

Intermediates in the Ing-Manske reaction

O. M. Sinead Curley, Joan E. McCormick, R. Stanley McElhinney,
and T. Brian H. McMurry*

University Chemical Laboratory, Trinity College, Dublin 2, Ireland

E-mail: tmcmurry@tcd.ie

Dedicated to Professor Tony McKervey on his 65th birthday
(received 12 Feb 03; accepted 08 May 03; published on the web 17 May 03)

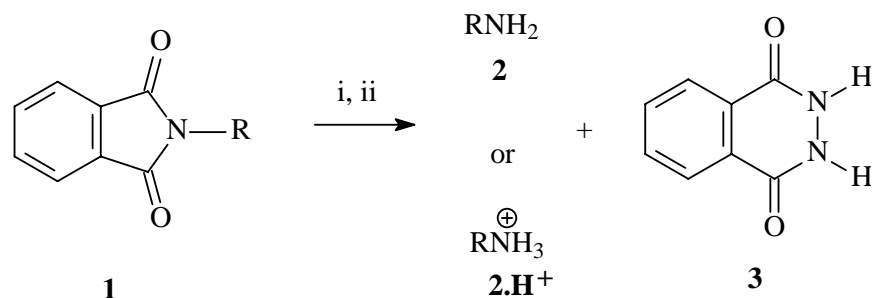
Abstract

Suggestions in the literature for the structures of the isolated intermediates formed in the Ing-Manske reaction under a variety of conditions are either confirmed or revised. The *N*-alkylphthalimide reacts with hydrazine at room temperature or under to afford the 2-(*N*-aminocarbamoyl)-*N*-alkylbenzamide. At higher temperatures, this cyclises to give the amine salt of phthalohydrazide. The amine can be isolated from either intermediate by acid, or from the salt with base.

Keywords: Ing-Manske reaction, phthalimides, hydrazinolysis

Introduction

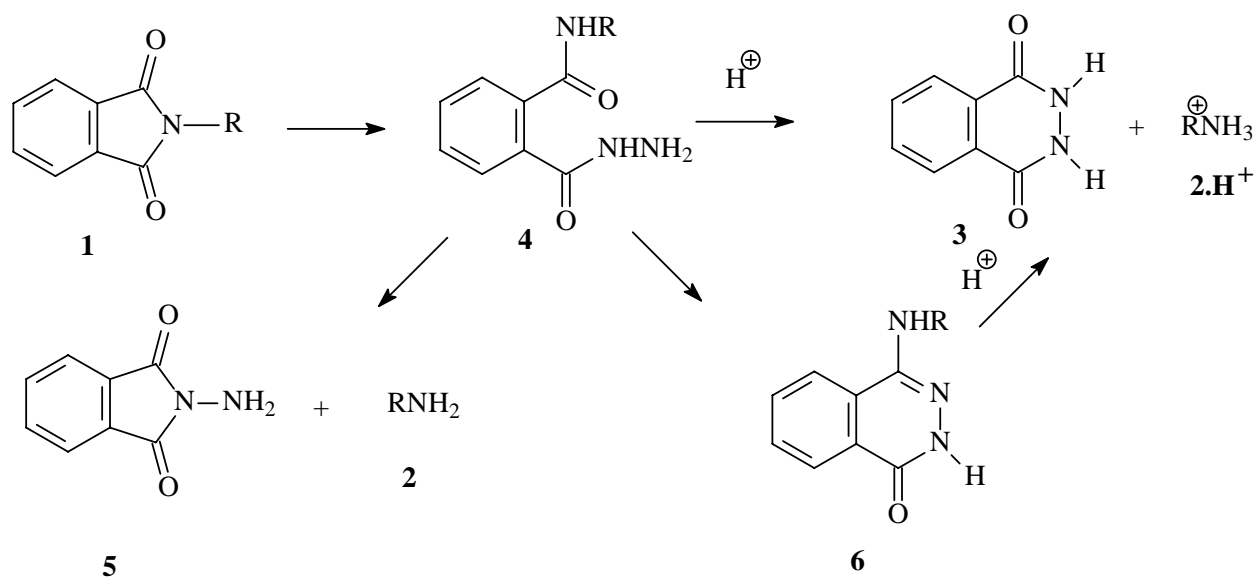
The Gabriel synthesis of primary amines¹ was greatly simplified when Ing and Manske² reported that a preparative method involving treatment of *N*-alkylphthalimides **1** with hydrazine followed by acid afforded the corresponding primary amine **2** as its salt **2.H⁺** and phthalohydrazide (2,3-dihydro-1,4-phthalazinedione) **3**. Radenhausen³ was the first person to report (incidentally) the hydrazinolysis of an *N*-substituted phthalimide, though he did not identify all the products. Over the years, many experimental procedures have been recorded for different *N*-alkylphthalimide substrates, with variations in the molar proportions of hydrazine, solvent, reaction temperature and time, and conditions of acid/alkaline work-up. Workers frequently used the method without discussing the reaction details. Intermediates have been postulated, sometimes isolated, and had different structures assigned to them. We shall summarise the significant developments, and outline our own findings.



