Synthesis of Perhydropyrazino[1,2-*d*][1,4]diazepine, a New Heterocyclic Compound

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A novel heterocycle, perhydropyrazino[1,2-*d*][1,4]diazepine, is prepared in good yield by an efficient method starting from facile available compounds.

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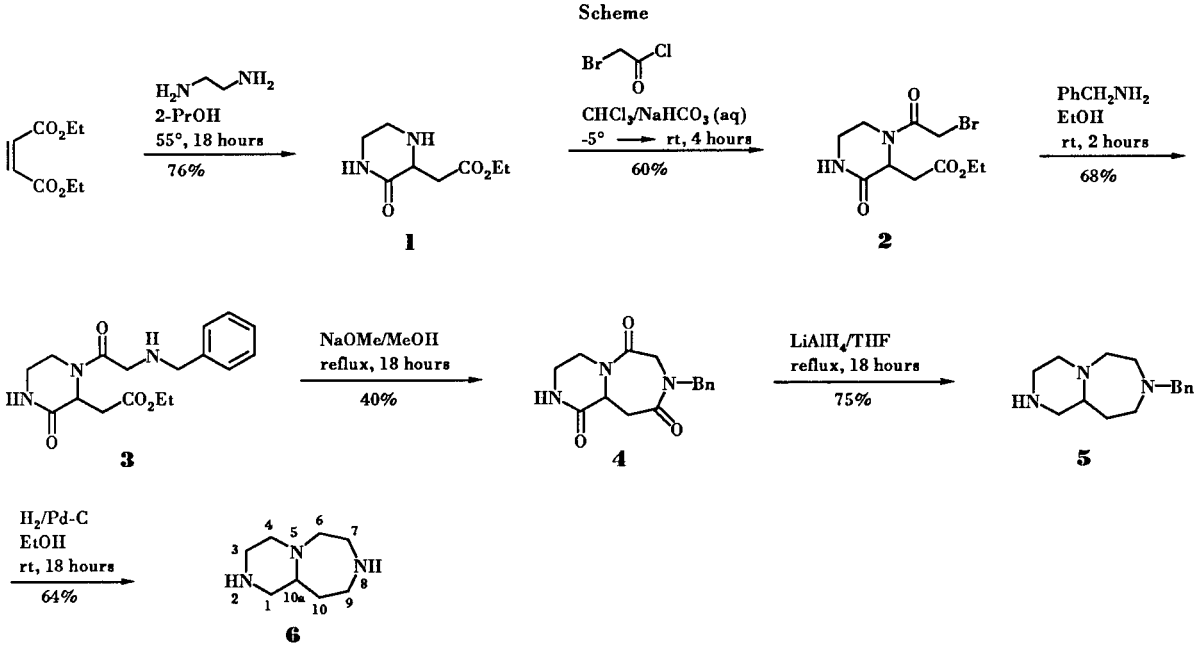
In a previous paper [1], we have reported the synthesis of a series of triazabicyclic compounds as precursors in the field of antibacterial quinolones. As a part of this program, which is aimed toward the research of new bicyclic heterocycles, we report here the total synthesis of perhydropyrazino[1,2-*d*][1,4]diazepine **6** (Scheme). The synthesis of related derivatives (bicyclic piperidinyl compounds) have been described [2] but there are no reports in the literature concerning the preparation of this unsubstituted bicyclic heterocycle. One of the main advantages of our synthesis is that different interesting derivatives may be readily prepared from a common intermediate **5** at late stage in the synthesis.

The 2-carbethoxymethylpiperazin-3-one **1** was prepared by addition of ethylenediamine to diethyl maleate followed by cyclization from nucleophilic attack of the remaining amino on the carbonyl of the ester function in a "one-pot" procedure [2]. The 1-bromoacyl derivative **2** was obtained by treatment of **1** with bromoacetyl chloride in a typical Schotten-Baumann procedure [3-5]. The final heterocyclic compound was achieved in three steps: A double nucleophilic substitution reaction with benzylamine, a posterior reduction with lithium aluminium hydride of the amide functions in the structure **4**, and a mild debenzylation of **5** with molecular hydrogen. The substitution of benzylamine for ammonia or methylamine, under the same reaction conditions, does not allow the direct cyclization step and, consequently, the synthesis of the final bicyclic structure.

