Phthaloylation of Amino-azoles and Amino-azines

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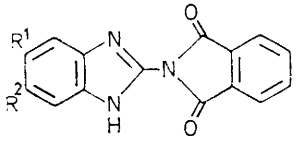
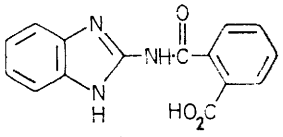
The phthaloylation of 2-aminobenzimidazoles, 3-amino-1,2,4-triazole, 3-amino-5-methylpyrazole, 2-aminopyridine, and 2-aminopyrimidine with phthaloyl chloride and with phthalic anhydride is described: in most series only phthalimide derivatives are formed, but some diazepines have been isolated.

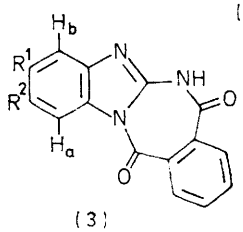
THE literature on 2-phthalimidobenzimidazole (1; $R^1 = R^2 = H$) is conflicting.[1,2] Grier [1] synthesised a compound, m.p. 266—268°, described as (1; $R^1 = R^2 = H$) from 2-aminobenzimidazole and phthaloyl chloride. Augustin and Kuppe [2] claimed that compound (1; $R^1 = R^2 = H$), obtained by dehydration of the acid (2), had m.p. 300°. Phthaloylation of 2-aminobenzimidazole could result in either (1; $R^1 = R^2 = H$) or the benzimidazobenzodiazepine (3; $R^1 = R^2 = H$), and we therefore reinvestigated this reaction.



(1)



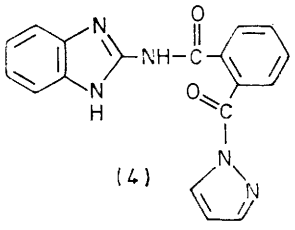
(2)



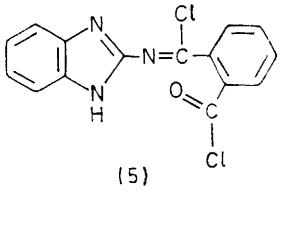
(3)

In our hands, 2-aminobenzimidazole with phthaloyl chloride in anhydrous pyridine or with phthalic anhydride at 200 °C yielded the same product, m.p. *ca.* 240°, with analytical figures corresponding to either (1; $R^1 = R^2 = H$) or (3; $R^1 = R^2 = H$) and showing ν(NH) and ν(C=O) absorption in the i.r. spectrum. The n.m.r. spectrum clearly excluded (1; $R^1 = R^2 = H$), which because of rapid NH exchange should show two symmetrical AA'BB' patterns for the eight CH protons. Instead, there occur a 1 H multiplet at τ 1.68—1.82 and a 7 H multiplet at τ 2.12—2.82. The n.m.r. spectrum is good evidence for the diazepine structure (3; $R^1 = R^2 = H$) since H_a should be considerably deshielded, relative to the remaining aromatic protons, by the γ-carbonyl group.

The benzimidazodiazepine (3; $R^1 = R^2 = H$) is stable at room temperature but can easily be converted into the thermodynamically more stable phthalimide (1; $R^1 = R^2 = H$). Thus treatment of (3; $R^1 = R^2 = H$) with a catalytic amount of pyrazole in acetonitrile gives (1; $R^1 = R^2 = H$) in 50% yield; since heating the benzimidazobenzodiazepine in the same solvent in the absence of base has no effect, the former reaction probably occurs by a ring cleavage to give an acylpyrazole (4) followed by ring closure to the more stable phthalimide. Suspension of (3; $R^1 = R^2 = H$) in boiling phosphoryl chloride gives the hydrochloride of (1; $R^1 = R^2 = H$), rather than the expected imino-chloride (5). Finally, sublimation of (3; $R^1 = R^2 = H$) also gives (1; $R^1 = R^2 = H$), in good yield; this simple thermal interconversion explains the indistinct m.p. of (3; $R^1 = R^2 = H$) (isomerisation around 240 °C) and the identical mass spectra of (1; $R^1 = R^2 = H$) and (3; $R^1 = R^2 = H$).