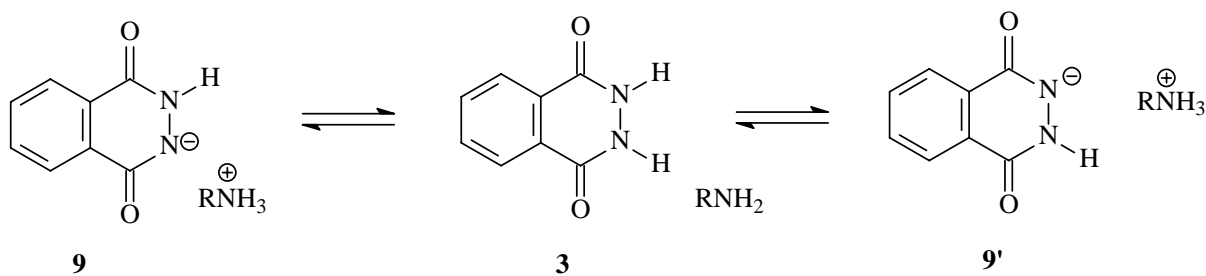
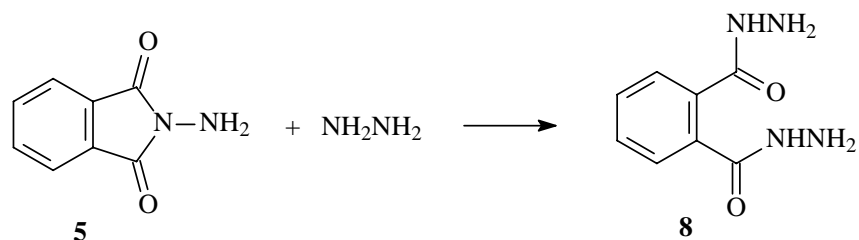
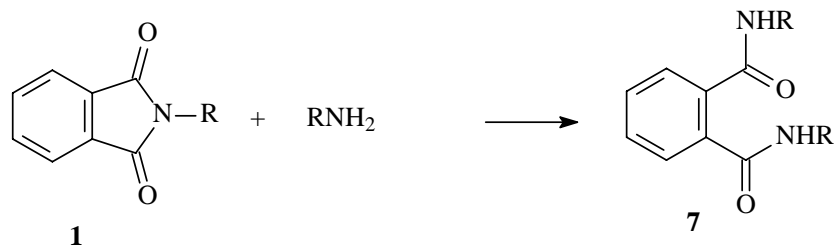
a, R = PhOCH₂CHOHCH₂ b, R = PhCH₂

Reagents: (i) NH₂NH₂, (ii) Heat or H[⊕]

The reaction pathway can be imagined as follows. Attack of hydrazine on the phthalimide would give the amidohydrazide **4** which could then ring close to give either phthalohydrazide **3** plus amine **2**, *N*-aminophthalimide **5** plus amine **2**, or the phthalazinone **6**. This last compound, and also the amidohydrazide **4**, could be envisaged as unstable in acid, breaking down to phthalohydrazide **3** plus the amine salt. Three further complications involve the attack of the liberated amine **2** on unreacted phthalimide **1** to afford the diamide **7**, the attack of hydrazine on the *N*-aminophthalimide **5** to afford the dihydrazide **8**, and thirdly the acidity of phthalohydrazide **3** so that relatively stable salts **9** are formed of it with the amine.



