

Synthesis of 2,5-Bis(2'-piperidylmethyl)piperidine and Related Compounds

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The triketones **3-6** were obtained by alkylation of cyclopentanone or cyclohexanone with the appropriate cycloalkanone bis-Mannich base (1) or (2). Schmidt reaction of the triketones **3-6** afforded the corresponding tricyclic lactames **7-10** respectively. Reduction of **7** and **9** gave compounds **11** and **12** respectively.

Key words: Tricyclic-triketones, Tricyclic lactames, Bis(piperidinomethyl)piperidine, Nitrogen heterocycles

INTRODUCTION

The chemistry of piperidines with a side chain in the 2-position, has attracted much attention because of their structural relation to the physiologically active hemlock alkaloids, e.g. coniine (Windholz, 1976), conhydrine and pseudoconhydrine. In particular, pipradrol and pipridocaine and β -coniceine (Windholz, 1976) showed properties ranging from central stimulant, antispasmodic to spinal anesthetic. In view of this, and in continuation of our work in this area (Afsah *et al.*, 1984; Hammouda *et al.*, 1987; Hamana *et al.*, 1988) it appeared to us that a convenient approach to compounds of the type **11**, having three 2-substituted piperidine units, would be available, starting from triketones of the type **3**.

MATERIALS AND METHODS

All melting points ($^{\circ}\text{C}$) were uncorrected and were taken in a Gallenkamp electric melting point apparatus. IR spectra were performed on a Unicam SP 2000 Infra-red Spectrophotometer using KBr. NMR spectra were obtained in CDCl_3 solution with a Varian Model A-60. Elementary analyses (C, H, N) of **3-12** were in good agreement with the proposed structures.

2,5-Bis(2'-oxocyclopentylmethyl)cyclopentanone (3), 2,6-bis(2'-oxocyclopentylmethyl)cyclohexanone (4), 2,5-bis(2'-oxocyclohexylmethyl)cyclopentanone (5) and

2,6-bis(2'-oxocyclohexylmethyl)cyclohexanone (6)

General procedure: A mixture of 2,5-bis(dimethylaminomethyl)cyclopentanone (**1**) (0.1 mol) or 2,6-bis(dimethylaminomethyl)cyclohexanone (**2**) (0.1 mol) and cyclopentanone (0.6 mol) was refluxed for 1.5 h. at $160-170^{\circ}$ by which time evolution of dimethylamine from the reaction mixture has ceased. On cooling, the mixture was diluted with ether, neutralized with dil. HCl and washed several times with water. The ethereal solution was dried (Na_2SO_4), the ether and excess cycloalkanone removed *in vacuo*. The residue was crystallized to give **3** and **4**.

Compounds **5** and **6** were obtained according to the same procedure from **1** or **2** and cyclohexanone. (cf. Table 1).

3,6-Bis[(2'-piperidon-6'-yl)methyl]-2-piperidone (7), 3,7-bis[(2'-piperidon-6'-yl)methyl]-2-azepinone (8), 3,6-bis[(2'-azepinon-7'-yl)methyl]-2-piperidone (9) and 3,7-bis[(2'-azepinon-7'-yl)methyl]-2-azepinone (10)

General procedure: To a solution (0.01 mol) of **3**, **4**, **5** or **6** in chloroform (30 ml) and conc. H_2SO_4 (10 ml), sodium azide (0.03 mol, 1.95g) was added at 0°C during 1 h. The reaction mixture was stirred at room temperature for 4 h., heated for 30 min. at $50-55^{\circ}\text{C}$, then poured into ice-cold water and basified with 40% ammonium hydroxide. The product was filtered, crystallized from a suitable solvent to give compounds **7-10**. (cf. Table 1).

2,5-Bis(2'-piperidylmethyl)piperidine (11) and 2,5-bis(2'-azepinylmethyl)piperidine (12)

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General procedure: To a cold suspension (0.008 mol, 0.31g) of LiAlH_4 in dry THF (25 ml), a solution

Table I. Synthetic data for compounds 3-12

Compounds (colour)	Crystallization solvent	Yield (%)	mp. °C	Molecular formula (m.wt.)
3 (White)	Pet. ether	65	115	$\text{C}_{17}\text{H}_{24}\text{O}_3$ (276.4)
4 (Cream)	MeOH	58	118-120	$\text{C}_{18}\text{H}_{26}\text{O}_3$ (290.4)
5 (White)	Pet. ether	56	73	$\text{C}_{19}\text{H}_{28}\text{O}_3$ (304.4)
6 (Cream)	MeOH	61	165	$\text{C}_{20}\text{H}_{30}\text{O}_3$ (328.4)
7 (Cream)	EA*/MeOH	70	205	$\text{C}_{17}\text{H}_{27}\text{N}_3\text{O}_3$ (321.4)
8 (Buff)	EA*/MeOH	66	234-237	$\text{C}_{18}\text{H}_{29}\text{N}_3\text{O}_3$ (335.4)
9 (Buff)	EA*/MeOH	59	135	$\text{C}_{19}\text{H}_{31}\text{N}_3\text{O}_3$ (349.5)
10 (Cream)	MeOH	63	>300	$\text{C}_{20}\text{H}_{33}\text{N}_3\text{O}_3$ (363.5)
11 (White)	MeOH/Ether	46	>300	$\text{C}_{17}\text{H}_{33}\text{N}_3(\text{C}_2\text{H}_4\text{O})_3$ (549.6)
12 (White)	EA*	34	99	$\text{C}_{19}\text{H}_{37}\text{N}_3$ (307.5)