EXPERIMENTAL

All reagents were of commercial quality from freshly opened containers. Ethylenediamine, diethyl maleate, bromoacetyl chloride, benzylamine, and lithium aluminium hydride were purchased from Merck Chemical Co., and 10% palladium over charcoal from Fluka Chemical Co. Other reagents including solvents were used without further purification. Analytical silica gel 60 tlc plates of 0.25 mm thickness with fluorescent indicator and silica gel (70-230 mesh) for column chromatography were purchased from Merck Chemical Co. Melting points were determined in open capillary tubes on a Büchi apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 1710 spectrophotometer. The ^{1}H-nmr spectra were measured on a Bruker

Scheme



WP80DW spectrophotometer using tetramethylsilane as an internal standard. Microanalyses were obtained using a Perkin-Elmer P.E. 2400 analyser.

Bromine was determined by Schöniger's method [6]. Basic groups were determined by potentiometric method in non-aqueous media.

2-Carbethoxymethylpiperazin-3-one (**1**).

Diethyl maleate (80.0 g, 465 mmoles) and ethylenediamine (23.5 g, 391 mmoles) were dissolved in 2-propanol (200 ml) and warmed at 55° for 18 hours. The solvents were removed under reduced pressure using a rotary evaporator. The white solid obtained was purified by recrystallization from acetone to yield 55 g (76%), mp 108-110°, one basic group 99.5%; ir (potassium bromide): 3360, 3200, 1720, 1650, 1200 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.25 (t, 3H, CH_3, J = 7 Hz), 2.40 (s, 1H, NH), 2.75-3.50 (m, 6H, NCH_2CH_2N and CH_2COOEt), 3.75 (dd, 1H, CH, J_{cis} = 7.5 Hz J_{trans} = 4 Hz), 4.15 (q, 2H, CH_2CH_3, J = 7 Hz), 7.35 (s, 1H, CONH).

Anal. Calcd. for $C_8H_{14}N_2O_3$: C, 51.60; H, 7.58; N, 15.04. Found: C, 51.48; H, 7.67; N, 15.04.

1-Bromoacetyl-2-carbethoxymethylpiperazin-3-one (**2**).

To a stirred suspension of compound **1** (50.8 g, 273 mmoles) and sodium bicarbonate (200 g) in chloroform (300 ml) at −5° was added dropwise bromoacetyl chloride (46.3 g, 293 mmoles) in chloroform (100 ml), and the mixture was stirred for 2 hours at the same temperature. Then, sodium bicarbonate (100 g) and water (50 ml) were added and this suspension was stirred for 4 hours at rt, filtered and the organic layer was dried over magnesium sulfate and evaporated to give the crude product **2**, which was recrystallized from ethyl acetate/hexane (6:4) to yield 50.2 g (60%), mp 90-92°; ir (potassium bromide): 3200, 1730, 1670, 1650 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.25 (t, 3H, CH_3, J = 7 Hz), 3.05 (d, 2H, CH_2COOEt), 3.25-3.70 (m, 4H, NCH_2CH_2) 3.95 (s, 2H, CH_2Br), 4.15 (q, 2H, CH_2CH_3, J = 7 Hz), 4.90 (t, 1H, CH, J = 5 Hz), 7.55 (s, 1H, CONH).

Anal. Calcd. for $C_{10}H_{15}BrN_2O_4$: C, 39.10; H, 4.92; N, 9.12; Br, 26.02. Found: C, 39.28; H, 4.98; N, 8.87; Br, 25.74.

1-Benzylaminoacetyl-2-carbethoxymethylpiperazin-3-one (**3**).