a, R = PhOCH₂CHOHCH₂ b, R = PhCH₂



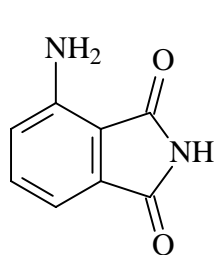
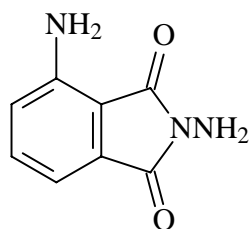
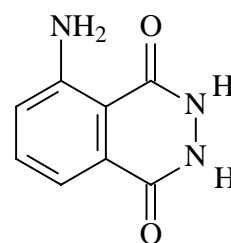
a, R = PhOCH₂CHOHCH₂ b, R = PhCH₂

In their original investigation in 1926, Ing and Manske² chose (without evidence) a phthalazinone **6** as the intermediate in the reaction, and stated that it was converted to the products, **2.H⁺** and **3** on treatment with acid. Later (1959), Roth⁴ in another system also adopted this type of structure, and produced analytical figures to support it, though his argument is weakened as calculations show that he had obtained greater than 100% yield. In 1993, the same type of intermediate was recorded uncritically by Toda *et al.*⁵ They had overlooked the work of Flitsch and Peters⁶ who already (1967) had synthesised compounds of the structure **6** by independent means, and shown that they were stable to acid under the conditions that converted the Ing-Manske intermediate to the amine salt.

Some years before, both Mosher⁷ and Barber and Wragg⁸ (1946) as part of a considerable effort to develop new anti-malarials examined a phthalimidopropylaminoquinoline. Reacting it with hydrazine in refluxing ethanol, the latter postulated the intermediates as **4** and the amine salt **9** of phthalohydrazide **3** but did not isolate them. However they did isolate and characterise the corresponding salt derived from *N*-benzylphthalimide. This has a different molecular formula from an intermediate of type **6**, and would show different analytical figures. The role of acid would merely release the phthalohydrazide from its salt. Both sets of authors realised the

possibility of alkali workup. Barber and Wragg also found that when they used 0.5 mol of hydrazine to 1 mol of phthalimide, appreciable quantities of the diamide were formed. Even with a 1:1 molar ratio, some diamide was among the products. Gibson and Bradshaw⁹ in 1968 in a review of the Gabriel synthesis favoured the amine salt of phthalohydrazide structure for the intermediate.

Petrow and Stephenson¹⁰ earlier (1953) had used the hydrazinolysis reaction (boiling ethanol) to prepare a series of hydroxyamines, and preferred the ring-opened amidohydrazide **4** as the intermediate. They showed that their compound was converted to the primary amine salt and phthalohydrazide on treatment with acid. The same type of structure was favoured by Connors and Ross (1960)¹¹ (using ethanol as solvent at room temperature). **4** and **9** have, of course, the same molecular formula and would provide the same analytical figures.

