Synthesis of 2,4-Benzodiazepines from Phthalimide Mannich Bases

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The synthesis of certain classes of benzodiazepines has been extensively studied[1], but the 2,4-benzodiazepines are not as readily accessible as some of the others. Although the phthalimido group has been used for protection in

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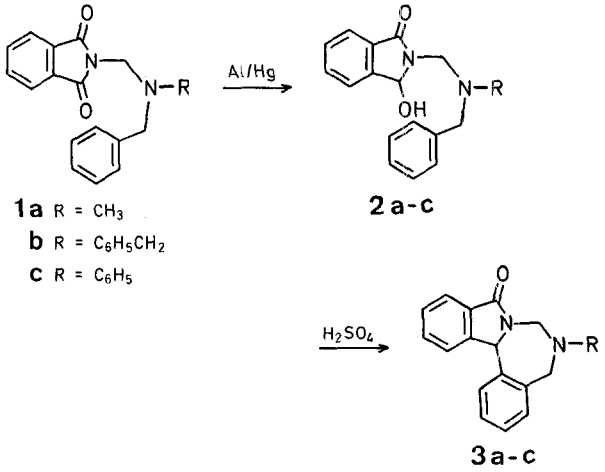
some diazepine syntheses, it has not been used in a reaction where part of the imide ring becomes incorporated into the new seven-membered ring. Examples in the literature of acid-promoted cyclisation of certain reduced *N*-benzyl- or *N*-phenethylphthalimides[2], and of *N*-[2-(3-phthalidylamino)-ethyl]anilines[3] led us to investigate the cyclisation of phthalimide Mannich bases. We now report that the isoindolo[1,2-*a*][2,4]benzodiazepines **3** can be readily prepared in three stages from phthalimide. The Mannich bases **1**, formed from phthalimide, formaldehyde, and a secondary amine, can be reduced using aluminium[4] to give *N*-substituted 3-hydroxyisoindolin-1-ones **2**. Cyclisation of **2** with hot concentrated sulphuric acid gives **3**.



The ring-closure reaction occurs readily when the amine nitrogen atom carries a benzyl or methyl group but not a phenyl group (**2a**, **2b**). With **2c**, the benzodiazepine is formed rather than the quinazoline derivative that would result from reaction at the phenyl group, but the yield is low and a substantial amount of *N*-phenylbenzylamine is formed. It appears that the presence of an *N*-phenyl group hinders reaction, and no product could be satisfactorily isolated from the compound derived initially from *N*-methylaniline.

The phthalimides **1** are not cyclised by the action of acid, but are slowly hydrolysed to phthalimide and then phthalic acid.

N-(Benzylaminomethyl)-phthalimides (1):
The general methods for making the Mannich bases have been described previously[5]; yields: 70% (**1a**); 85% (**1b**); 79% (**1c**).

Reduction of Mannich Bases:

***N*-(*N'*-Benzyl-*N'*-methylaminomethyl)-3-hydroxyisoindolin-1-one (2a; R = CH_3):**
Phthalimide **1a** (13.3 g, 0.047 mol) in benzene (200 ml) and tetrahydrofuran (35 ml) is added to a mixture of mercury(I) acetate (0.7 g) and aluminium turnings (10 g) in water (100 ml). After 24 h the mixture is filtered, the filtrate is extracted with benzene (2 × 50 ml), the precipitate is shaken with water (500 ml) and benzene (100 ml). The combined organic layers are dried with magnesium sulphate and treated with decolourising charcoal. Evaporation of the benzene followed by recrystallisation from benzene/petroleum ether (b.p. 60–80 °C) gives **2a**; yield: 13.3 g (71%); m.p. 107–109 °C.

$C_{17}H_{18}N_2O_2$	calc.	C 72.32	H 6.43	N 9.94
(282.3)	found	72.09	6.43	9.94

M.S.: *m/e* = 282 (M^+); 132; 120; 91.

I.R. ($CHCl_3$): ν = 3325 (s); 1700 (s) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 2.16 (s, 3H); 3.58 (s, 2H); 4.19 (s, 2H); 5.22 (s, 1H, reduced on addition of CD_3OD); 5.96 (s, 1H); 7.0–7.7 ppm (m, 9H).

***N*-(Dibenzylaminomethyl)-3-hydroxyisoindolin-1-one (2b; R = $C_6H_5CH_2$):**
Product **2b** is prepared using a similar procedure; yield: 72%; m.p. 122–124 °C.

$C_{23}H_{22}N_2O_2$	calc.	C 77.07	H 6.19	N 7.83
(358.4)	found	77.01	6.15	7.84

I.R. (Nujol): ν = 3300 (s); 1675 (s) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 3.60 (s, 4H); 4.18 (s, 2H); 4.61 (s, 1H, reduced by addition of CD_3OD); 5.88 (s, 1H); 7.2–7.5 ppm (m, 14H).

