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Synthesis of 2,5-Bis(piperidinomethyl)piperidine and 1,5-Bis(aminomethyl)-3-azabicyclo[3.2.1]octanones

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Schmidt reaction of mono- and bis-*Mannich* bases **1** and **2c** derived from cyclopentanone gave the corresponding basically substituted 2-piperidones **3** and **4**, respectively. Reduction of the latter afforded **5**. Double *Mannich* reaction of **2a–c** with primary amines gave 3-azabicyclo[3.2.1]octanone derivatives **6a–e** and **7**. The transamination of **2a** was investigated.

(Keywords: Bis(piperidinomethyl)piperidine; 3-Azabicyclo[3.2.1] octane; Nitrogen heterocycles)

Synthese von 2,5-Bis(piperidinomethyl)piperidin und 1,5-Bis(aminomethyl)-3-azabicyclo[3.2.1]octanonen

Die *Schmidt*-Reaktion der von Cyclopentanon abgeleiteten Mono- und Bis-*Mannich*-Basen **1** und **2c** ergaben die entsprechenden basisch substituierten 2-Piperidone **3** und **4**. Die Reduktion des letzteren ergab **5**. Doppel-*Mannich*-Reaktion von **2a—c** mit primären Aminen führte zu den 3-Azabicyclo[3.2.1]octanon-Derivaten **6a—e** und **7**. Die Transaminierung von **2a** wurde untersucht.

Introduction

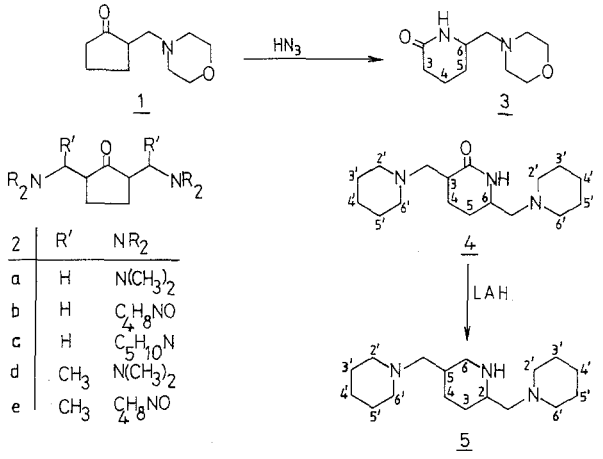
Interest has been expressed in the pharmacological action and the synthetic potentialities of various ketonic *Mannich* bases[1–4]. From a synthetic point of view, such compounds are of considerable importance as intermediates in the synthesis of certain heterocycles carring potential basic side-chains[5–7]. In particular, the *Schmidt* reaction with 2-piperidinomethylcyclohexanone provides a route to 2-piperidinomethylazepine via reduction of the intermediate ε-piperidinomethylcaprolactam[6].

Therefore, it appeared of interest to study this reaction with mono and bis-*Mannich* bases derived from cyclopentanone.

Results and Discussion

2-*N*-Morpholinomethylcyclopentanone[8] (**1**) and 2,5-bis-(*N*-piperidinomethyl)cyclopentanone (**2c**) were subjected to *Schmidt* reaction to give 6-(*N*-morpholinomethyl)-2-piperidone (**3**) and 3,6-bis(*N*-piperidinomethyl)-2-piperidone (**4**), respectively. The presence of a (CO—NH) grouping in **3** and **4** is confirmed by IR and NMR spectral data. The assignment of the (NH) group between the (CO) group and the substituted carbon atom in **3**, is based on previous studies by *Schmidt* et al.[6].

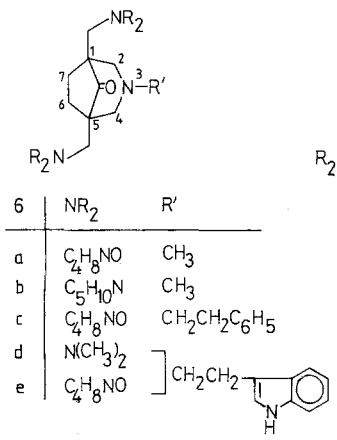
In the present work advantage of this reactivity has been taken in the synthesis directed towards 2,5-bis(*N*-piperidinomethyl)piperidine (**5**), via reduction of **4** by lithium aluminium hydride.



