Formation of *N*,*N*′-dihydroxy- and *N*,*N*′-dimethoxy-1,4-diazepine derivatives in the reaction of 1,2-bis(hydroxyamines) and 1,2-bis(methoxyamine) with enone Mannich bases

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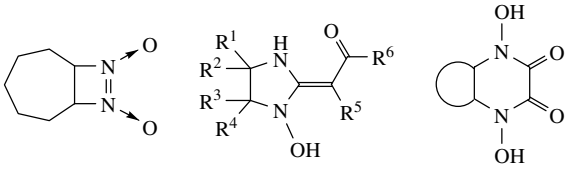
Previously unknown 6-acyl-*N*,*N*′-dihydroxyperhydro-1,4-diazepines and *N*,*N*′-dimethoxyperhydro-1,4-diazepine were obtained by the reaction of 1,2-bis(hydroxyamines) and 1,2-bis(methoxyamine) with enone Mannich bases.

1,2-Bis(hydroxyamines) belong to a new class of binucleophiles, which are useful starting compounds in the synthesis of nitrogen heterocycles. In contrast to 1,2-diamines, the structure and reactivity of 1,2-bis(hydroxyamines) allow one to obtain N-oxides, N-hydroxy compounds and cyclic hydroxamic acids directly and to avoid drastic nitrogen heterocycle oxidation step, which often gives a complex mixture of products.

Thus, four-, five- and six-membered heterocyclic compounds – 1,2-diazetine **1**,[1,2] imidazolidine **2**,[3–5] and pyrazine **3**[6–8] (Figure 1) derivatives – have been obtained *via* the reactions of 1,2-bis(hydroxyamines) with electrophilic agents. Nevertheless, all attempts to synthesise seven-membered heterocycles from 1,2-bis(hydroxyamines) have yet been unsuccessful.[4,9]

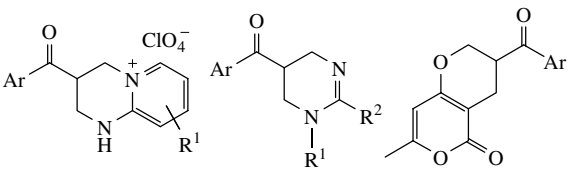


1 **2** **3**

Figure 1

In the course of the systematic research of the chemistry of 1,2-bis(hydroxyamines), we found that these compounds form perhydro-1,4-diazepine derivatives in the reaction with enone Mannich bases.

Enone Mannich bases are highly reactive species with three electrophilic centres, which allows them to be active with several equivalents of nucleophile(s) or polynucleophiles to form heterocyclic compounds. Reactions of enone Mannich bases with O-, C- and N-1,3-binucleophiles to form six-membered heterocycles are known[10,11] (Figure 2), but there are no such examples with 1,4-binucleophiles.



R^1, R^2 = H, Me, Ph
Ar = Ph, 4-$MeOC_6H_4$, 3,4-$Cl_2C_6H_3$

Figure 2

Compounds **4a** and **4b** were found to react with 1,2-bis(hydroxylamino)cyclohexane **5a** and 1,2-bis(hydroxylamino)cycloheptane **5b** in absolute ethanol at room temperature (Scheme 1).† The IR spectra of the isolated products contain absorption bands at 1650–1686 cm^{-1} typical of conjugated carbonyl groups. The NMR spectra (^1H and ^{13}C) contain signals that are characteristic of symmetrical 1,4-diazepines and a singlet at 8.25–8.32 ppm peculiar to the hydroxy group of cyclic hydroxyamines **6a–d**.‡

1,4-Diazepine formation is assumed to involve the addition of a hydroxylamino group to a carbon–carbon double bond

† *General procedure.* A solution of enone Mannich base (3 mmol) and 1,2-bis(hydroxylamino)cycloalkane (3 mmol) in 3.5 ml of absolute ethanol was stirred at room temperature for 2 weeks. The precipitated white solid was filtered off and recrystallised (EtOAc–EtOH).

In the case of 1,2-bis(methoxyamino)cyclohexane **8** the reaction mixture was stirred for 72 h. Solvent was evaporated *in vacuo* and the residue was purified with column chromatography on SiO_2 (eluent, hexane–EtOAc, 4:1).