***N*-(*N'*-Benzyl-*N'*-phenylaminomethyl)-3-hydroxyisoindolin-1-one (2c; R = C_6H_5):**
Product **2c** is prepared using a similar procedure; yield: 77%; m.p. 160–162 °C.

$C_{22}H_{20}N_2O_2$	calc.	C 76.72	H 5.86	N 8.14
(344.4)	found	76.50	6.01	8.03

M.S.: *m/e* = 344 (M^+); 183; 133; 105; 104; 91; 77.

I.R. ($CHCl_3$): ν = 3340 (m); 1690 (s) cm^{-1}.

^{1}H-N.M.R.: δ = 3.36 (s, 1H, reduced by addition of CD_3OD); 4.78 (s) and 4.92 (d) (total 3H); 5.52 (d, 1H); 5.80 (s, 1H); 6.6–7.7 ppm (m, 14H).

Cyclisation of the 3-Hydroxyisoindolin-1-ones:

8-Methyl-7,8,9,13b-tetrahydro-5*H*-isoindolo[1,2-*a*][2,4]benzodiazepin-5-one (3a):
A mixture of **2a** (4.0 g, 0.014 mol) and concentrated sulphuric acid (40 ml) is heated at 100 °C for 2 h. After cooling, the mixture is poured into ice/water (100 g), neutralised with aqueous sodium hydroxide (40%) and extracted with chloroform/petroleum ether (b.p. 60–80 °C) to give **3a**; yield 3.1 g (85%); m.p. 161–164 °C.

$C_{17}H_{16}N_2O$	calc.	C 77.25	H 6.11	N 10.66
(264.3)	found	77.06	6.08	10.66

M.S.: *m/e* = 264 (M^+); 263; 233; 220; 219; 193; 178; 165; 144.

I.R. ($CHCl_3$): ν = 1690 (s) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 2.20 (s, 3H); 3.89 (d, 1H); 4.37 (d, 2H); 5.20 (d, 1H); 5.72 (s, 1H); 7.1–7.2 (m, 4H); 7.4–7.6 (m, 3H); 7.8–7.9 ppm (m, 1H).

^{13}C-N.M.R. (acetone-d_6): δ = 39.3 (q); 60.2 (t); 64.7 (d); 68.0 (t); 125.3; 127.1; 128.9; 129.3; 130.2; 132.7; 133.9; 138.2; 139.6; 144.7; 169.6 ppm (s).

8-Benzyl-7,8,9,13b-tetrahydro-5*H*-isoindolo[1,2-*a*][2,4]benzodiazepin-5-one (3b):
Compound **2b** is cyclised using sulphuric acid as before to give **3b**; yield: 63%; m.p. 152–154 °C. Purification by chromatography using alumina and 1:1 chloroform/petroleum ether (b.p. 60–80 °C) is required to remove **2b** impurity.

$C_{23}H_{20}N_2O$	calc.	C 81.15	H 5.92	N 8.23
(340.4)	found	81.02	5.98	8.36

M.S.: *m/e* = 340 (M^+); 339; 249; 234; 220; 193; 91.

I.R. (Nujol): ν = 1680 (s) cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ = 3.38 (s, 2H); 3.92 (d, J = 12 Hz, 1H); 4.54 and 4.78 (two d, J = 6 Hz, 2H); 5.14 (d, J = 12 Hz, 1H); 6.10 (s, 1H); 7.1–7.3 (m, 9H); 7.6–7.9 ppm (m, 4H).

^{13}C-N.M.R. (DMSO-d_6): δ = 55.0 (t); 58.7 (t); 64.6 (d); 65.4 (t); 125.2; 127.1; 128.4; 128.9; 129.2; 129.5; 130.3; 132.8; 133.7; 139.4; 169.4 ppm (s).

8-Phenyl-7,8,9,13b-tetrahydro-5*H*-isoindolo[1,2-*a*][2,4]benzodiazepin-5-one (3c):
Compound **2c** is cyclised using sulphuric acid as before to give a mixture which is separated by chromatography using silica gel and 1:1 chloroform/petroleum ether. The crude sample of **3c** is purified by recrystallisation from methanol; yield 7%; m.p. 161–163 °C.

$C_{22}H_{18}N_2O$	calc.	C 80.95	H 5.56	N 8.58
(326.4)	found	81.00	5.55	8.63

M.S.: *m/e* = 326 (M^+); 325; 232; 220; 205; 193; 165; 83; 77.

I.R. ($CHCl_3$): ν = 1680 (s) cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 4.88$ (s, 2H); 5.31 (s, 2H); 5.80 (s, 1H); 6.7–6.9 (m, 1H); 7.0–7.4 (m, 8H); 7.6 (m, 3H); 8.0 ppm (m, 1H).

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