59·8; H, 4·6; N, 26·3. Calc. for $C_8H_8N_3O$: C, 59·6; H, 4·4; N, 26·1%), $\lambda_{max.}$ 325, 275, and 217 nm (ε 9280, 9280, and 20,000), $\nu_{max.}$ (KBr) 3200s and 3053 (NH_2, NH), 1711s (CO), 1661 (C=N), 1614, and 1472 cm^{-1}. When the compound (480 mg) was boiled in ethanol (10 ml) under reflux with benzaldehyde (0·31 ml) for 1 h, and the solution was cooled, 3-benzylidenehydrazonoisoindolinone (14; R^1 = H, R^2 = Ph) separated (m.p. *ca.* 203°) as pale yellow needles (extractively from methanol, 3 ×), m.p. 199° (lit.,[12] 224°) (Found: C, 72·0; H, 4·4; N, 17·0. Calc. for $C_{15}H_{11}N_3O$: C, 72·3; H, 4·5; N, 16·9%), $\lambda_{max.}$ (2-methoxyethanol) 332, 302, 292infl, 241infl, and 223 nm (ε 27,400, 16,550, 14,200, 11,450, and 22,650). Use of acetone, similarly, afforded 3-isopropylidenehydrazonoisoindolinone (14; R^1 = R^2 = Me) as needles, m.p. 104—105° [from light petroleum (b.p. 100—120°)] (lit.,[12] 108°) (Found: C, 65·8; H, 5·4; N, 20·7. Calc. for $C_{11}H_{11}N_3O$: C, 65·7; H, 5·5; N, 20·9%).

3-Hydrazonoisoindolinone (250 mg) and pyridine hydrochloride (1 g) were heated under reflux in methanol (15 ml) for 13 h. Evaporation and addition of 2N-hydrochloric acid (15 ml) precipitated phthalimide (115 mg) (mixed m.p.).

3-Hydrazonoisoindolinone (54 mg) was dissolved in warm 2N-hydrochloric acid (1 ml). Yellow *NN'*-bis-(3-oxoisoindolin-1-ylidene)hydrazine [12] (15) separated (45 mg) (Found: C, 66·0; H, 3·8; N, 19·3%; *m/e* 290. Calc. for $C_{16}H_{10}N_4O_2$: C, 66·2; H, 3·5; N, 19·3%; *M*, 290), $\lambda_{max.}$ (2-methoxyethanol) 367, 350, 290, and 226 nm (ε 28,800, 31,400, 11,550, and 30,250), $\nu_{max.}$ (Nujol) 3155 (NH), 1724s (CO), 1658s (C=N), and 1626 cm^{-1}.

3-*Hydrazono*-1-*iminoisoindoline* (17).—Hydrazine hydrate (2 ml) was added to phthalonitrile (5 g) in ethanol (60 ml) and the solution heated under reflux. On cooling, phthalonitrile separated (mixed m.p.). At 50°, the nitrile redissolved; addition of ethanolic sodium ethoxide [from sodium (200 mg)] then produced a red colour and caused the solution to boil, and a solid separated (5·31 g). Several crystallisations from ethanol afforded pale cream needles, m.p. 213° (inst.), of 3-*hydrazono*-1-*iminoisoindoline ethanolate* (Found: C, 58·0; H, 6·9; N, 27·0. $C_8H_8N_4,C_2H_6O$ requires C, 58·2; H, 6·8; N, 27·2%). Crystallisation from methanol gave the *methanolate*, m.p. 210° (inst.) (Found: C, 56·4; H, 6·1; N, 29·3. $C_8H_8N_4,CH_4O$ requires C, 56·2; H, 6·3; N, 29·2%). The *base* had m.p. 218° (inst.) (from water) (Found: C, 60·0; H, 5·2. $C_8H_8N_4$ requires C, 60·0; H, 5·0%), $\lambda_{max.}$ 338, 278, and 225 nm (ε 10,900, 7600, and 17,300), $\nu_{max.}$ (KBr) 3268s and 3221s (NH_2) 3015s (NH), 2970, 1695s (C=N), 1637w, 1600w, 1544s, 1486w, 1465w, and 1431s cm^{-1}. The *picrate*, prepared in ethanol, had m.p. 227° (inst.) (Found: C, 43·2; H, 3·2; N, 25·4. $C_{14}H_{11}N_7O_7$ requires C, 43·2; H, 2·9; N, 25·2%).