**10****11****12**

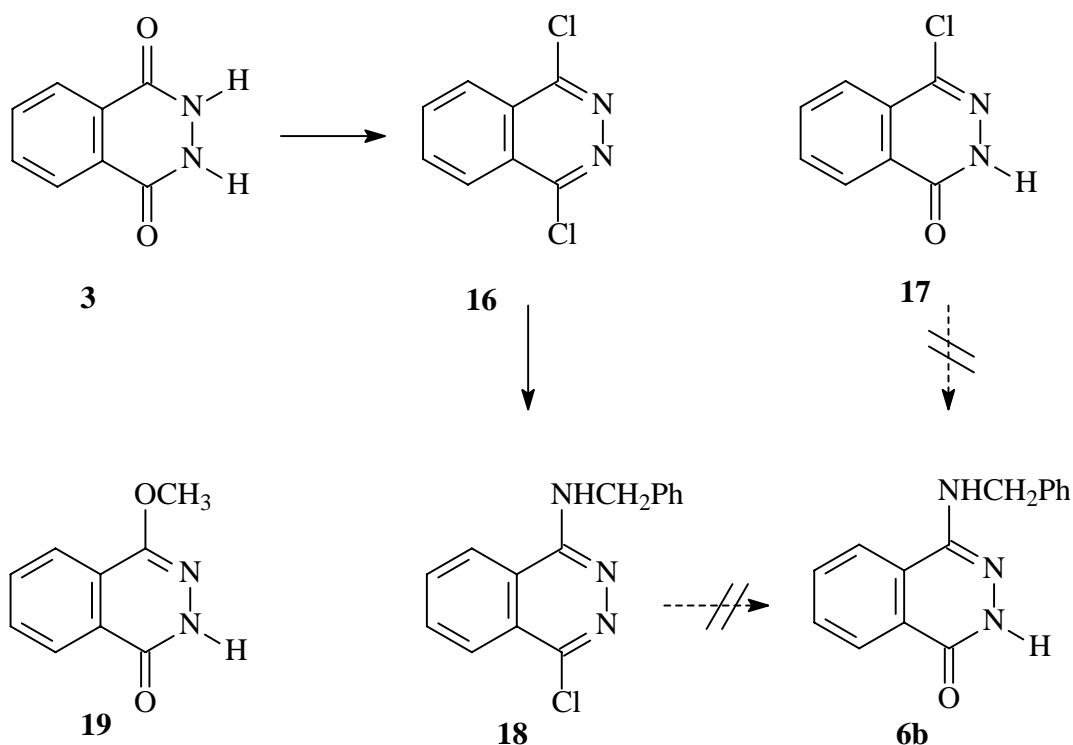
Niyaz Khan¹² in a kinetic study implicates the existence of **4**, **5**, **8** and **3**. Drew and Pearman¹³ had found that ring opening and subsequent closure of 4-aminophthalimide **10** using one equivalent of hydrazine gave *N*,4-diaminophthalimide **11**, while with two equivalents of hydrazine, it gave the six-membered aminophthalazinedione **12**. Other substituted phthalimides gave the same result (4-chloro, 4,7-dichloro, 4,5,6,7-tetrachloro) while yet others (4-hydroxy, 5-amino, and 5,6-dichloro) afforded only the phthalohydrazide under all conditions.

It seemed worthwhile to sort out the conflicting results, and to determine the structures of the intermediates.

Results and Discussion

We decided to repeat experiments using the substituted phthalimide **1a** reported by Roth,⁴ which was very close in structure to those synthesised by Petrow and Stephenson¹⁰ – these carried *p*-chloro- and *p*-nitro-substituents on the phenyl ring. Using the conditions described by Roth (7.5 equivalents of hydrazine in MeOH, reflux for 40 min) and also those of Petrow and Stephenson (1 equivalent of hydrazine added to refluxing ethanol, followed by cooling), we obtained the same product. This proved to be the amine salt of phthalohydrazide **9a**.

In order to confirm that compounds of type **6** were not intermediates, we synthesised **6b** using a method employed by Flitsch and Peters.⁶ Reaction of 2-cyanobenzamide¹⁴ with sodium hydroxide solution for a short period afforded the monoimino analogue **14** of phthalimide,¹⁴ which in turn reacted with benzylamine hydrochloride⁶ to give 3-benzyliminoisoindolin-1-one **15**. This with hydrazine afforded **6b** and 4-aminophthalazin-1-one **6c**.⁶ In another attempt to synthesise **6b** from **3**, we reacted the latter with phosphorus pentachloride, which gave a mixture of 1,4-dichlorophthalazine **16** and 4-chlorophthalazin-1-one **17**.¹⁵ The former compound reacted with benzylamine to afford 1-benzylamino-4-chlorophthalazine **18**,⁶ but we were unable to convert this into **6b**. Flitsch and Peters⁶ had been successful in a number of related reactions to make compounds of the general formula **6**, but did not investigate the benzyl derivative. The monochloro compound **16** failed to react with benzylamine. We also made 4-methoxyphthalazin-1-one **19**,¹⁶ in the hope that we could replace the methoxy-group using benzylamine. We were unsuccessful.



