Synthesis of 1,2-bis(methoxyamino)cycloalkanes from alicyclic 1,2-bis(hydroxyamines)

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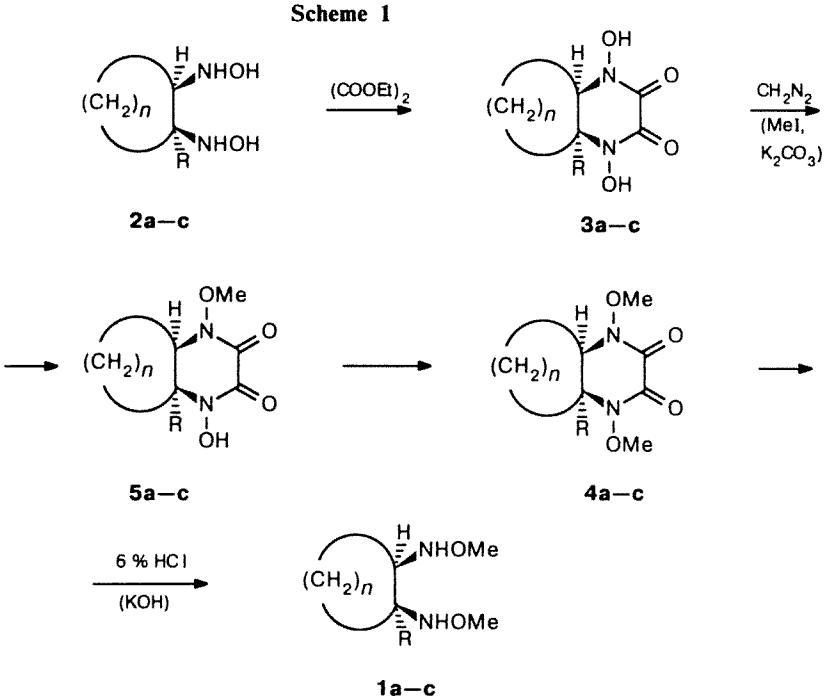
Derivatives of 1,4-dihydroxypiperazine-2,3-dione were obtained by reaction of *cis*-1,2-bis(hydroxyamino)cycloalkanes with diethyl oxalate. Their alkylation with CH_2N_2 or MeI afforded 1,4-dimethoxypiperazine-2,3-diones. Hydrolysis of the latter gave 1,2-bis(methoxyamino)cycloalkanes.

Key words: 1,2-bis(hydroxyamines), 1,2-bis(methoxyamines), 1,2-bis(methoxyamino)cycloalkanes, piperazinediones, cyclic hydroxamic acids, alkylation, hydrolysis.

Alkoxyamines ($RONHR^1$) are widely used for the synthesis of biologically active α-hydroxy amino acids[1] and β-lactams.[2] However, there are no literature data on 1,2-bis(alkoxyamines), which are also of interest for the synthesis of biologically active compounds. *N*-Substituted hydroxylamines are alkylated primarily at the nitrogen atom,[3] therefore, in the present work we propose the synthesis of aliphatic 1,2-bis(methoxyamino)cycloalkanes (BMA) (**1a—c**) from the corresponding *cis*-1,2-bis(hydroxyamines) (BHA) (**2a—c**), which involves *N*-acylation of BHA, *O*-alkylation of the bishydroxamic acids obtained, and the removal of the acyl protection (Scheme 1).

It is known that the acylation of sterically hindered 2,3-bis(hydroxyamino)-2,3-dimethylbutane[4] with oxalyl chloride in the presence of a base affords 1,4-dihydroxy-

Scheme 1



2a—c **3a—c** **5a—c** **4a—c** **1a—c**

a: R = H, n = 4; **b:** R = H, n = 5; **c:** R = Me, n = 4

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5,5,6,6-tetramethylpiperazine-2,3-dione.[5] However, significant resinification is observed on the interaction of the BHA **2c** with oxalyl chloride under the same conditions. Therefore, we used diethyl oxalate, the reactions of which with *cis*-BHA **2a—c** (see Ref. 6) afforded the fused 1,4-dihydroxypiperazine-2,3-diones (**3a—c**) in good yields, thus providing the acyl protection of NH-groups.