The ethanolate (200 mg) was boiled with acetone (5 ml) for 1 h. Evaporation afforded 1-*imino*-3-*isopropylidenehydrazonoisoindoline* (19; R = Me) which crystallised from dioxan–light petroleum (b.p. 60—80°) as yellow rods, m.p. 170° (inst.) (Found: C, 65·9; H, 6·1; N, 27·6. $C_{11}H_{12}N_4$ requires C, 66·0; H, 6·0; N, 28·0%), $\lambda_{max.}$ 317, 275, and 225 nm (ε 11,350, 12,900, and 19,650), $\nu_{max.}$ (KBr) 3125br (NH), 3030, 1652s,br (C=N, NH def.), 1610sh, 1531s, 1472, 1431, and 1409 cm^{-1}.

The ethanolate (750 mg) and hydroxylamine hydrochloride (520 mg) were heated in ethanol under reflux for 3 h. Filtration and evaporation of the filtrate gave 1,3-bis(hydroxyimino)isoindoline (18) (790 mg), m.p. 252° (from methanol) (Found: C, 54·55; H, 4·15; N, 23·2. Calc. for $C_8H_7N_3O_2$: C, 54·2; H, 4·0; N, 23·7%), mixed m.p.[24] 252—253°.

3-Hydrazono-1-iminoisoindoline ethanolate (800 mg) was stirred with water (20 ml) at 0°. Concentrated hydrochloric acid (1·5 ml) was added, followed by aqueous sodium nitrite, in slight excess (to starch–iodide paper). After 1 h, the cloudy solution was clarified and kept at room temperature. Phthalimide separated (370 mg), m.p. and mixed m.p. 234—235°.

3-*Diphenylmethylenehydrazono*-1-*iminoisoindoline* (19; R = Ph).—Benzophenone hydrazone [25] (1 g) was heated with 1,3-di-iminoisoindoline (730 mg) in ethanol (5 ml) under reflux for 24 h. Evaporation of the solution and

[22] A. Darapsky and P. Heinrichs, *J. prakt. Chem.*, 1936, **146**, 307.
[23] H. D. K. Drew and D. B. Kelly, *J. Chem. Soc.*, 1941, 625.
[24] J. A. Elvidge and R. P. Linstead, *J. Chem. Soc.*, 1954, 442.
[25] T. Curtius and R. Kastner, *J. prakt. Chem.*, 1911, **83**, 215.

trituration of the residue with dioxan provided the yellow *product* (610 mg), m.p. 190—195° (inst.) [from dioxan–light petroleum (b.p. 60—80°)] (Found: C, 78·2; H, 4·8; N, 17·1. $C_{21}H_{16}N_4$ requires C, 77·8; H, 5·0; N, 17·3%), $\lambda_{max.}$ 340, 265, and 225 nm (ε 18,800, 14,900, and 26,300). When this derivative (200 mg) in ethanol (2 ml) was heated with concentrated hydrochloric acid (5 ml) on a steam-bath for 1 h, the solution was evaporated, and the residue washed with benzene, phthalimide (50 mg) remained, m.p. 229—230° (from water), mixed m.p. 233—234°.

Reaction of Acetone Hydrazone with Di-iminoisoindoline and with 3-Iminoisoindolinone: Isomerisations to Phthalazines.—1,3-Di-iminoisoindoline (700 mg) was dissolved in acetone hydrazone [26] (2 ml) at 50°. When the solid which separated (534 mg), m.p. 198° (inst.), was crystallised from ethanol, a mixture of fine needles m.p. 212° (inst.) and orange prisms m.p. *ca.* 225°, was obtained: the former passed through a sieve, leaving the latter. Recrystallisation of the needles from ethanol afforded 3-hydrazono-1-iminoisoindoline ethanolate (mixed m.p.; u.v. spectrum). Recrystallisation of the prisms from water gave colourless 1,4-diaminophthalazine hydrate (mixed m.p. 247°).

3-Iminoisoindolinone (1 g) was similarly treated with acetone hydrazone (2 ml). The product (850 mg) was 4-aminophthalazin-1(2*H*)-one, m.p. and mixed m.p. 268—269°.

Further Experiments on the Isomerisation of Hydrazonoisoindolines into Aminophthalazines.—3-Hydrazono-1-iminoisoindoline ethanolate (280 mg) was heated with hydrazine hydrate (1·5 ml) for 2 min on a steam-bath. On cooling the solution, 1,4-diaminophthalazine hydrate separated (130 mg), m.p. 248°, raised on admixture with authentic material.

No isomerisation was effected in boiling ethanol alone, or in the presence of sodium ethoxide or of ammonia.

When the ethanolate (750 mg) was heated in ethanol (5 ml) with benzophenone hydrazone (2 g) for 12 h under reflux, the solution was evaporated, and the residue extracted with light petroleum (b.p. 40—60°), the starting isoindoline remained (560 mg), identified by mixed m.p. and u.v. spectrum.

3-Isopropylidenehydrazonoisoindolinone (100 mg) was dissolved in warm hydrazine hydrate (0·5 ml). Solid (50 mg), m.p. *ca.* 261°, soon precipitated, identified after crystallisation from water as 4-aminophthalazin-1(2*H*)-one, m.p. and mixed m.p. 268—269°.