These results clarify which compounds earlier workers had isolated as intermediates during the hydrazinolysis reaction; this proceeds from **1** to give the amidohydrazide **4** that then cyclises to afford the amine salt **9**. It is clear that the phthalazinone **6** is not an intermediate. Furthermore, no *N*-aminophthalimide **5** was detected, even in the crude reaction mixtures as determined by NMR, though the kinetic scheme¹² implies that it might not be found. Substituted analogues of this compound are implicated in the reactions of the corresponding phthalimides.¹³

Structural assignments

We measured the IR, ^1H - and ^{13}C -NMR spectra of the various compounds described above. For comparison purposes, we also examined the spectra of phthalic acid and phthalic anhydride. In the IR spectra, phthalic anhydride shows peaks at 1852 and 1790 cm^{-1} , *N*-benzylphthalimide at 1777 and 1711 cm^{-1} , the benzylammonium salt of phthalohydrazide **9b** at 1667 cm^{-1} , the amidohydrazide **4b** at 1648 cm^{-1} , 3-benzyliminoisoindolin-1-one **15** at 1679 cm^{-1} , and 4-benzylaminophthalazin-1-one **6b** at 1648 and 1595 cm^{-1} .

The principal features of the ^1H -NMR spectra that enable us to distinguish the various compounds are the methylene protons and the aromatic, excluding the phenyl protons. Where there is symmetry, the aromatic protons appear as an AA'BB' signal, and where there is not, as a more complex pattern. In the former category are *N*-benzylphthalimide **1b** and the amine salt **9b**, and in the latter, **5b**, **15** and **4b**. The amine salt **9b** is in the former category because of rapid proton exchange between the two hydrogens on the nitrogens (cf. **9** and **9'**). All the methylene signals are singlets but at distinctive positions. Exceptionally that of **4b** is a doublet as it couples to the neighbouring NH. The NH signals themselves are also distinctive for the individual compounds.

Similar symmetry considerations also apply to the ^{13}C -NMR spectra and provide means of distinguishing between the different classes of compounds. The CO peak of the salt **9b** occurs downfield (δ_{C} 155.2) of those of the other compounds as expected from the deshielding effects of the anion.

Experimental Section

General Procedures. Melting points are uncorrected. The hydrazine hydrate solution used in some experiments refers to a 5M solution of 98% hydrazine hydrate in DMF. The ^1H - and ^{13}C -NMR spectra were measured on a Bruker MSL 300 spectrometer at 300 and 75 MHz respectively. d_6 -DMSO was used as solvent and as internal standard. Chemical shifts are measured in ppm from TMS and coupling constants in Hertz. IR spectra were measured in cm^{-1} using a Perkin Elmer 883 IR or a Paragon 1000 FT-IR instrument in Nujol mulls.

***N*-(2-Hydroxy-3-phenoxypropyl)phthalimide¹⁰ (1a).** Pyridine (0.1 ml) was added to a mixture of 1,2-epoxy-3-phenoxypropane (4.0 ml, 30 mmol) and phthalimide (4.41 g, 30 mmol) in ethanol (30 ml). The reaction mixture was refluxed for 1h. A further quantity of ethanol (15 ml) was added and the mixture heated for a further 1.5 h. On cooling, the product was collected. A further crop was obtained on partial evaporation of the filtrate. The combined crops were recrystallized from ethyl acetate - hexane to give the phthalimide **1a** (7.57 g, 85%), mp. 108°C (lit.⁴ 110°C). δ_{H} 3.72 (2H, m, 3'-CH₂), 3.92 (2H, d, *J* 5.3, 1'-CH₂-N), 4.16 (1H, m, 2'-CHOH), 5.36 (1H, d, OH), 6.85-6.94 (3H, m), 7.26 (2H, t, *J* 8.1) and 7.82-7.89 (4H, m, all ArH). δ_{C} 41.3, (1'-CH₂), 65.9 (2'-CH₂), 70.2 (3'-CH₂), 114.4 (*o*-PhC), 120.6 (*p*-PhC), 122.9 (4-

and 7-ArC), 129.4 (*m*-PhC), 131.8 (3a- and 7a-ArC) 134.2 (5- and 6-ArC), 158.4 (*ipso*-PhC) and 168.0 (CO x 2).