(4)



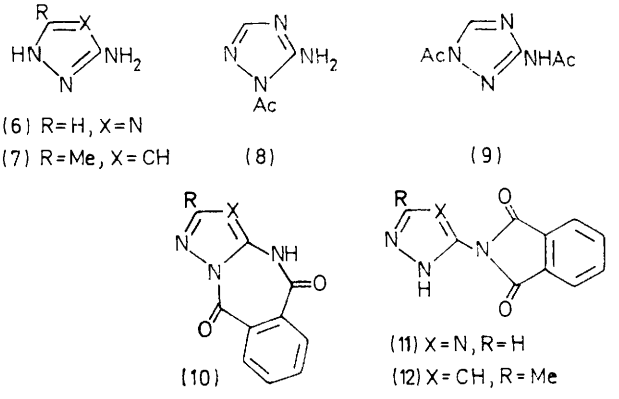
(5)

The formation of benzimidazobenzodiazepines by phthaloylation of aminobenzimidazoles was confirmed by treatment of 2-amino-5,6-dimethylbenzimidazole with phthaloyl chloride. Compound (3; $R^1 = R^2 = Me$) was obtained in good yield, and the n.m.r. spectrum again illustrated the deshielding effect of the carbonyl group with the H_a signal as a singlet at τ 1.68 and that of H_b as a singlet at τ 2.46. Reaction of 2-amino-5,6-dimethylbenzimidazole with phthalic anhydride at 230 °C gave the corresponding phthalimide (1; $R^1 = R^2 = Me$). Thermal interconversion did not occur as readily as in the demethyl series; sublimation of (3; $R^1 = R^2 = Me$) resulted in a mixture of (1; $R^1 = R^2 = Me$) and (3; $R^1 = R^2 = Me$).

Acetylation of 3-amino-1,2,4-triazole (6) is known to take place initially on N(2) [3,4] to give 1-acetyl-5-amino-1,2,4-triazole (8) (shown by n.m.r.[5]). Further acetylation yields 1-acetyl-3-acetylamino-1,2,4-triazole (9) in a reaction involving migration of the acetyl group from N(1) of compound (8) to N(2).[5] 5-Aminopyrazoles similarly undergo acylation at both the amino-group and a ring nitrogen, affording *N*(1),*N*(5)-derivatives when treated with an excess of acetic anhydride [6] or benzoyl

[1] N. Grier, Ger. Offen. 1,945,452/1970 (*Chem. Abs.*, 1970, **72**, 132,730*j*).
[2] M. Augustin and K. R. Kuppe, *Z. Chem.*, 1974, **14**, 306.
[3] H. A. Staab and G. Seel, *Chem. Ber.*, 1959, **92**, 1302.
[4] B. G. Van den Bos, *Rec. Trav. chim.*, 1960, **79**, 836.
[5] M. D. Coburn, E. D. Loughran, and L. C. Smith, *J. Heterocyclic Chem.*, 1970, **7**, 1149.
[6] S. Checchi, P. Papini, and M. Ridi, *Gazzetta*, 1955, **85**, 1160.

chloride,[7] but no evidence of acyl group migration was reported.[6,7] The phthaloylation of 3-amino-1,2,4-triazole (6) and 5-amino-3-methylpyrazole (7) was investigated to establish whether initial formation of a benzodiazepine (10) occurred. However, both phthaloyl chloride and phthalic anhydride gave the corresponding phthalimide [(11) or (12)] as shown by the symmetry of the aromatic absorption in their n.m.r. spectra expected for an A_2B_2 pattern, and comparison of their i.r. and mass spectra with those of the benzimidazole derivatives (1). The stability of phthalimides (11) and (12) was confirmed by their recovery unchanged after prolonged heating above their m.p.s. In view of the behaviour of 2-aminobenzimidazole, benzodiazepines of type (10) may well be formed initially, but if so they isomerise to the thermodynamically more stable phthalimides [(11) or (12)] under the reaction conditions.