To 1-imino-3-isopropylidenehydrazonoisoindoline (19; R = Me) (300 mg) in ethanol (10 ml), hydrazine hydrate (1 ml) was added. After a few minutes, 3-hydrazono-1-iminoisoindoline ethanolate precipitated (210 mg), m.p. and mixed m.p. 210—212°.

Benzoyl Derivatives of 4-Aminophthalazinone and the 2-Methyl Analogue.—Benzoylation [17] of 4-aminophthalazin-1(2*H*)-one gave 4-dibenzoylaminophthalazin-1(2*H*)-one (20) as needles, m.p. 261—262° (from dimethylformamide) [lit.,[17] 252—253° (from trichloroethylene–ethanol)] (Found: N, 11·6. Calc. for $C_{22}H_{15}N_3O_3$: N, 11·6%), $\nu_{max.}$ (Nujol) 3155 (NH), *ca.* 1692s and 1681s (merged, 3 × CO), 1572, and 1558w cm^{-1}, τ(Me_2SO) 2·70—1·45 (m, 14 × aryl H), and −2·66br (s, ring NH).

This dibenzoyl derivative (200 mg) was shaken with ethanol (3 ml) and aqueous ammonia (*d* 0·88; 3 ml) for several days. The solution was evaporated and the residue extracted several times with ether. Crystallisation of the residue from dimethylformamide–water then afforded 4-*benzamidophthalazin*-1(2H)-*one* (21) as rods, m.p. 273° (Found: C, 67·5; H, 4·5; N, 15·9. $C_{15}H_{11}N_3O_2$ requires C, 67·9; H, 4·2; N, 15·8%), $\nu_{max.}$ (Nujol) 3236 (4-NH), 3165 (ring NH), 1678s (CO of 4-substituent), 1661s (ring CO), 1617w, 1602w, 1577w, 1558w, and 1508 cm^{-1}, τ(Me_2SO) 2·5—1·6 (m, 9 × aryl H), −0·68br (s, 4-NH), and −2·63br (s, ring NH). Evaporation of the ethereal extract left benzamide (40 mg), m.p. and mixed m.p. 128°.

4-Benzamidophthalazinone (193 mg) was heated under reflux with dimethyl sulphate (0·08 ml), potassium hydroxide (40 mg), and water (5 ml) for 90 min. Unchanged starting material (163 mg) (mixed m.p.) was rejected. From the filtrate, 4-benzamido-2-methylphthalazin-1(2*H*)-one crystallised (5 mg), identical (mixed m.p.) with the sample described later.

4-Amino-2-methylphthalazin-1(2*H*)-one (545 mg), pyridine (15 ml), and benzoyl chloride (0·58 ml) were heated together at 70—80° for 6 h. Evaporation of the solution under reduced pressure and trituration of the residue with ethanol provided 4-*dibenzoylamino*-2-*methylphthalazin*-1(2H)-*one* (22) (577 mg) as needles, m.p. 217—218° (from dimethylformamide–water) (Found: C, 71·8; H, 4·8; N, 11·1. $C_{23}H_{17}N_3O_3$ requires C, 72·1; H, 4·5; N, 11·0%), $\nu_{max.}$ (Nujol) 1708s and 1698s (merged 2 × CO), 1672s (CO), 1602w, 1577, and 1548w cm^{-1}, τ(Me_2SO) 6·47 (s, N–Me) and 2·67—1·58 (m, 14 × aryl H).

This dibenzoyl derivative (175 mg) was shaken with ethanol (3 ml) and aqueous ammonia (*d* 0·88; 3 ml). After 3 days, the solution was evaporated; the residue was washed with ether several times, and then crystallised from ethanol–water to afford 4-*benzamido*-2-*methylphthalazin*-1(2H)-*one* (23) (100 mg) as the *hemihydrate*, m.p. 153—154° (Found: C, 67·1; H, 5·0; N, 14·8. $C_{16}H_{13}N_3O_2,0{\cdot}5H_2O$ requires C, 66·7; H, 4·9; N, 14·6%), converted into the anhydrous *compound* at 80—100° and 10^{-4} mmHg (Found: C, 68·7; H, 4·8. $C_{16}H_{13}N_3O_2$ requires C, 68·8; H, 4·7%), $\nu_{max.}$ (Nujol) 3268 (NH), 1678 (CO of 4-substituent), 1663s (ring CO), 1636s, 1603w, 1577s, 1548, and 1506s cm^{-1}, τ(Me_2SO) 6·22 (s, NMe), 2·5—1·5 (m, 9 × aryl H), and −0·80br (s, 4-NH).

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[26] A. Kirrmann, *Compt. rend.*, 1943, **217**, 148.