The structure of the products is confirmed by the spectral data (Tables 1—3). The IR spectra (KBr pellets) of compounds **3a—c** contain νCO bands at 1650—1700 cm^{-1}. The bishydroxamic acids **3a—c** are soluble in water and form brightly colored complexes with ions of transition metals.

The alkylation of **3a—c** with CH_2N_2 or MeI in the presence of a base affords 1,4-dimethoxypiperazine-2,3-diones (**4a—c**). The intermediate formation of the monomethoxy derivatives (**5a—c**) is confirmed by TLC (color reaction with Fe^{3+} for the detection of hydroxamic acids is used) and the isolation of compound **5a**. Mono- and dialkylation of **3a** occur in 0.5 and 12 h (CH_2N_2) and in 3 and 72 h (MeI), respectively. The yields of dimethoxy compounds **4a—c** are 16—53 % (CH_2N_2) and 87—99 % (MeI/K_2CO_3). The reaction of compounds **3a,c** with CH_2N_2 gives side products of the alkylation of the C=O group at the oxygen atom and probably methoxynitrones (*cf.* Ref. 7), which could not be isolated due to their instability on SiO_2.

Acid hydrolysis of **4a—c** with 6 % HCl affords BMA **1a—c** in the form of dihydrochlorides. The action of NaOH on the latter leads to the isolation of the free bases **1a—c** in a quantitative yield. Bis(methoxyamine) **1a** is isolated in 85 % yield after prolonged boiling of **4a** with methanolic KOH. However, we failed to obtain the desired product **1c** from **4c** under the same conditions.

BMA **1a—c** are colorless oils with a characteristic odor, readily soluble in organic solvents, and insoluble in water. Their structure is confirmed by the spectral data (Tables 1—3). The IR spectra of BMA **1a—c** in CCl_4 contain a broad νNH band at 3200—3350 cm^{-1}.

The reaction of BMA **1a** with CH_2O affords 1,3-dimethoxyimidazolidine (**6**), which is readily hydrolyzed in acidic medium to give the starting BMA **1a**.

Table 1. Physicochemical characteristics of the compounds synthesized

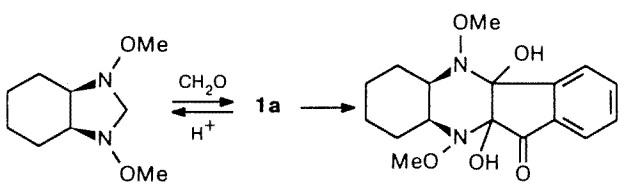
Compound	Yield (%)	M.p./°C (n_D)[a]	λ_{max}/nm (log ε)	Found / Calculated (%) C	H	N	Cl	Molecular formula
1a · 2HCl	85	171—173[b] (1.4652[c])	—	38.4 / 38.9	8.3 / 8.2	11.2 / 11.3	29.3 / 28.7	$C_8H_{20}Cl_2N_2O_2$
1b · 2HCl	88	172—175[b] (1.4730[c])	—	41.3 / 41.4	8.6 / 8.5	10.7 / 10.7	27.3 / 27.1	$C_9H_{22}Cl_2N_2O_2$
1c · 2HCl	92	171—174[b] (1.4650[c])	—	41.1 / 41.4	8.7 / 8.5	10.7 / 10.7	27.2 / 27.1	$C_9H_{22}Cl_2N_2O_2$
3a	87	249—251[d]	232 (3.95)	48.1 / 48.0	6.0 / 6.0	14.0 / 14.0		$C_8H_{12}N_2O_4$
3b	85	237 (decomp.)[d]	230 (4.03)	50.0 / 50.5	6.8 / 6.6	13.0 / 13.1		$C_9H_{14}N_2O_4$
3c	71	213—216[b]	234 (4.04)	50.4 / 50.5	6.8 / 6.6	13.1 / 13.1		$C_9H_{14}N_2O_4$
4a	94	130—131[e]	230 (3.92)	52.9 / 52.6	7.4 / 7.1	12.2 / 12.3		$C_{10}H_{16}N_2O_4$
4b	99	105—108[c]	227 (3.91)	54.2 / 54.5	7.2 / 7.5	12.0 / 11.6		$C_{11}H_{18}N_2O_4$
4c	87	114—115[e]	231 (4.03)	54.7 / 54.5	7.6 / 7.5	11.8 / 11.6		$C_{11}H_{18}N_2O_4$
5a	23	86—91[b]	229 (3.95)	46.8 / 46.5	7.2 / 6.9	12.1 / 12.1		$C_6H_{16}N_2O_5$
6	82	—[f]	—	58.7 / 58.0	9.6 / 9.7	15.4 / 15.0		$C_9H_{18}N_2O_2$
7	32	145—150[f] (decomp.)	229 (4.02), 243 (3.96), 290 sh. (3.11)	60.9 / 61.1	6.7 / 6.6	8.1 / 8.4		$C_{17}H_{22}N_2O_5$