*EA: Ethyl acetate

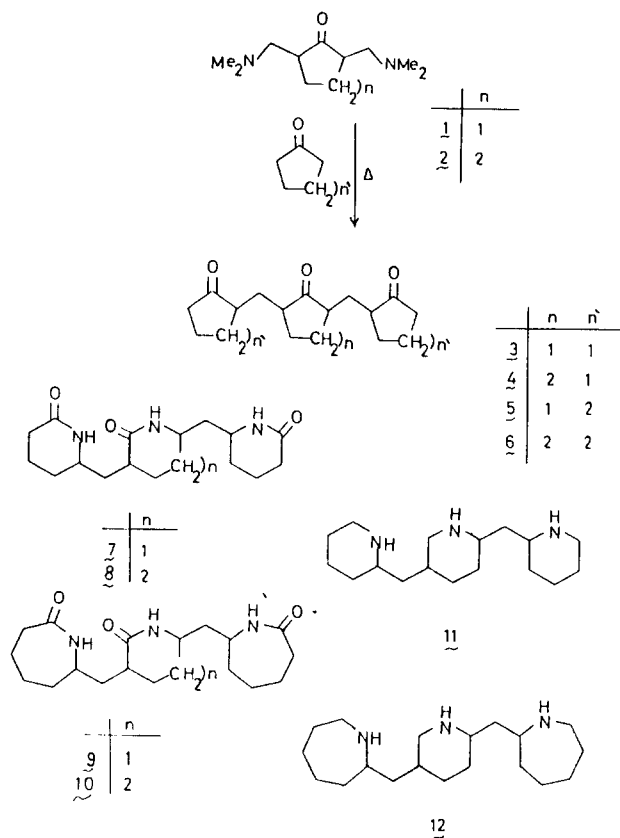


Table II. IR and $^1\text{H-NMR}$ data

Compound	IR[cm^{-1}] (selected bands)	$^1\text{H-NMR}$; δ ppm
3	1745-1730 (CO, pentanones)	2.0 (broad m, 16H, 3-H ₂ , 4-H ₂ , 2×3'-H ₂ , 2×4'-H ₂ and 2CH ₂ of side chain), 2.2 (m, 4H, 2×5'-H ₂) and 2.4 (broad m, 4H, 2-H, 5-H and 2×2'-H)
4	1740-1735 (CO, pentanones) 1710-1705 (CO, hexanone)	1.9 (broad, m, 18H, 3-H ₂ , 4-H ₂ , 5-H ₂ , 2×3'-H ₂ , 2×4'-H ₂ and CH ₂ of side chain), 2.2 (m, 4H, 2×5'-H ₂) and 2.4 (broad m, 4H, 2-H, 6-H and 2×2'-H).
5	1735 (CO, pentanone) 1715-1705 (CO, hexanones)	1.9 (broad m, 20H, 3-H ₂ , 4-H ₂ , 2×3'-H ₂ , 2×4'-H ₂ , 2×5'-H ₂ and 2CH ₂ of side chain), 2.2 (m, 4H, 2×6'-H ₂) and 2.4 (broad m, 4H, 2-H, 5-H and 2×2'-H)
6	1720-1705 (CO, hexanones)	1.8 (m, 22H, 3-H ₂ , 4-H ₂ , 5-H ₂ , 2×3'-H ₂ , 2×4'-H ₂ , 2×5'-H ₂ and 2CH ₂ of side chain), 2.2 (m, 4H, 2×6'-H ₂) and 2.4 (m, 4H, 2-H, 6-H and 2×2'-H)
7	1670-1640 (CONH of 6-membered ring lactams)	2.0 (m, 16H, 4-H ₂ , 5-H ₂ , 2×4'-H ₂ , 2×5'-H ₂ and 2CH ₂ of side chain), 2.4 (m, 5H, 3-H, 2×3'-H ₂), 3.4 (m, 3H, 6-H, 2×6'-H) and 6.5 (m, 3H, 3×CONH)
8	1670-1630 (CONH of 6- and 7-membered ring lactams)	1.8 (m, 18H, 4-H ₂ , 5-H ₂ , 6-H ₂ , 2×4'-H ₂ , 2×5'-H ₂ and 2CH ₂ of side chain), 2.4 (m, 5H, 3-H, 2×3'-H ₂), 3.3 (m, 3H, 7-H, 2×6'-H) and 6.4 (m, 3H, 3×CONH)
9	1660-1630 (CONH of 6- and 7-membered ring lactams)	1.9 (m, 20H, 4-H ₂ , 5-H ₂ , 2×4'-H ₂ , 2×5'-H ₂ , 2×6'-H ₂ and 2CH ₂ of side chain), 2.4 (m, 5H, 3-H, 2×3'-H ₂), 3.3 (m, 3H, 6-H, 2×7'-H) and 6.4 (m, 3H, 3×CONH)
10	1660-1630 (CONH of 7-membered ring lactams)	1.7 (m, 22H, 4-H ₂ , 5-H ₂ , 6-H ₂ , 2×4'-H ₂ , 2×5'-H ₂ , 2×6'-H ₂ and 2CH ₂ of side chain), 2.4 (m, 5H, 3-H, 2×3'-H ₂), 3.3 (m, 3H, 7-H, 2×7'-H) and 6.4 (m, 3H, 3×CONH)
12	3330-3350 (NH) groups	1.0 (m, 4H, 2CH ₂ of side chain), 1.5-2 (m, 21H, 3-H ₂ , 4-H ₂ , 2×3'-H ₂ , 2×4'-H ₂ , 2×5'-H ₂ , 2×6'-H ₂ and 5-H), 2..5 (m, 6H, 6-H ₂ and 2×7'-H ₂) and 3.5-3.7 (m, 3H, 2-H and 2×2'-H)

