Use of the Mannich Reaction in the Synthesis of Bispidine

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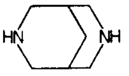
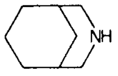
A three-step synthesis of bispidine (**1**) is described. Mannich condensation of *N*-benzyl-4-piperidone, formaldehyde, and benzylamine afforded *N,N'*-dibenzylbispidinone (**5**), which was reduced under modified Wolff-Kishner conditions to yield *N,N'*-dibenzylbispidine (**6**). Catalytic debenzylation of this compound gave **1**.

J. Heterocyclic Chem., 13, 1111 (1976).

Bispidine (**1**) has been of interest as a ligand in the study of complexation by certain transition metals (3), and as an intermediate for the synthesis of pharmacologically active compounds (4). It was first prepared (5) as shown in Scheme I (X = N) in a manner similar to that initially used (6) to prepare its monoazabicyclic counterpart **2** (X = CH).

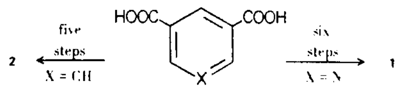


1

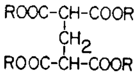


2

Scheme I



Both syntheses involved catalytic reduction of the aromatic rings of the esterified acids, followed by formation of the respective 1,3-dicarboximides which were reduced chemically to yield **1** and **2**. (More recently, **1** has been prepared (4) from **3** *via* a four-step procedure.)

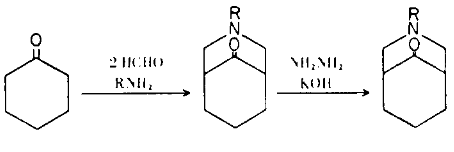


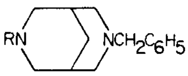
$$\begin{array}{c}\text{ROOC-CH-COOR}\\ |\\ \text{CH}_2\\ |\\ \text{ROOC-CH-COOR}\end{array}$$

3

An alternate route to *N*-alkyl derivatives of **2**, *via* the initial double-Mannich condensation followed by Wolff-Kishner reduction of the intermediate amino ketone (Scheme II), has been studied by several groups (7). Using this approach, we have found that *N*-substituted bispidines (**4**) may be prepared in good yield from *N*-alkyl-4-piperidones, benzylamine, and excess paraformaldehyde (8). These compounds may then be debenzylated catalytically to give *N*-alkylbispidines (**5**). Thus, it occurred to us that an analogous sequence utilizing appropriate starting materials would furnish an intermediate capable of facile conversion to **1**.

Scheme II





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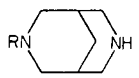
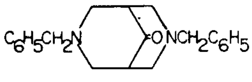
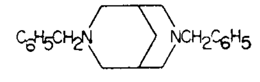


5

Condensation of *N*-benzyl-4-piperidone, benzylamine, and paraformaldehyde afforded the bicyclic amino ketone **6** in good yield. This compound was not completely purified or characterized due to its instability. It was reduced uneventfully to **1** under modified Wolff-Kishner conditions (9) (Scheme II). A small amount of starting amino ketone, accompanying **6** as an impurity, was reduced concomitantly and separated from **7** by azeotropic distillation with the water formed during the reduction.



6



7

Treatment of **7** with 10% palladium on carbon under hydrogen (10) gave **1**. The overall yield of this sequence is 61% (based on *N*-benzyl-4-piperidone), which compares favorably with that of other syntheses.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (ir) were taken on a Beckman IR 33 spectrophotometer. Nuclear magnetic resonance spectra (nmr) and electron impact mass spectra (EIMS) were determined on Varian T-60 and CH 5 spectrometers respectively. Elemental analyses were obtained using a Hewlett-Packard 185 C,H,N analyzer.

N,N'-Dibenzylbispidinone (**6**).

A solution of 18.9 g. (0.1 mole) of *N*-benzyl-4-piperidone and 6.0 g. of glacial acetic acid (0.1 mole) in 100 ml. of methanol was added in increments over a period of five days to a magnetically stirred solution of 10.7 g. (0.1 mole) of benzylamine and 6.0 g. of glacial acetic acid (0.1 mole) in 400 ml. of methanol in which 24 g. (0.8 mole) of paraformaldehyde were suspended. After stirring for an additional 25 days, the solution was concentrated ***in vacuo***. The residue was shaken with 200 ml. of water and 250 ml. of ether. The ether was removed, and the aqueous phase was washed with two additional 250 ml. portions of ether. The ethereal extracts were discarded. The aqueous phase was cooled in ice, and made strongly basic by addition of sodium hydroxide pellets. The resulting suspension was extracted with two 350 ml. portions of ether. These extracts were combined, dried (sodium sulfate), filtered, and concentrated ***in vacuo*** to yield 25.7 g. (83%) of the crude amino ketone as a deep red liquid which darkened readily on exposure to air; nmr (carbon tetrachloride, 1% TMS): δ 3.40 (s, 4, NCH_2Ph), 7.17 (m, 10, C_6H_5).