[a] The refractive index of the free base is given. [b] From an ethanol—ethyl acetate mixture. [c] Purified by chromatography. [d] From ethanol. [e] From a hexane—ethyl acetate mixture. [f] Without purification.

Table 2. ^{1}H NMR spectra of compounds **1a—c, 3a—c, 4a—c, 5a, 6,** and **7**

Compound	Solvent	δ, *J*/Hz						
		Me	CH_2	CH	OH	NH	MeO	H_{arom}
1a	$CDCl_3$	—	1.15—1.38 (m); 1.42—1.72 (m)	3.00—3.13 (m)	—	5.67 (s)	3.45 (s)	—
1b	$CDCl_3$	—	1.30—1.68 (m)	3.12—3.20 (m)	—	5.66 (s)	3.41 (s)	—
1c	$CDCl_3$	1.13 (s)	0.98—1.70 (m)	2.76 (t, *J* = 6.0)	—	5.65 (s)	3.41 (s) 3.42 (s)	— —
3a	$(CD_3)_2SO$	—	1.20—1.65 (m); 1.65—2.00 (m)	3.85—4.10 (m)	10.17 (s)	—	—	—
3b	$(CD_3)_2SO$	—	1.20—2.10 (m)	3.90—4.15 (m)	8.5—10.5 (br.s)	—	—	—
3c	$(CD_3)_2SO$	1.28 (s)	1.10—1.70 (m); 2.00—2.30 (m)	3.50—3.65 (m)	10.5 (br.s)	—	—	—
4a	$CDCl_3$	—	1.26—1.67 (m); 1.71—1.98 (m)	3.94 (m)	—	—	3.74 (s)	—
4b	$CDCl_3$	—	1.22—1.45 (m); 1.65—1.80 (m); 1.90—2.05 (m)	4.02 (m)	—	—	3.71 (s)	—
4c	$CDCl_3$	1.39 (s)	1.15—1.80 (m); 2.10—2.42 (m)	3.47 (dd, *J* = 4.0 and 10.5)	—	—	3.77 (s); 3.88 (s)	— —
5a	$(CD_3)_2SO$	—	1.22—2.00 (m)	3.90—4.05 (m); 4.07—4.20 (m);	—	—	3.70 (s)	
6	$CDCl_3$	—	1.15—1.70 (m); 4.20* and 4.48 (H_A and H_B, J_{AB} = 13, NCH_2N)	3.40—3.60 (m)	—	—	3.51*(d, *J* = 0.6)	—
7	$(CD_3)_2SO$	—	1.00—1.85 (m); 2.10—2.30 (m)	2.85—2.95 (m); 3.15—3.50 (m)	5.90 (s); 6.60 (s)	—	3.13 (s) 3.74 (s)	7.42—7.70 (m); 8.02 (d, *J* = 7.5)

* The spin-spin coupling ^5J of the H_A proton with the protons of methyl groups was established from the analysis of the NMDR spectra.