To a solution of **2** (50.0 g, 163 mmoles) in ethanol (400 ml) was added a solution of benzylamine (52.4 g, 488 mmoles) in the same solvent (100 ml) and the mixture was stirred at rt for 2 hours. Then the solvent was evaporated at reduced pressure and the crude product was purified by column chromatography (silica gel, chloroform/methanol, 9.5:0.5 to 8:2) to give the product **3** as an oil which was used further without purification. Yield 38.4 g (68%), one basic group 100.3%; ir (liquid film): 3340, 3220, 1740, 1670, 1650 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.20 (t, 3H, CH_3, J = 7 Hz), 2.35 (s, 1H, NH), 3.0 (d, 2H, CH_2COOEt), 3.20-3.60 (m, 6H, NCH_2CH_2N and $COCH_2NH$), 3.80 (s, 2H, CH_2Ph), 4.15 (q, 2H, CH_2CH_3, J = 7 Hz), 5.0 (t, 1H, CH), 7.25 (s, $5H_{arom}$), 7.70 (s, 1H, CONH).

8-Benzylperhydropyrazino[1,2-*d*][1,4]diazepine-1,6,9-trione (**4**).

To a solution of sodium (3.92 g, 171 mmoles) in methanol (250 ml) was added a solution of compound **3** (38 g, 114 mmoles) in the same solvent (250 ml). The mixture was refluxed for 18 hours, cooled to rt and water (200 ml) was added. The resultant solution was acidified to *p*H = 2-3 with aqueous 1*M* hydrochloric acid, the methanol was evaporated and the aqueous layer was extracted with chloroform (3 x 250 ml); the organic layer was dried over sodium sulfate and evaporated to give the product **4** as an oil, yield 13.0 g (40%); ir (liquid film): 3230, 1660, 1465, 1350 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 3.05-4.9 (m, 7H, H-3, 4, 10, 10_a), 3.4 (s, 2H, H-4), 4.65 (s, 2H, CH_2Ph), 7.15 (s, 1H, CONH), 7.25 (s, $5H_{arom}$).

Anal. Calcd. for $C_{15}H_{17}N_3O_3$: C, 62.71; H, 5.96; N, 14.63. Found: C, 62.49; H, 5.87; N, 14.52.

8-Benzylperhydropyrazino[1,2-*d*][1,4]diazepine (**5**).

A suspension of the trione **4** (6.3 g, 22 mmoles) in anhydrous THF (100 ml) was added dropwise with stirring to a slurry of lithium aluminium hydride (2.7 g, 71 mmoles) in anhydrous THF (100 ml) under nitrogen. The mixture was refluxed for 18 hours, cooled to 0-5° and water (12 ml) was added dropwise with stirring. After 2 hours, the mixture was filtered and the collected salts were washed with a mixture of hot ethanol/2-propanol (1:1, 300 ml). The filtrates were combined, dried over sodium sulfate and the solvents were removed *in vacuo*. The crude solid was treated with hot chloroform (50 ml), filtered and the organic phase was evaporated to give **5** as a pale yellow resinous solid which was used in the next step without purification, yield 4.2 g (79%), one basic group 99.05%; ir (liquid film): 3260, 1460 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.5-3.1 (m, 16H, ring protons + NH), 3.65 (s, 2H, CH_2Ph), 7.30 (s, $5H_{arom}$).

Perhydropyrazino[1,2-*d*][1,4]diazepine (**6**).

The bicyclic compound **5** (1.0 g, 4.07 mmoles) in ethanol (40 ml) was hydrogenated using 10% palladium on carbon (0.2 g) at rt (hydrogen, 1 atm). After 18 hours the reaction was complete, then the mixture was filtered and the organic layer was evaporated in a rotary evaporator to give the crude product as a clean oil which was distilled at reduced pressure (bp 119-122°, 0.15 mm) to obtain the pure product **6** as an oil, yield 0.4 g (64%); ir (liquid film): 3240, 2960, 1480, 1150 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.85-3.05 (m).

Anal. Calcd. for $C_8H_{17}N_3$: C, 61.93; H, 10.96; N, 27.09. Found: C, 61.71; H, 10.92; N, 26.98.

An analytical sample of perhydropyrazino[1,2-*d*][1,4]diazepine dihydrochloride was prepared by addition of ethanolic hydrogen chloride to the sample followed by recrystallization in 2-propanol-ether to obtain a white crystalline solid, mp >250° dec.

Anal. Calcd. for $C_8H_{17}N_3 \cdot 2HCl$: C, 42.11; H, 8.39; N, 18.41; Cl, 31.08. Found: C, 41.87; H, 8.18; N, 18.09; Cl, 30.96.

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