Hydrazinolysis of *N*-(2-hydroxy-3-phenoxypropyl)phthalimide 1a (a) Roth's conditions.⁴

Hydrazine hydrate 25% (15 ml, 75 mmol) was added to the *N*-substituted phthalimide **1a** (2.97g, 10 mmol) in methanol and the mixture refluxed for 40 min. After cooling, the product was collected and recrystallized from ethanol to give the 2-hydroxy-3-phenoxypropylammonium salt **9a** of 2,3-dihydrophthalazine-1,4-dione (2.20 g, 67%), m.p.176°C (lit.⁹ 177°C). Found: C, 61.9; H, 5.85, N, 12.7. Calc. for C₁₇H₁₉N₃O₄ C, 62.0; H, 5.8; N, 12.8%). ν_{\max} 3600-3000, 1675, 1580, and 1450. δ_{H} 2.70 (2H, br m, CH₂-NH₃⁺), 3.79-3.92, (m, 2-CH OH and 3-CH₂), 6.37 (5H, br s, NH₃⁺, NH and OH), 6.92 (2H, m, *o*-Ph), 7.27 (3H, m, *m*- and *p*-Ph), 7.84 (2H, m, 6- and 7-ArH), and 8.05 (2H, m, 5- and 8-ArH). δ_{C} 43.6 (1-CH₂), 68.5 (2-CH), 69.9 (3-CH₂), 114.4 (*o*-PhC), 120.5 (*p*-PhC), 125.3 (5- and 7-ArC), 128.4 (4a- and 8a-ArC), 129.4 (*m*-PhC), 131.8 (6- and 7-ArC), 156.1 (CO) and 158.5 (*ipso*-PhC).

(b). Petrow and Stephenson's conditions.¹⁰ Hydrazine hydrate 50% (1 ml, 10 mmol) was added to a solution of the phthalimide (2.97g, 10 mmol) in boiling ethanol (22 ml). On cooling, the precipitate was collected, and recrystallized from ethanol to give the same product (2.94g, 89%),m.p. and mixed m.p.,176°C). The IR and NMR spectra were identical to those recorded above.

Hydrazinolysis of *N*-benzylphthalimide 1b. (a) Roth's conditions.⁴ Hydrazine hydrate 25% (15 ml, 7.5 mmol) was added to the phthalimide **1b** (2.37 g, 10mmol) in methanol (12 ml), and the mixture refluxed for 40 min. The precipitate which formed on cooling was collected as the benzylammonium salt **9b** of 2,3-dihydrophthalazine-1,4-dione (1.91 g, 71%) m.p. >300°C (lit.⁸ 342-346°C). ν_{\max} 3200 –2400, 1667, and 1580. δ_{H} 3.78 (2H, s, CH₂), 5.92 (4H, br s, NH and NH₃⁺), 7.20 – 7.38 (5H, m, PhH), 7.85 (2H, dd, *J* 3.3 and 6.0, 6- and 7-ArH), and 8.08 (2H, dd, *J* 3.3 and 6.0, 5- and 8-ArH); δ_{C} 44.8 (CH₂), 125.2 (5- and 8-ArC), 126.5 (4-PhC), 127.3 (3- and 5-PhC), 127.7 (1-PhC and 4a- and 8a-ArC), 128.1 (2- and 6-PhC), 132.2 (6- and 7-ArC), and 155.2 (CO).

(b) Petrow and Stephenson's conditions.¹⁰ Hydrazine hydrate 25% (1 ml, 10 mmol) was added to the phthalimide **1b** (2.37 g, 10 mmol) in refluxing ethanol (12 ml). On cooling, the solid was collected to give the salt **9b** (2.31 g, 86%). It was identical to the product obtained from the reaction carried out under Roth's conditions. (c) At -15°C. Hydrazine hydrate solution (0.22 ml, 1.1 mmol) was added to *N*-benzylphthalimide (237 mg, 1 mmol) in DMF (1.80 ml) at -15°C and set aside for 14 h. The precipitate formed was collected and the filtrate concentrated under reduced pressure to afford a further crop of 2-(*N*-aminocarbamoyl)-*N*-benzylbenzamide **4b** (122 mg, 76%) m.p. 128-130°C (shrinkage), decomposition 300°C. (Found: C, 66.6; H, 5.55; N, 15.6. C₁₅H₁₅N₃O₂ requires C, 66.9; H, 5.6; N, 15.6%).

δ_{H} 4.36 (2H, d, *J* 2.8, NH-NH₂), 4.46 (2H, d, *J* 5.6, NH-CH₂), 7.21–7.53 (9H, m, Ar and PhH), 8.76 (1H, t, NH-CH₂) and 9.44 (1H, br s, NH-NH₂). δ_{C} 42.4 (CH₂), 126.6 (*p*-PhC), 127.2 (*m*-PhC), 127.7 and 127.8 (3- and 6-ArC), 128.2 (*o*-PhC), 129.3 and 129.4 (4- and 5-ArC), 134.9 and 136.4 (1- and 2-ArC), 139.5 (1-PhC), 167.7 and 168.0 (CO).

