2-(Aminomethyl)phthalimide. A New Reagent for the Synthesis of 2,4-Benzodiazepines

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2,4-Benzodiazepines can be prepared by condensation of an activated 2-benzoylbenzoic acid with 2-(aminomethyl)phthalimide. A synthesis of this reagent is described.

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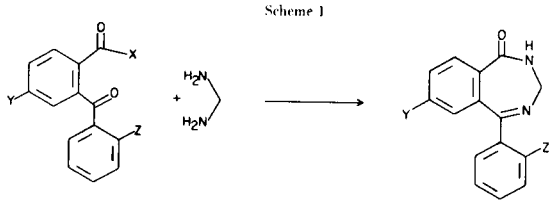
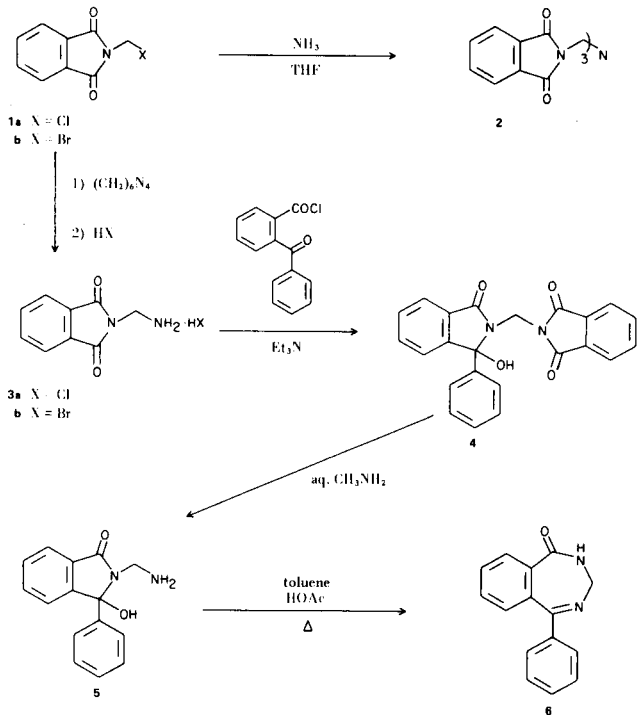
Although 2,4-benzodiazepines have shown CNS activity (1,2), their relative difficulty of preparation (1,2) has limited the number of compounds which have been examined. We now wish to report a new synthesis of these compounds.

In a formal sense, the easiest route to 2,4-benzodiazepines involves condensation of an appropriate 2-benzoylbenzoic acid derivative with 1,1-diaminomethane (Scheme I). Since the latter compound is not accessible, the synthetically equivalent moiety **3** was prepared.

Scheme 1



Scheme 2



Direct displacement of the halogen from **1** with hexamethylenetetramine followed by acid hydrolysis gave the desired product as either the hydrochloride **3a** or hydrobromide **3b** salt. All attempts to prepare the free base were unsuccessful. Reaction of **1** with excess liquid ammonia afforded only the tertiary amine **2**. Condensation of either **3a** or **3b** with *o*-benzoylbenzoyl chloride in the presence of triethylamine yielded the isoindole **4**. Aqueous methylamine smoothly removed the phthalimide protecting group from **4** to give the amine **5**. Cyclization to the 2,4-benzodiazepine **6** was carried out by refluxing a solution of **5** in toluene containing a catalytic amount of acetic acid.

The use of either **3a** or **3b** permits a convenient entry into the 2,4-benzodiazepine series, and may be useful for the preparation of other 1,3-aza heterocycles.

EXPERIMENTAL

Melting points were determined in a capillary using a Hoover melting point apparatus and are uncorrected. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer. Nmr spectra were recorded with a Varian T-60 instrument with TMS as internal standard. Ir spectra were determined on a Beckman IR-9 spectrometer. Mass spectra were recorded on a CEC-110B instrument.

N-(Bromomethyl)phthalimide (**1b**) was purchased from Eastman Organic Chemicals and used without further purification.

N-(Chloromethyl)phthalimide (**1a**).

A suspension of 51.0 g. (0.35 mole) of phthalimide, 29 ml. of 35% aqueous formaldehyde and 175 ml. of water was refluxed for 5 minutes, cooled and filtered. The solid was washed with water and dried *in vacuo* to give 55.3 g. (89%) of *N*-(hydroxymethyl)phthalimide, m.p. 139.5-142.5° (lit. (3) 141-142°).

A solution of 55.0 g. (0.31 mole) of the above compound in 200 ml. of thionyl chloride and 200 ml. of chloroform was refluxed for 5 hours then evaporated *in vacuo*. Crystallization of the residue from petroleum ether-ether gave 57 g. (95%) of crude (**1a**), m.p. 119.5-122.5°. Recrystallization from methylene chloride-petroleum ether (Norite) raised the melting point to 123.5-126.5° (lit. (3) 136.5°). All physical data were consitent with the structure.

Tri-(phthalimidomethyl)amine (**2**).