‡ IR spectra were recorded on a Bruker Vector 22 spectrometer as KBr pills or neat. UV spectra were measured on an HP Agillent 8453 instrument. NMR spectra were recorded on a Bruker AM-400 (400.13 MHz), Bruker WP-200SY (200.2 MHz) and Bruker AC-200 (200.2 MHz) spectrometers. High resolution mass spectra were obtained using a Finnigan MAT 8200 mass spectrometer. Melting points were measured on Kofler plate and are uncorrected. Analytical and preparative TLC was performed on Silufol UV254 plates (Cavalier, CSFR).

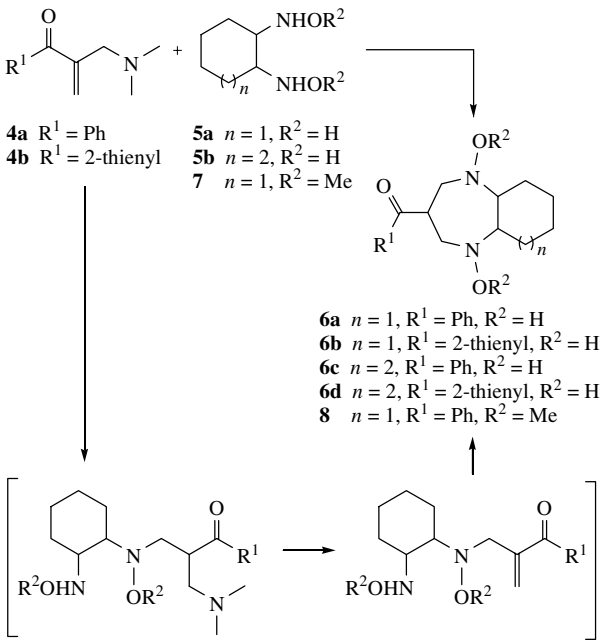
*(1,4-Dihydroxyperhydrobenzo[*b*]-1,4-diazepin-3-yl)phenylmethanone* **6a**: yield 39%, mp 170–172 °C. ^1H NMR ([$^2H_6$]DMSO) δ: 1.12–2.00 (m, 8H, $4CH_2$), 2.7–2.9 (m, 2H, 2CH), 3.11 (dd, 2H, $2CH_aH_e$, *J* 7 and 14 Hz), 3.50 (dd, 2H, $2CH_aH_e$, *J* 7 and 14 Hz), 4.15–4.30 (m, 1H, CHCO), 7.47–7.70 (m, 3H, $3CH_{Ph}$), 8.00–8.10 (m, 2H, $2CH_{Ph}$), 8.30 (s, 2H, 2OH). IR (KBr, ν/cm^{-1}): 1681 ($\nu_{C=O}$). UV [λ_{max}/nm (lg ε)]: 244 (3.98). Found (%): C, 65.88; H, 7.80; N, 9.67. Calc. for $C_{15}H_{22}N_2O_3$ (%): C, 66.18; H, 7.64; N, 9.65.

*(1,4-Dihydroxyperhydrobenzo[*b*]-1,4-diazepin-3-yl)thiophen-2-ylmethanone* **6b**: yield 41%, mp 175–178 °C. ^1H NMR ([$^2H_6$]DMSO) δ: 1.00–2.00 (m, 8H, $4CH_2$), 2.7–2.9 (m, 2H, 2CH), 3.11 (dd, 2H, $2CH_aH_e$, *J* 7 and 14 Hz), 3.51 (dd, 2H, $2CH_aH_e$, *J* 7 and 14 Hz), 4.0–4.2 (m, 1H, CHCO), 7.22 (t, 1H, CH_{Th}), 8.02 (d, 2H, CH_{Th}), 8.32 (s, 2H, 2OH). ^{13}C NMR ([$^2H_6$]DMSO) δ: 22.60 (+, $2CH_2$), 27.79 (+, $2CH_2$) 39.50 (–, 2CH), 50.01 (+, $2NCH_2$), 64.63 (–, CH), 128.73 (–, CH_{Th}), 133.08 (–, CH_{Th}), 134.06 (–, CH_{Th}), 142.83, (+, C_{Th}), 193.98 (+, C=O). IR (KBr, ν/cm^{-1}): 1661 ($\nu_{C=O}$), 1415 (ν_{N-OH}). UV [λ_{max}/nm (lg ε)]: 261 (4.64), 287 (3.58). MS, *m*/*z*: 296.1188 [M$^+$]; calc. for $C_{14}H_{20}N_2O_3S$, *m*/*z*: 296.1195.