(d) At 20°C. Hydrazine hydrate solution (0.22 ml, 1.10 mmol) was added to *N*-benzylphthalimide (237 mg, 1 mmol) in DMF (1.80 ml) and the mixture stirred at 20°C for 3 h. Removal of the DMF under reduced pressure (0.2 mmHg) gave a solid (278 mg) which was shown to contain starting phthalimide and 2-(*N*-aminocarbamoyl)-*N*-benzylbenzamide **4b** in the ratio 2:7. Recrystallization gave pure amidohydrazide **4b**.

(e) At 50°C. Hydrazine hydrate solution (0.22 ml, 1.1 mmol) was added to *N*-benzylphthalimide (237 mg, 1 mmol) in DMF (1.8 ml) and the solution heated to 50°C for 5 h. The solvent was removed under reduced pressure to give a mixture (1:2) (215 mg) of amidohydrazide **4b** and benzylammonium salt **9b**. Recrystallisation gave the salt. The products were identified by comparison of their spectra with those of the compounds described above.

The benzylammonium salt 9b of 2,3-dihydro-phthalazine-1,4-dione. Benzylamine (1.07 ml, 10 mmol) was added to 2,3-dihydrophthalazine-1,4-dione (1.62 g, 10 mmol) in DMF (10 ml) and the solution heated at 50°C for 30 min. Removal of the solvent afforded the salt (2.47 g, 92%), which was identified by spectral comparison with the sample described above.

Acid treatment of the benzylammonium salt (9b). The above salt (279 mg, 1 mmol), ethanol (2.5 ml) and concentrated hydrochloric acid (2.5 ml) were heated at 50°C for 10 min, and cooled. The product was 2,3-dihydrophthalazine-1,4-dione **3** (131 mg, 81%). m.p. > 300°C. The sample showed IR and NMR spectra identical to those of an authentic sample.

Acid treatment of 2-(*N*-aminocarbamoyl)-*N*-benzylhydrazide (4b). The amidohydrazide **4b** (269 mg, 1 mmol), ethanol (2.5 ml) and concentrated hydrochloric acid (2.5 ml) were heated at 50°C for 10 min. The precipitate (105 mg, 65%) was collected, to give phthalhydrazide **3**, identical in all respects to an authentic sample.

2-(*N*-Benzylideneaminocarbamoyl)-*N*-benzylbenzamide (13). Benzaldehyde (0.056 ml, 0.55 mmol) and acetic acid (0.1 ml) were added to a slurry of the amidohydrazide **4b** (134 mg, 0.5 mmol) in DMF (2 ml) at room temperature, and the mixture stirred for 3 h. The solvent was removed *in vacuo*, and the residual syrup triturated with water (4 ml). The solid was collected at the pump to give the benzylidene derivative (160 mg, 90%), m.p. 135- 136°C, λ_{\max} 293 nm. A sample was recrystallized from acetonitrile, (Found: C, 73.72; H, 5.3; N, 11.8. C₂₂H₁₉N₃O₂ requires C, 73.93; H, 5.35; N, 11.75%).

3-Benzylaminoisindolin-1-one (15). Benzylamine hydrochloride (240 mg, 1.6 mmol) was added to 3-iminoisindolin-1-one **14**⁶ (146 mg, 1 mmol) in ethanol (8 ml) and the mixture refluxed for 1h. Removal of the solvent gave a solid **15** (150 mg, 64%). 155°C, (Found: C, 74.6; H, 5.3; N, 11.9. C₁₅H₁₂N₂O requires C, 74.6; H, 5.1; N, 11.9%); δ_{H} 4.71 (2H, s, CH₂), 7.26 – 7.41 (5H, m, Ph-H), 7.62 – 7.87 (4H, m, Ar-H), and 11.10 (1H, br s, NH); δ_{C} 53.7 (CH₂), 121.6 and 122.7 (4- and 5-ArC), 126.6 (*p*-PhC), 127.8 (*m*-PhC), 128.3 (*o*-PhC), 131.3 (3a-ArC), 131.7 and 133.4 (5- and 6-ArC), 136.5 and 139.9 (7a-ArC and *ipso*-PhC), 149.6 (C=N) and 169.0 (C=O); ν_{\max} 3269, 3180, 1679, and 1616.