(6) R=H, X=N
(7) R=Me, X=CH

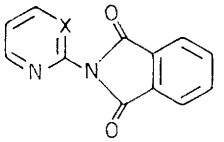
(8)

(9)

(10)

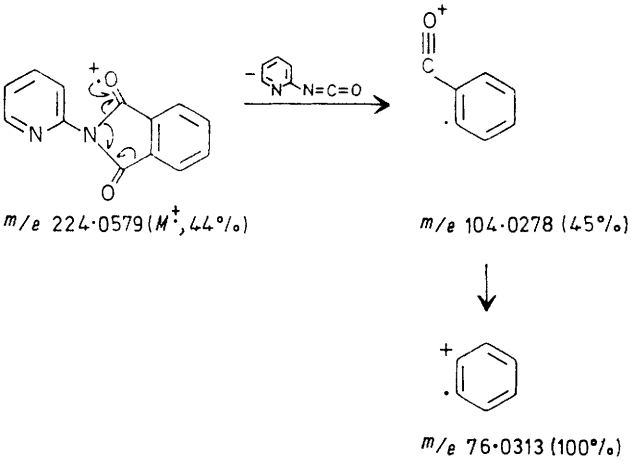
(11) X=N, R=H
(12) X=CH, R=Me

Phthaloylation of 2-aminopyridine and 2-aminopyrimidine also resulted exclusively in phthalimide derivatives [(13) and (14)], with characteristic symmetrical aromatic absorption in their n.m.r. spectra. *N*(2),*N*(2)-bisacylation of these compounds at the amino-group has been reported.[8-10]

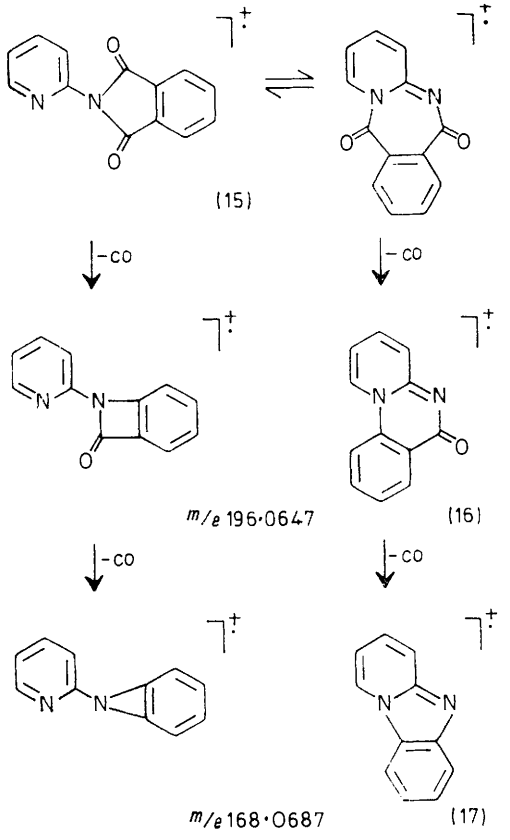


(13) X=CH
(14) X=N

Mass Spectra of the Phthalimides.—*N*-Methyl and *N*-phenyl-phthalimides fragment by loss of carbon dioxide.[11,12] For other *N*-alkyl-phthalimides, β-cleavage is important.[13] All the phthalimides described in this paper have high-intensity peaks at *m/e* 104 and 76 due to the fragmentation shown in Scheme 1. Loss of CO_2 (44 a.m.u.) does occur but is only significant with the pyridine (13) and the pyrimidine (14). A more important fragmentation involves loss of 2 molecules of carbon