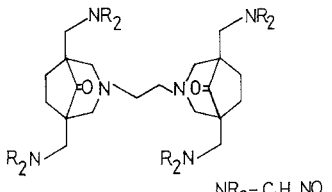
2	R′	NR_2
a	H	$N(CH_3)_2$
b	H	C_4H_8NO
c	H	$C_5H_{10}N$
d	CH_3	$N(CH_3)_2$
e	CH_3	C_4H_8NO

In a study of the possible synthesis of 1,5-bis(dimethylaminomethyl)-3-methyl-3-azabicyclo[3.3.1]nonan-9-one, the application of the double *Mannich* reaction to 2,6-bis(dimethylaminomethyl)cyclohexanone has been investigated by *Blicke* and *McCarty*[7]. In the light of their investigations, treatment of **2b**[9]–**2c** with formalin and methylamine in a molar ratio of (1 : 2 : 1) afforded 1,5-bis(*N*-morpholinomethyl and *N*-piperidinomethyl)-3-methyl-3-azabicyclo[3.2.1]octan-8-ones (**6a** and **b**), respectively. A similar treatment of **2b** with 2-phenylethylamine gave **6c**. In addition, the recent interest in the pharmacological activity of tryptamine and its derivatives[10] prompted us to prepare **6d**–**6e**, in which the aliphatic

nitrogen of the tryptamine moiety is involved in a 3-azabicyclooctane ring system having bridgehead basic side-chains.

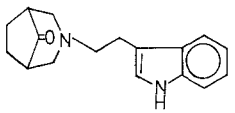


6	NR_2	R′
a	C_4H_8NO	CH_3
b	$C_5H_{10}N$	CH_3
c	C_4H_8NO	$CH_2CH_2C_6H_5$
d	$N(CH_3)_2$	CH_2CH_2
e	C_4H_8NO	CH_2CH_2



7

$NR_2 = C_4H_8NO$



8

Furthermore, when **2b** was subjected to a double *Mannich* reaction using ethylenediamine, it afforded 3,3′-ethylenebis[1,5-bis(*N*-morpholinomethyl)-3-azabicyclo[3.2.1]octan-8-one] (**7**). The characteristic feature of the NMR spectrum of **6a** is the presence of a signal at δ 2.85 ppm attributable to (CH_2—N—CH_2) of the 3-azabicyclooctane ring system[11].

In connection with the present work, we obtained **8** via a double transamination[12] between **2a**[9] and tryptamine.

Experimental

All melting points (°C) were uncorrected and were taken in a Gallenkamp electric melting point apparatus. IR spectra were performed on a Unicam SP 2000 Infrared Spectrophotometer using KBr. NMR spectra were obtained in $CDCl_3$ solution with a Varian Model "A-60". Elementary analyses (C, H, N) of **2c–e**, **3**, **4**, **5**, **6a–e**, **7** and **8** were in good agreement with the proposed structures.

2,5-Bis(piperidinomethyl)cyclopentanone dihydrochloride (**2c**)
2,5-Bis(dimethylaminoethylidene)cyclopentanone dihydrochloride (**2d**) *and*
2,5-Bis(morpholinoethylidene)cyclopentanone dihydrochloride (**2e**)

A mixture of cyclopentanone (8.4 g, 0.1 mol), piperidine hydrochloride (30.25 g, 0.25 mol) and paraformaldehyde (9 g, 0.3 mol) in ethanol (50 ml) was refluxed for 24 h, then cooled and treated with acetone. The crystalline precipitate was washed with acetone, dried and recrystallized from methanol-acetone to give **2c** in 55% yield. M.p. 233°.

In a similar manner as above, **2d–2e** were obtained, except that dimethylamine or morpholine hydrochloride and paraldehyde were used. Yield 20% for **2d**, 32% for **2e**; m.p. 165° (**2d**), 170° (**2e**).

6-(N-Morpholinomethyl)-2-piperidone (**3**)

1 (3.4 g, 0.015 mol) was added to sulphuric acid (50 ml, 90%) at 0°, followed by addition of (1 g) sodium azide. After stirring for 1 h at 0° and 4 h at 25°, the reaction mixture was diluted with ice water, basified with sodium carbonate and extracted with ether. The ethereal solution was dried on potassium carbonate and evaporated to give a light yellow oil. Treating with ethyl acetate gave colourless needles of **3** in 20% yield. M.p. 80°. IR (KBr): 1 670 cm^{-1} (CO·NH, 6-membered ring lactam); NMR ($CDCl_3$): 1.7 (m, 2 H, 4-H_2), 2.2 (m, 4 H, 3-H_2 and 5-H_2), 2.35–2.65 (m, 6 H, cyclic CH_2—N—CH_2 and side-chain N—CH_2), 3.45 (m, 1 H, 6-H), 3.7 (m, 4 H, CH_2OCH_2) and 6.5 (broad s, 1 H, CO·NH).

3,6-Bis(N-piperidinomethyl)-2-piperidone (**4**)

It was synthesized from **2c** (4.6 g, 0.012 mol) in the same manner as **3**. Colourless crystals of **4** were obtained in 45% yield. M.p. 62°. IR (KBr): 1 675 cm^{-1} (CO·NH, 6-membered ring lactam); NMR ($CDCl_3$): 1.5 [m, 12 H, 2 (3′-H_2), 2 (4′-H_2) and 2 (5′-H_2)], 1.75 (m, 2 H, 4-H_2), 2.1–2.25 [broad s, 12 H, 2 (2′-H_2), 2 (6′-H_2) and 2 (N—CH_2) of side-chain], 2.3–2.55 (m, 3 H, 5-H_2 and 3-H), 3.3–3.5 (m, 1 H, 6-H) and 6.55 (broad s, 1 H, CO·NH).