N,N'-Dibenzylbispidine (**7**).

The product obtained above (***ca.*** 0.08 mole) was dissolved in 250 ml. of triethylene glycol and 20 g. (0.4 mole) of hydrazine hydrate were added. Heating and magnetic stirring were begun, and 30 g. of 85% potassium hydroxide pellets (0.45 mole) were added. The solution was stirred and refluxed under nitrogen for 4 hours, after which time a Dean Stark trap was introduced. Distillate was removed until the temperature of the reaction solution reached 200°. From the distillate was recovered 4.0 g. of a colorless, water-immiscible liquid with ir and nmr spectra identical to those of authentic *N*-benzylpiperidine. The reaction solution was cooled to room temperature and poured into 200 ml. of water. The resulting suspension was extracted with four 200 ml. portions of ether. The ethereal extracts were combined and washed with two 100 ml. portions of 0.1 *N* aqueous sodium hydroxide. The ether layer was dried (sodium sulfate), filtered, and concentrated ***in vacuo*** to give 17.9 g. (73%) of a yellow oil; nmr (carbon tetrachloride, 1% TMS): δ 1.48 (t, $J = 3$ Hz, 2, methylene bridge), 1.79 (m, 2, bridgehead methine), 2.24 (dd, $J_1 = 11$ Hz, $J_2 = 4$ Hz, 4, *exo-N*-methylene), 2.75 (dd, $J_1 = 11$ Hz, $J_2 = 2$ Hz, 4, *endo-N*-methylene), 3.35 (s, 4, NCH_2Ph), 7.17 (s, 10, C_6H_5); EIMS (70 eV): m/e 306 (M), 91 (B). Treatment of a cold ethereal solution of the base with excess cold 40% perchloric acid in aqueous ethanol furnished the monoperchlorate, which separated from methanol as orange crystals, m.p. 210-217° dec.; ir (potassium bromide): 3040 (arom. CH), 2960, 2850, 1460, 1305, 1080, 760, 740, 720, 690 cm^{-1}.

Anal. Calcd. for $C_{21}H_{27}ClN_2O_4$: C, 61.99; H, 6.69; N, 6.88. Found: C, 62.01; H, 6.39; N, 6.85.

Bispidine (**1**).

A solution of 9.2 g. (30 mmoles) of *N,N'*-dibenzylbispidine was dissolved in 30 ml. of glacial acetic acid and 2 ml. of 70% aqueous perchloric acid was added. This solution was added to a suspension of 1.0 g. of 10% palladium on carbon in 15 ml. of glacial acetic acid, which had been stirred for 1 hour under 1 atmosphere of hydrogen. The mixture was shaken at an initial pressure of 3.3 atmospheres of hydrogen (ambient temperature). After 72 hours, the catalyst was filtered, and the solvent was removed ***in vacuo***. The product was dissolved in 30 ml. of water. The solution was cooled in ice, and made strongly basic by addition of sodium hydroxide pellets. Extraction of the resulting mixture with three 80 ml. portions of ether, followed by drying (sodium sulfate), filtration, and concentration of the combined extracts afforded 2.75 g. (73%) of the product as a yellow oil. This was dissolved in 70 ml. of ether and precipitated with aqueous ethanolic perchloric acid. The precipitate was dissolved in 30 ml. of water, after washing it with two 50 ml. portions of ether. The aqueous solution was filtered through Celite, and the filtrate was concentrated at the oil pump. Residual water was azeotropically removed ***in vacuo*** with benzene. The product, a mixture of the mono and diperchlorates, crystallized from isopropanol as small white needles, m.p. 232-234° dec. Conversion of this salt to the free base as above gave a low-melting solid; nmr (benzene, 1% TMS): δ 1.23 (m, 2, CH_2 bridge), 1.63 (t, $J = 3$ Hz, 2, bridgehead CH), 2.15 (s, 2, deuterium oxide exchangeable, NH), 2.95 (d, $J = 3$ Hz, 8, NCH_2). Treatment of an ethereal solution of the base with ethereal hydrogen chloride gave the dihydrochloride which crystallized from isopropanol as small needles, m.p. 262-266° dec.; ir (potassium bromide): 3440 (NH), 2990, 2810, 1625, 1435, 1395, 1300, 1250, 1140, 1015 cm^{-1}; EIMS (70 eV): m/e 126 (M), 44 (B). Alternatively, treatment of an ethereal solution of the base with a solution of picric acid in ethanol-ether (1:10) furnished the dipicrate as yellow needles, m.p. 229-233° dec.

Anal. Calcd. for $C_{19}H_{20}N_8O_{14}$: C, 39.04; H, 3.45; N, 19.17. Found: C, 39.36; H, 3.53; N, 19.37.

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