SCHEME 1

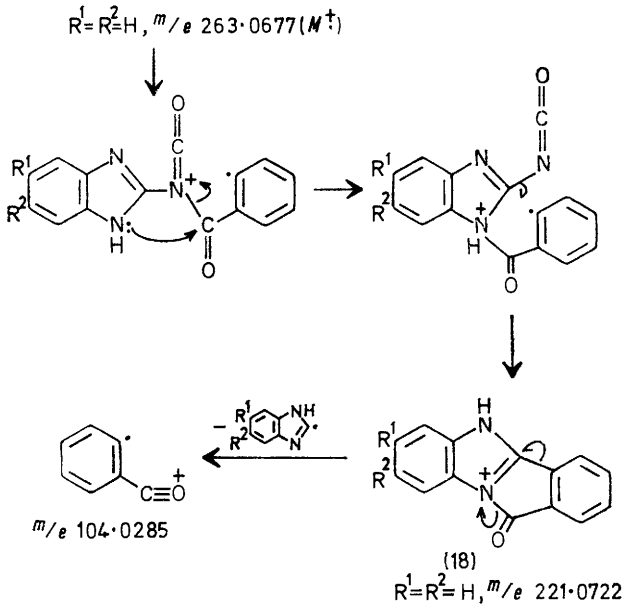


SCHEME 2

monoxide. This preference for loss of CO rather than CO_2 suggests that the equilibrium shown in (15) occurs

[7] S. Checchi, M. Ridi, and P. Papini, *Gazzetta*, 1955, **85**, 1558.
[8] L. Schmid and H. Mann, *Monatsh.*, 1954, **85**, 864.
[9] P. A. Lyon and C. B. Reese, *J.C.S. Perkin I*, 1974, 2645.
[10] E. Dyer and H. Richmond, *J. Medicin. Chem.*, 1965, **8**, 195.
[11] R. A. W. Johnstone, B. J. Millard, and D. S. Millington, *Chem. Comm.*, 1966, 600.
[12] J. L. Cotter and R. A. Dine-Hart, *Chem. Comm.*, 1966, 809.
[13] J. Sharvit and A. Mandelbaum, *Israel. J. Chem.*, 1967, **5**, 33.

and the benzodiazepine governs the fragmentation as in Scheme 2. Elimination of CO by the proposed pathway from the benzodiazepine passes through energetically favoured pyridoquinazoline and benzimidazopyridine structures, (16) and (17) respectively. Similar structures can be drawn for each of the phthalimides.



SCHEME 3

The stability derived from the presence of aromatic rings in an ion is reflected in a fragmentation peculiar to the benzimidazolylphthalimides only. A loss of 42 a.m.u. occurs in both cases and is due to N=C=O (41.9955 a.m.u.) being eliminated, probably as shown in Scheme 3.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded with a Varian HA-100 spectrometer (Me_4Si as internal standard), i.r. spectra with a Perkin-Elmer 257 spectrometer, and mass spectra with Hitachi–Perkin-Elmer and A.E.I. MS902 spectrometers.

6H-*Benzimidazo*[1,2-b][2,4]*benzodiazepine*-7,12-*dione*.—*Method* (*a*). Well mixed 2-aminobenzimidazole (0.5 g) and phthalic anhydride (0.55 g) were heated at 200 °C for 2 h. Extraction with boiling absolute EtOH (2 × 25 ml) then afforded the *benzodiazepine* (0.7 g, 66%), m.p. *ca.* 240° (isomerisation) (as needles from EtOH) (Found: C, 68.5; H, 3.7; N, 16.2. $C_{15}H_9N_3O_2$ requires C, 68.4; H, 3.4; N, 16.0%); $\nu_{max.}$ (Nujol) 3310 (NH), 1790, and 1720 (C=O) cm^{-1}; τ (CF_3·CO_2H) 1.68—1.82 (1 H, m) and 2.12—2.82 (7 H, m).

Method (*b*). 2-Aminobenzimidazole (5.8 g), phthaloyl chloride (10 g), and pyridine (60 ml; anhydrous) were heated under reflux for 1.5 h. After cooling, addition of water (70 ml) yielded the benzodiazepine (8.4 g, 65%), m.p. *ca.* 240° (isomerisation), as needles from ethanol.