2,5-Bis(piperidinomethyl)piperidine oxalate (**5**)

4 (2 g, 0.007 mol) was treated with (1 g) lithium aluminium hydride in tetrahydrofuran (50 ml) under reflux for 6 h, cooled, poured into 200 ml ice-water, basified with 40% ammonia and filtered. The filterate was evaporated, extracted with ether, dried and ethereal oxalic acid was added to give the oxalate of **5** in 84% yield. Recrystallized from methanol-ether, m.p. 212°. Basification of the oxalate salt gave the free base. IR (KBr): 3 340 cm^{-1} (NH); NMR ($CDCl_3$): 1.45 [m, 17 H, 2 (3′-H_2), 2 (4′-H_2), 2 (5′-H_2), 3-H_2, 4-H_2 and 5-H], 2.0 (broad s, 1 H, NH) and 1.9–2.5 [m, 15 H, 2 (2′-H_2), 2 (6′-H_2), 6-H_2, 2-H and 2 (N—CH_2) of side-chain].

1,5-Bis(morpholinomethyl)-3-methyl-3-azabicyclo[3.2.1]octan-8-one (**6a**)
1,5-Bis(piperidinomethyl)-3-methyl-3-azabicyclo[3.2.1]octan-8-one (**6b**)
1,5-Bis(morpholinomethyl)-3-(1-phenylethyl)-3-azabicyclo[3.2.1]octan-8-one (**6c**)

To a stirred solution of methylamine hydrochloride (2.1 g, 0.03 mol) or 2-phenylethylamine (3.6 g, 0.03 mol), 37% formalin (5 g, 0.062 mol) and ethanol (15 ml), there was added dropwise a solution of **2b** (10.6 g, 0.03 mol) or **2c** (11.5 g, 0.03 mol) in water (60 ml). The mixture was stirred for 8 h, made alkaline with NaOH solution, extracted with ether, dried and the solvent was removed. The residue was crystallized from ethanol—ether to give **6a**–**6b**, and from ethyl acetate to give **6c** in 20–23% yield. M.p. 112° (**6a**), 96° (**6b**), 98° (**6c**).

6a: IR (KBr): 1 735 cm^{-1} (CO); NMR ($CDCl_3$): 2.25 (s, 3 H, N—CH_3), 2.3–2.55 (m, 12 H, 2 CH_2—N—CH_2 of morpholines and 2 CH_2—N of side-chains), 2.85 (s, 4 H, 2-H_2 and 4-H_2) and 3.5 (t, 8 H, 2 CH_2OCH_2). **6c**: NMR ($CDCl_3$): 2.05 (broad s, 4 H, 6-H_2 and 7-H_2), 2.3–2.5 (m, 14 H, 2 CH_2—N—CH_2 of morpholines and 3 CH_2—N of side-chains at C-1, C-5 and position 3), 2.75 (s, 4 H, 2-H_2 and 4-H_2), 2.9 (m, 2 H, benzylic CH_2), 3.55 (t, 8 H, 2 CH_2OCH_2) and 7.2 (s, 5 H, aromatic protons).

1,5-Bis(dimethylaminomethyl)-3-[2-(indolyl)ethyl]-3-azabicyclo[3.2.1]octan-8-one (**6d**) *and 1,5-Bis(morpholinomethyl)-3-[2-(indolyl)ethyl]-3-azabicyclo[3.2.1]octan-8-one* (**6e**)

These compounds were synthesized in the same manner as above, from **2a–2b**, except that tryptamine (4.8 g, 0.03 mol) was used, and the precipitated product was washed thoroughly with boiling ethanol, dried and crystallized from dilute acetic acid to give **6d–6e** in 30–32% yield. M.p. 206° (**6d**), 155° (**6e**).

3,3'-Ethylenebis[1,5-bis(morpholinomethyl)-3-azabicyclo[3.2.1]octan-8-one] (**7**)

This compound was synthesized from **2b** in the same manner as **6a**, except that ethylenediamine dihydrochloride (2 g, 0.015 mol) was used and the reaction time was 24 h. The ethereal solution of the product was treated with ethereal oxalic acid to give the oxalate of **7** in 30% yield, m.p. > 300°.

3-[2-(3-Indolyl)ethyl]-3-azabicyclo[3.2.1]octan-8-one (**8**)

A mixture of **2a** (1.6 g; 0.006 mol) and tryptamine (0.96 g, 0.006 mol) in aqueous ethanol (1 : 1) was refluxed for 10 h. The precipitate was filtered and crystallized from dilute acetic acid to give **8** in 70% yield, m.p. 225° (decomp.).

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