6 **7**

It is known that the condensation of BHA with ninhydrin leads to the formation of *N,N'*-dihydroxyhexahydroindeno[1,2-*b*]pyrazines, which are readily hydrolyzed to give the corresponding *N,N'*-dioxides.[8] We have found that the reaction of BMA **1a** with ninhydrin affords the stable *N,N'*-dimethoxypiperazine (**7**), whose structure is confirmed by spectral methods (see Tables 1—3).

Experimental

IR spectra were obtained on UR-20 and Specord M-80 spectrophotometers in KBr pellets (concentration 0.25 %, *l* = 1 mm) and in CCl_4. UV spectra were recorded on a Specord UV-VIS spectrophotometer in EtOH. ^{1}H NMR spectra were obtained on Bruker WP-200SY (200.2 MHz) and Bruker AC-200 (200.2 MHz) instruments for solutions (5—15 %) in $CDCl_3$ and $(CD_3)_2SO$. ^{13}C NMR spectra were recorded on a Bruker AC-200 spectrometer (50.3 MHz). The reactions were monitored by TLC on Silufol UV-254 plates. Iodine and ammonia vapors were used for the detection of compounds **1a—c** and **2a—c**; other compounds were detected under UV light. The characteristics of the products are given in Table 1; Tables 2 and 3 present the ^{1}H and ^{13}C NMR spectral data.

1,4-Dihydroxyperhydroquinoxaline-2,3-dione (3a). Bishydroxyamine **2a** (21.90 g, 0.15 mol) was added dropwise to a solution of diethyl oxalate (24.4 mL, 0.18 mol) in EtOH (200 mL) at 40—50 °C with stirring. The mixture was refluxed for 2.5 h and then kept for 24 h at −12 °C. The precipitate formed was filtered off, washed with EtOH, and dried to give 21.03 g of the bishydroxamic acid **3a**. The filtrate was concentrated, the residue was triturated with acetone (35 mL) and kept for 12 h at −12 °C, and the precipitate formed was filtered off to give additionally 5.12 g of the product.

1,4-Dihydroxy-5,6-pentamethylenepiperazine-2,3-dione (3b) was obtained from BHA **2b** by a similar procedure. The mixture was refluxed for 3.5 h and cooled, and the precipitate formed was filtered. The filtrate was concentrated, the residue