*(1,4-Dihydroxyperhydrocyclohepta[*b*]-1,4-diazepin-3-yl)phenylmethanone* **6c**: yield 40%, mp 160–164 °C. ^1H NMR ([$^2H_6$]DMSO) δ: 1.00–2.00 (m, 10H, $5CH_2$), 3.00–4.00 (m, 4H, 2CH, $2CH_aH_e$), 4.45 (m, 2H, $2CH_aH_e$), 4.30 (s, 1H, CHCO) 7.54–7.62 (m, 3H, $3CH_{Ph}$), 8.07–8.10 (m, 2H, $2CH_{Ph}$), 8.26 (s, 2H, 2OH). IR (KBr, ν/cm^{-1}): 1668 ($\nu_{C=O}$), 1446 (ν_{N-OH}). UV [λ_{max}/nm (lg ε)]: 244 (4.01). MS, *m*/*z*: 287.1828 [M$^+$ – OH]; calc. for $C_{16}H_{25}N_2O_2$, *m*/*z*: 287.1835.

*(1,4-Dihydroxyperhydrocyclohepta[*b*]-1,4-diazepin-3-yl)thiophen-2-ylmethanone* **6d**: yield 10%, mp 166–168 °C. ^1H NMR ([$^2H_6$]DMSO) δ: 1.00–2.00 (m, 10H, $5CH_2$), 3.00–4.00 (m, 4H, 2CH, $2CH_aH_e$), 4.30 (m, 2H, $2CH_aH_e$), 4.30 (s, 1H, CHCO) 7.27 (t, 1H, CH_{Th}), 8.03–8.08 (m, 2H, $2CH_{Th}$), 8.28 (s, 2H, 2OH). IR (KBr, ν/cm^{-1}): 1651 ($\nu_{C=O}$), 1413 (ν_{N-OH}). MS, *m*/*z*: 310.1212 [M$^+$]; calc. for $C_{15}H_{22}N_2O_3S$, *m*/*z*: 310.1258.

*(1,4-Dimethoxyperhydrobenzo[*b*]-1,4-diazepin-3-yl)phenylmethanone* **8**: yield 40%. ^1H NMR ($CDCl_3$) δ: 1.00–2.00 (m, 8H, $4CH_2$), 2.9–3.00 (m, 2H, 2CH), 3.19 (dd, 2H, CH_aH_e, *J* 7 and 14 Hz), 3.50 (s, 6H, 2OMe), 3.60 (dd, 2H, $2CH_aH_e$, *J* 7 and 14 Hz), 4.0–4.2 (m, 1H, CHCO), 7.24–7.50 (m, 3H, CH_{Ph}), 8.00–8.05 (m, 2H, CH_{Ph}). ^{13}C NMR ($CDCl_3$) δ: 28.05, 29.55 (–, $2CH_2$), 60.25 (+, OMe), 63.64 (+, CHN), 128.50 (+, Ph), 132.91 (+, Ph), 135.73 (–, Ph), 200.21 (–, CO). IR (KBr, ν/cm^{-1}): 1686 ($\nu_{C=O}$). UV [λ_{max}/nm (lg ε)]: 244 (4.16). MS, *m*/*z*: 287.1758 [M$^+$ – OMe]; calc. for $C_{17}H_{23}N_2O_2$, *m*/*z*: 287.1759.



Scheme 1

according to the Michael type reaction, followed by the elimination of dimethylamine with subsequent addition of the second nucleophilic centre to the double bond newly formed. Simultaneous occurrence of the first two steps is also not excluded.

The reaction of enone Mannich base **4a** with another binucleophile, 1,2-bis(methoxyamino)cyclohexane **7**, under the same conditions leads in a similar way to 1,4-dimethoxydiazepine **8**.

Thus, new *N*,*N*′-dihydroxyperhydro-1,4-diazepine derivatives were obtained by the reaction of enone Mannich bases with 1,2-bis(hydroxyamines). The above transformation is the first example of the reaction of enone Mannich bases with 1,4-binucleophiles.

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