A solution of 10.0 g. (0.05 mole) of (**1a**) in 80 ml. of tetrahydrofuran was added dropwise with stirring to 75 ml. of liquid ammonia; upon completion of addition the reaction

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was allowed to warm to room temperature overnight, permitting the ammonia to evaporate. The solvent was removed *in vacuo* and the residue was dissolved in 30 ml. of dimethylformamide; a solution of 5.8 g. (0.075 mole) of acetyl chloride in 10 ml. of dimethylformamide was added, and the mixture was stirred for 1.5 hours. Addition of 200 ml. of water gave 1.2 g. of (**2**). Recrystallization from methylene chloride-methanol (Norite) followed by methylene chloride-petroleum ether, gave colorless prisms, m.p. 224-228° (lit. (4) 232-234.5°). All physical data were consistent with the structure.

2-(Aminomethyl)phthalimide Hydrochloride (**3a**) and Hydrobromide (**3b**).

A solution of 28.5 g. (0.2 mole) of hexamethylenetetramine in 300 ml. of chloroform was refluxed with stirring while a solution of 45.0 g. (0.19 mole) of **1b** in 160 ml. of chloroform was added during 15 minutes. After 2 hours the reaction was cooled and the product collected to give 50.3 g. (70%) of the crude quaternary bromide salt, m.p. 170-175°. Use of **1a** gave a 61% yield of the quaternary chloride salt, m.p. 192-196°; in this case the reaction was first refluxed for 3 hours, then stirred at room temperature for 16 hours.

A suspension of 11.0 g. (0.029 mole) of bromide salt in 21 ml. of 48% hydrobromic acid and 50 ml. of ethanol was stirred at room temperature for 18 hours. The product was collected, washed with methanol-ether, ether and dried *in vacuo* to give 9.6 g. of crude **3b**, m.p. 206-210°. The crude product was used in all subsequent reactions without purification. The analytical sample was recrystallized three times from methanol-ether, m.p. 213-215°; ir (potassium bromide): 3000, 1790 and 1720 cm^{-1}; nmr (deuterium oxide): δ 5.60 (s, 2H) and 8.50 (m, aromatic, 4H), uv: 217 (ϵ = 44500), 235 (9600), 293 (1920) and 301 nm (1780).

Anal. Calcd. for $C_9H_9BrN_2O_2$: C, 42.1; H, 3.5; N, 10.9. Found: C, 42.0; H, 3.4; N, 10.8.

In a similar manner the quaternary chloride salt was converted into **3a** (m.p. 190-224°) using hydrochloric acid.

2-[(2,3-Dihydro-3-hydroxy-1-oxo-3-phenyl-1*H*-isoindol-2-yl)methyl]-1*H*-isoindole-1,3(2*H*)dione (**4**).

A solution of 7.7 g. (0.034 mole) of *o*-benzoylbenzoic acid and 120 ml. of thionyl chloride was refluxed 30 minutes, evaporated *in vacuo*, treated with benzene and evaporated *in vacuo* again. The residue was dissolved in 125 ml. of triethylamine and *vigorously* stirred while 7.7 g. (0.036 mole) of crude **3a** was added. After 30 minutes the solvent was removed *in vacuo* and the residue was partitioned between methylene chloride-water. The organic layer was dried, concentrated to a small volume and chromatographed over 200 g. of silica gel using ether to give 1.9 g. (15%) of colorless prisms, m.p. 201-204°. The analytical sample was recrystallized from methylene chloride-petroleum ether, m.p. 203-205°; ir (potassium bromide) 3580, 3400, 1778, 1718 and 1645 cm^{-1}; uv 218 (ϵ = 56000), 277 (2250), 286 (2265) and 300 nm (1745); ms: m/e 384 (M^+).

Anal. Calcd. for $C_{23}H_{16}N_2O_4$: C, 71.9; H, 4.2; N, 7.3. Found: C, 71.6; H, 4.3; N, 7.4.

An identical product was obtained (18%) when **3b** was the starting material.

2-(Aminomethyl)-2,3-dihydro-3-hydroxy-3-phenyl-1*H*-isoindol-1-one (**5**).

A mixture of 0.8 g. (0.002 mole) of **4**, 1.0 ml. of 40% aqueous methylamine and 8 ml. of ethanol was stirred for 1 hour, then partioned between ether-water. The ether layer was dried and evaporated *in vacuo;* crystallization of the residue gave 0.28 g. (55%) of colorless prisms, m.p. 117-121°. Recrystallization from methylene chloride-petroleum ether, gave pure material, m.p. 120-123°, which was identical in all respects to material prepared by an independent route (1).

2,3-Dihydro-5-phenyl-1*H*-2,4-benzodiazepin-1-one (**6**).

A solution of 0.4 g. (0.0016 mole) of **5** in 0.1 ml. of acetic acid and 5 ml. of toluene was refluxed 30 minutes, then diluted with petroleum ether. The collected product (0.15 g., 40%) was recrystallized from methylene chloride-ether, to give colorless prisms, m.p. 200-205°. This material was identical to an authentic sample prepared by an alternate route (1).

REFERENCES AND NOTES

(1) U. Golik, *J. Heterocyclic Chem.*, **12**, 903 (1975).
(2) U. Golik, *Tetrahedron Letters*, 1327 (1975).
(3) E. J. Sakellarios, *J. Am. Chem. Soc.*, **70**, 2822 (1948).
(4) F. B. Kipping and F. G. Mann, *J. Chem. Soc.*, 528 (1927).