2-*Phthalimidobenzimidazole* (1; $R^1 = R^2 = H$).—*Method* (*a*). The diazepine (3; $R^1 = R^2 = H$) (0.26 g), pyrazole (0.05 g), and acetonitrile (10 ml) were heated under reflux for 10 h. The *phthalimide* (0.15 g, 58%) crystallised as plates, m.p. 279—280° (Found: C, 68.0; H, 3.4; N, 16.1%; $M^{+\cdot}$, 263. $C_{15}H_9N_3O_2$ requires C, 68.4; H, 3.4; N, 16.0%; *M*, 263); $\nu_{max.}$ (Nujol) 3310 (NH), 1790, 1780, 1760, and 1725 (C=O) cm^{-1}; τ (CF_3·CO_2H) 1.82 (4 H, m) and 2.20 (4 H, m).

Method (*b*). The diazepine (3; $R^1 = R^2 = H$) (0.1 g) was sublimed at 250 °C and 0.01 mmHg to give the phthalimide (0.066 g, 66%), m.p. and mixed m.p. 279—280°.

Method (*c*). The diazepine (3; $R^1 = R^2 = H$) (0.2 g) and phosphoryl chloride (8 ml) were heated under reflux for 4 h. The *phthalimide hydrochloride* (0.2 g, 86%) separated from the cooled solution as needles, m.p. 224° (from methanol–ether) (Found: C, 60.3; H, 3.3; N, 13.6. $C_{15}H_{10}ClN_3O_2$ requires C, 60.1; H, 3.4; N. 14.1%); $\nu_{max.}$ (Nujol) 1805, 1755, and 1735 (C=O) cm^{-1}. The hydrochloride (0.2 g) was stirred with sodium carbonate (5 ml; saturated aqueous) for 0.75 h. The precipitate crystallised as plates from dimethylformamide–water to give the phthalimide (0.11 g, 55%), m.p. and mixed m.p. 279—280°.

5,6-*Dimethyl*-2-*phthalimidobenzimidazole* (1; $R^1 = R^2 =$ Me).—2-Amino-5,6-dimethylbenzimidazole (0.8 g) and phthalic anhydride (0.82 g) were heated at 230 °C for 4 h. The *product* crystallised from dimethyl sulphoxide as plates (0.34 g, 23%), m.p. 314° (decomp.) (Found: C, 68.2; H, 4.8; N, 13.7%; $M^{+\cdot}$, 291. $C_{17}H_{13}N_3O_2$,0.5H_2O requires C, 68.0; H, 4.7; N, 14.0%; *M*, 291); $\nu_{max.}$ (Nujol) 3 360 (NH), 1790, and 1725 (C=O) cm^{-1}; τ (CF_3·CO_2H) 1.80 (4 H, m), 2.34 (2 H, s), and 7.5 (6 H, s).

2,3-*Dimethyl*-6H-*benzimidazo*[1,2-b][2,4]*benzodiazepine*-7,12-*dione* (3; $R^1 = R^2 =$ Me).—2-Amino-5,6-dimethylbenzimidazole (1.61 g), phthaloyl chloride (2.03 g), and anhydrous pyridine (10 ml) were stirred for 0.5 h. Water (10 ml) was added and the precipitated *benzodiazepine* (1.71 g, 58%) crystallised from dimethylformamide as plates, m.p. 250—260° (isomerisation) (Found: C, 69.9; H, 4.6; N, 14.7. $C_{17}H_{13}N_3O_2$ requires C, 70.1; H, 4.5; N, 14.4%); $\nu_{max.}$ (Nujol) 3200—2650br (NH) and 1680 (C=O) cm^{-1}; τ (CF_3·CO_2H) 1.2—1.5 (2 H, m), 1.68 (1 H, s), 1.80—2.0 (2 H, m), and 2.46 (1 H, s).