Table 3 ^{13}C NMR spectra of compounds **1a—c, 3a—c, 4a—c, 5a, 6,** and **7**

Compound	Solvent	δ				
		C_{aliph}*	C_{arom}	C=O	OMe	Other signals
1a	$CDCl_3$	22.05 (t); 25.83 (t); 58.19 (d)	—	—	62.20 (q)	—
1b	$CDCl_3$	23.99 (t); 27.35 (t); 27.83 (t); 60.65 (d)	—	—	61.80 (q)	—
1c	$CDCl_3$	21.22 (t); 22.81 (t); 25.49 (t); 32.74 (t); 58.38 (s); 63.66 (d)	—	—	61.70 (q); 62.44 (q)	23.07 (q)
3a	$(CD_3)_2SO$	21.21 (t); 26.07 (t); 57.30 (d)	—	156.16 (s)	—	—
3b	$(CD_3)_2SO$	22.45 (t); 26.24 (t); 28.22 (t); 60.86 (d)	—	154.26 (s)	—	—
3c	$(CD_3)_2SO$	20.87 (t); 23.12 (t); 27.93 (t); 33.16 (t); 60.45 (s); 64.30 (d)	—	153.42 (s); 155.77 (s)	—	24.06 (q)
4a	$CDCl_3$	21.29 (t); 26.16 (t); 56.35 (d)	—	155.18 (s)	62.10 (q)	—
4b	$CDCl_3$	22.91 (t); 26.45 (t); 28.42 (t); 59.96 (d)	—	154.32 (s)	61.83 (q)	—
4c	$CDCl_3$	21.48 (t); 23.33 (t); 27.77 (t); 33.72 (t); 61.83 (s); 63.72 (d)	—	153.99 (s); 156.90 (s)	61.73 (q); 63.91 (q)	25.01 (q)
5a	$(CD_3)_2SO$	20.74 (t); 21.61 (t); 25.93 (t); 26.03 (t); 55.62 (d); 57.20 (d)	—	154.74 (s); 155.11 (s)	61.94 (q)	—
6	$CDCl_3$	21.96 (t); 26.53 (t); 64.44 (d)	—	—	61.33 (q)	80.00 (t)
7	$(CD_3)_2SO$	21.14 (t); 23.63 (t); 24.80 (t); 27.11 (t); 59.87 (d); 64.04 (d)	123.37 (d); 127.53 (d); 129.12 (d); 133.93 (d); 134.67 (s); 149.80 (s)	196.88 (s)	57.95 (q); 60.53 (q)	91.95 (s); 92.81 (s)

* Carbon atoms of the cycloalkane skeleton.

was triturated with ethyl acetate, and the precipitate was filtered off to give additionally the product **3b**.

1,4-Dihydroxy-4a-methylperhydroquinoxaline-2,3-dione (3c). A suspension of bishydroxyammonium sulfate **2c** (7.74 g, 30.0 mmol) in MeOH (90 mL) was titrated with a 4 *M* solution of MeONa in abs. MeOH with stirring using phenolphthalein as the indicator. The mixture was centrifuged for 15 min, the supernatant was separated, and a solution of diethyl oxalate (4.87 mL, 36.0 mmol) was added to the solution of bishydroxyamine **2c** obtained. The mixture was refluxed for 6 h, MeOH was evaporated, and the residue was kept at −12 °C for 2 days. The crystals formed were triturated with 30 mL of a 1 : 1 ether—acetone mixture and the precipitate was filtered off to afford 4.54 g of bishydroxamic acid **3c**.

1,4-Dimethoxyperhydroquinoxaline-2,3-dione (4a). *A.* An ethereal solution of CH_2N_2 prepared from *N*-nitroso-*N*-methylurea (15.91 g, 154.5 mmol) was added to a suspension of bishydroxamic acid **3a** (3.09 g, 15.45 mmol) in MeOH (80 mL) over 20 min with stirring. The mixture was kept at 20 °C for 12 h and concentrated. The residue was treated with ether (20 mL) and cooled. The precipitate formed was filtered off and washed with ether to give 1.86 g (53 %) of **4a**. The filtrate was concentrated, the residue was treated with a 2 : 1 Et_2O—$CHCl_3$ mixture, and the mixture was kept at −12 °C for 2 weeks. The precipitate was filtered off and washed with ether to give 0.83 g of **1-hydroxy-4-methoxyperhydroquinoxaline-2,3-dione (5a).**

B. A fine powder of bishydroxamic acid **3a** (25.00 g, 125 mmol) and MeI (46.7 mL, 733 mmol) were added to a solution of K_2CO_3 (31.05 g, 225 mmol) in H_2O (110 mL) and MeOH (250 mL) with stirring. The suspension was stirred until dissolution, and the solution was left for 3 days. The precipitate formed was filtered off, and the filtrate was concentrated. The residue was combined with the isolated precipitate and dissolved in H_2O (100 mL). The solution was saturated with NaCl and extracted with $CHCl_3$ (5×50 mL), the extract was dried with $MgSO_4$ and concentrated. The residue was treated with hexane, and the precipitate was filtered off to give 26.67 g of **4a**.