4-Benzylaminophthalazin-1-one 6b and 4-aminophthalazin-1-one (6c). Hydrazine hydrate 100% (0.2 ml, 1 mmol) was added to 3-benzyliminoisindolin-1-one (236 mg, 1 mmol) in ethanol. The solution was refluxed for 6 h, and the solvent removed. The crude mixture was

trituated with dilute hydrochloric acid (3 x 10 ml), the insoluble portion collected, and crystallized to give 4-benzylaminophthalazin-1-one **6b** (12 mg) m.p. 168°C, ν_{\max} 3360, 3191, 1648, and 1595. δ_{H} 3.94 (1H, br s, NHCH_2), 4.50 (2H, s, NHCH_2), 7.17-7.37 (5H, m, PhH), 7.80-7.93 (2H, m, 6- and 7-ArH), 8.23 (8.23, d, J 7.8, 5- and 8-ArH), and 11.56 (1H, br s, 2-NH); δ_{C} 44.4 (CH_2), 123.1 and 126.3 (6- and 7-ArC), 124.9 (4a-ArC), 126.4 (4-PhC), 127.1 (3- and 5-PhC), 128.1 (2- and 6-PhC), 131.2 and 132.9 (5- and 8-ArC), 140.1 and 144.5 (8a-ArC and 1-PhC), 157.8 (4-ArC), and 174 (CO).

The acid-soluble fraction was neutralised to give 4-aminophthalazin-1-one, **6c** (65 mg, 40%), m.p. 270°C (lit.⁶ m.p. 266°C). ν_{\max} 3259, 3176, 1656, and 1599. δ_{C} 5.97 (2H, s, NH_2), 7.77-7.92 (2H, m, 5- and 6-ArH), 8.06 (1H, d, J 7.9, 6- or 7-ArH), 8.21 (1H, d, J 7.9, 7- or 6-ArH), and 11.51 (1H, s, NH); δ_{C} 123.9 (6- or 7-ArC), 124.9 (4a-ArC), 126.1 (7- or 6-ArC), 128.3 (8aC), 131.2 and 132.9 (5- and 8-ArC), 146.1 (4-ArC), and 158.1 (CO).

References

1. Gabriel, S. *Chem. Ber.* **1887**, *20*, 2224.
2. Ing, H.R.; Manske, R.H.F. *J. Chem. Soc.* **1926**, 2349.
3. Radenhausen, R. *J. Prakt. Chem.* **1895**, *52*, 446.
4. Roth, H.J. *Arch. Pharm.* **1959**, *194*, 292.
5. Toda, F.; Soda, S.; Goldberg, I. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2357.
6. (a) Flitsch, W.; Peters, H. *Angew. Chem., Int. Ed.* **1967**, *6*, 173. (b) *Chem. Ber.* **1969**, *102*, 1304.
7. Mosher, H.S. *J. Amer. Chem. Soc.* **1946**, *68*, 1565.
8. Barber, H.J.; Wragg, W.R. *Nature* **1946**, *158*, 514; *J. Chem. Soc.* **1947**, 1332.
9. Gibson, M.S.; Bradshaw, R.W. *Angew. Chem., Int. Ed.* **1968**, *7*, 928.
10. Petrow, V.; Stephenson, O. *J. Pharm. Pharmacol.* **1953**, *5*, 359.
11. Connors, T.A.; Ross, W.C.J. *J. Chem. Soc.* **1960**, 2118.
12. Niyaz Khan, M. *J. Org. Chem.* **1995**, *60*, 4536; **1996**, *61*, 8063.
13. Drew H.D.K.; Pearman, F.H. *J. Chem. Soc.* **1937**, 26.
14. Braun, A.; Tcherniac, J. *Chem. Ber.* **1907**, *40*, 2709.
15. Drew, H.D.K.; Hatt, H.H. *J. Chem. Soc.* **1937**, 16.
16. Rowe, F.M.; Peters, A.T. *J. Chem. Soc.* **1933**, 1331.