of **7** or **9** (0.002 mol) in dry THF (25 ml) was added. The reaction mixture was refluxed for 4 h., left overnight, then worked up by addition of excess aqueous NaOH (5%) and extraction with ethyl acetate. After drying on (Na_2SO_4), the extract was evaporated under reduced pressure to give a solid product in case of **12**. In case of **11** the obtained highly viscous material was converted into its oxalate salt by the addition of an ethereal solution of oxalic acid to the crude product in the same solvent. The precipitate was washed several times with ether (cf. Table I).

RESULTS AND DISCUSSION

The triketones, 2,5-bis(2'-oxocyclopentylmethyl)cyclopentanone (**3**) and 2,6-bis(2'-oxocyclopentylmethyl)cyclohexanone (**4**) were obtained by alkylation of cyclopentanone with 2,5-bis(dimethylaminomethyl)cyclopentanone (**1**) and 2,6-bis(dimethylaminomethyl)cyclohexanone (**2**) respectively. Similarly, alkylation of cyclohexanone with the bis-Mannich bases **1** and **2** afforded 2,5-bis(2'-oxocyclohexylmethyl)cyclopentanone (**5**) and 2,6-bis(2'-oxocyclohexylmethyl)cyclohexanone (**6**) respectively. The formation of **3-6** is in line with many reported cases (Brown *et al.*, 1968; Austin *et al.*, 1969), in which ketones have been alkylated with mono- or bis-Mannich bases. The structure of **3-6** has been supported by analytical and spectral data. The NMR spectrum of **3**, as example, showed signals at δ 2.0 (broad m, 16H, 3-H₂, 4-H₂, 2×3'-H₂, 2×4'-H₂ and 2CH₂ of side chain), 2.2 (m, 4H, 2×5'-H₂) and 2.4 (broad m, 4H, 2-H, 5-H and 2×2'-H).

The triketones **3-6** were subjected to reaction with three equivalents of hydrazoic acid under Schmidt reaction conditions to give the corresponding tricyclic lactams **7-10** respectively. The presence of (CONH) in these compounds was confirmed by IR and NMR spectral data. The insertion of the (NH) group between the (CO) group and the substituted carbon atom in **7-10** is based on previous studies by Schmidt *et al.* (1956) and on the work of Brikofler and Engels (1962) who reported the formation of di(2-piperidon-6-yl)-me-

thane from di(2-oxocyclopentyl)methane via Schmidt reaction.

Such tricyclic lactams **7-10**, could conceivably function as a precursors to the tricyclic alkaloidal systems of the type **11** and **12**. Thus, reduction of **7** and **9** with lithium aluminium hydride afforded 2,5-bis(2'-piperidylmethyl)piperidine (**11**) and 2,5-bis(2'-azepinylmethyl)piperidine (**12**) respectively. The structure of **11** and **12** was supported by analytical and spectral data. In addition, the formation of these compounds is in line with the reported formation of di(2-piperidyl)-methane (Brikofler and Engels, 1962) by reduction of di(2-piperidon-6-yl)methane.

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