1,4-Dimethoxy-5,6-pentamethylenepiperazine-2,3-dione (4b) was obtained from **3b** similarly to **4a** by the procedure *B*.

1,4-Dimethoxy-4a-methylperhydroquinoxaline-2,3-dione (4c) was obtained in 16 % yield similarly to **4a** (the residue was chromatographed on a silica gel column using ether as the eluent) and from **3c** by the procedure *B*.

1,2-Bis(methoxyamino)cyclohexane (1a) and its dihydrochloride (1a · 2HCl). *A.* Compound **4a** (1.60 g, 7.02 mmol) was added to a solution of KOH (1.23 g, 22.0 mmol) in MeOH (15 mL). The mixture was refluxed for 16 h, the precipitate was filtered off, and methanol was evaporated. The residue was treated with H_2O (10 mL) and extracted with $CHCl_3$ (4×10 mL). The extract was dried with $MgSO_4$ and concentrated. The residue was dissolved in dry ether (20 mL) and the solution was added to a solution of ether saturated with hydrogen chloride (30 mL). The precipitate formed was filtered off to give 1.47 g of BMA dihydrochloride **1a (1a · 2HCl)**.

B. A solution of **4a** (22.38 g, 98.2 mmol) in a 6 % solution of hydrogen chloride in MeOH (2.5 mL of the solution per mmol of the diether) was refluxed for 11 h; the mixture

was cooled, 30 % aqueous NaOH was added to pH 8, and filtered. The filtrate was concentrated, H_2O (25 mL) was added to the residue, and the solution was extracted with $CHCl_3$ (4×50 mL). The extract was dried with $MgSO_4$ and concentrated. The residue was chromatographed on a silica gel column (eluent hexane—ether, 2 : 1) to give 14.91 g (87 %) of BMA **1a**.

1,2-Bis(methoxyamino)cycloheptane (1b) was obtained from **4b** in 86 % yield similarly to **1a** by the procedure ***B*** (the mixture was refluxed for 5.5 h).

1,2-Bis(methoxyamino)cycloheptane dihydrochloride (1b · 2HCl). Ether (4 mL) saturated with hydrogen chloride was added to a solution of BMA **1b** (0.19 g, 1 mmol) in ether (10 mL). The precipitate was triturated and filtered off to give 0.23 g of BMA **1b** dihydrochloride **(1b · 2HCl)**.

1,2-Bis(methoxyamino)-1-methyl-cyclohexane (1c) was obtained from **4c** in 84 % yield similarly to **1a** by the procedure ***B*** (the reaction mixture was refluxed for 15 h).

1,2-Bis(methoxyamino)-1-methyl-cyclohexane dihydrochloride (1c · 2HCl) was obtained from the BMA **1c** similarly to the **1b · 2HCl**.

1,3-Dimethoxyperhydrobenzimidazole (6). A 30 % aqueous solution of CH_2O (0.096 mL) was added to a solution of bismethoxyamine **1a** (0.17 g, 0.98 mmol) in MeOH (2 mL). The mixture was allowed to stand for 2 h and then concentrated. The residue was treated with H_2O (5 mL) and extracted with CH_2Cl_2 (3×3 mL). The extract was dried with $MgSO_4$ and concentrated *in vacuo* to give 0.15 g of **6**.

5a,10a-Dihydroxy-5,11-dimethoxy-10-oxo-1,2,3,4,4a,5,5a,10a,11,11a-decahydro-10*H*-indeno[1,2-*b*]pyrazine (7). A solution of ninhydrin (0.20 g, 1.12 mmol) in MeOH (1.5 mL) was added to a solution of bismethoxyamine **1a** (0.20 g, 1.15 mmol) in MeOH (1.5 mL). The mixture was allowed to stand for 2.5 h, and the colorless crystals were then filtered off and washed with MeOH (5 mL) to give 0.12 g of **7**.

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