3-*Phthalimido*-1,2,4-*triazole* (11).—*Method* (*a*). 3-Amino-1,2,4-triazole (0.42 g) and phthalic anhydride (0.74 g) were heated at 200 °C for 2 h. Extraction with acetic acid gave the *product* (0.44 g, 42%) as needles, m.p. 285—286° (Found: C, 55.8; H, 3.0; N, 25.8%; $M^{+\cdot}$, 214. $C_{10}H_6N_4O_2$ requires C, 56.0; H, 2.8; N, 26.2%; *M*, 214); $\nu_{max.}$ (C_4Cl_6) 3200—2600 (NH), 1795, 1770, 1740, and 1710 (C=O) cm^{-1}; τ (CF_3·CO_2H) 0.82 (1 H, s) and 1.82 (4 H, m).

Method (*b*). 3-Amino-1,2,4-triazole (0.84 g), phthaloyl chloride (2.03 g), and anhydrous pyridine (10 ml) were stirred for 2.5 h. Water (10 ml) was added and the phthalimide (1.1 g) isolated, m.p. 285—286°.

3-*Methyl*-5-*phthalimidopyrazole* (12).—*Method* (*a*). 5-Amino-3-methylpyrazole (0.49 g) and phthalic anhydride (0.74 g) were heated at 200 °C for 2 h. The *product* crystallised from ethanol (40 ml) as needles (0.62 g, 56%), m.p. 278° (Found: C, 63.2; H, 4.1; N, 18.3%; $M^{+\cdot}$, 227. $C_{12}H_9N_3O_2$ requires C, 63.4; H, 4.0; N, 18.6%; *M*, 227); $\nu_{max.}$ (Nujol), 3240 (NH), 1775, 1755, and 1730 (C=O) cm^{-1}; τ (CF_3·CO_2H) 1.90 (4 H, m), 2.72 (1 H, s), and 7.33 (3 H, s).

Method (*b*). Treatment as for the triazole case gave the product (17%), m.p. 278° (from ethanol).

2-*Phthalimidopyridine* (13).—*Method* (*a*). Treatment as for the pyrazole case gave the product (24%) as needles (from ethanol), m.p. 238° (lit.,[8] 225°) (Found: C, 69.1; H, 3.7; N, 12.4%; $M^{+\cdot}$, 224. Calc. for $C_{13}H_8N_2O_2$: C, 69.6;

H, 3.2; N, 12.5%; *M*, 227); $\nu_{max.}$ (Nujol) 1790, 1780, 1765, 1748, and 1720 (C=O) cm^{-1}; τ ($CF_3 \cdot CO_2H$) 0.93—1.07 (1 H, m), 1.18—1.38 (2 H, m), 1.92 (4 H, m), and 2.07—2.17 (1 H, m).

Method (*b*). 2-Aminopyridine (1.85 g) and pyridine (15 ml, anhydrous) were stirred at 5 °C during dropwise addition of phthaloyl chloride (4 g). Stirring was continued for 1 h, and addition of water (15 ml) gave the product (4 g, 91%), m.p. 238° (from ethanol).

2-*Phthalimidopyrimidine* (14).—*Method* (*a*). Treatment as for the pyrazole case gave the *product* (34%) as needles (from MeCN), m.p. 226° (lit.,[10] 120°) (Found: C, 63.8; H, 3.3; N, 18.7%; $M^{+\cdot}$, 225. Calc. for $C_{12}H_7N_3O_2$: C, 63.9; H, 3.1; N, 18.7%; *M*, 225), $\nu_{max.}$ (Nujol) 1790, 1760, and 1720 (C=O) cm^{-1}; τ ($CF_3 \cdot CO_2H$) 0.57 (2 H, d, *J* 5 Hz), 1.82 (4 H, m), and 1.93 (1 H, t, *J* 5 Hz).

Method (*b*). Treatment as for the pyridine case gave the product (82%) as needles (from MeCN), m.p. 226°.

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