SYNTHESES OF PIPERAZINES SUBSTITUTED ON THE NITROGEN ATOMS WITH ALLYL, PROPYL, 2-HYDROXYPROPYL AND 3-HYDROXYPROPYL GROUPS

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The paper describes synthesis of 1,4-diallylpiperazine (*I*), 1-allylpiperazine (*III*), 1-propylpiperazine (*IV*), 1-(1-piperazinyl)-2-propanol (*V*), 3-(1-piperazinyl)-1-propanol (*VI*), 1-allyl-4-propylpiperazine (*VII*), 1-(4-allyl-1-piperazinyl)-2-propanol (*VIII*), 3-(4-allyl-1-piperazinyl)-1-propanol (*IX*), 1,4-dipropylpiperazine (*X*), 1-(4-propyl-1-piperazinyl)-2-propanol (*XI*), 3-(4-propyl-1-piperazinyl)-1-propanol (*XII*), 1,4-bis(2-hydroxypropyl)piperazine (*XIII*), 3-[4-(2-hydroxypropyl)-1-piperazinyl]-1-propanol (*XIV*) and 1,4-bis(3-hydroxypropyl)piperazine (*XV*). Retention indices of *I*—*XV* are reported and mass spectra of the compounds are discussed.

In connection with hydroboration of 1,4-diallylpiperazine[1] (*I*) we needed all possible piperazine derivatives bearing allyl, propyl, 2-hydroxypropyl or 3-hydroxypropyl groups on the nitrogen atoms and to distinguish them analytically. These are the following compounds: compound *I*, piperazine (*II*), 1-allylpiperazine (*III*), 1-propylpiperazine (*IV*), 1-(1-piperazinyl)-2-propanol (*V*), 3-(1-piperazinyl)-1-propanol (*VI*), 1-allyl-4-propylpiperazine (*VII*), 1-(4-allyl-1-piperazinyl)-2-propanol (*VIII*), 3-(4-allyl-1-piperazinyl)-1-propanol (*IX*), 1,4-dipropylpiperazine (*X*), 1-(4-propyl-1-piperazinyl)-2-propanol (*XI*), 3-(4-propyl-1-piperazinyl)-1-propanol (*XII*), 1,4-bis(2-hydroxypropyl)piperazine (*XIII*), 3-[4-(2-hydroxypropyl)-1-piperazinyl]-1-propanol (*XIV*) and 1,4-bis(3-hydroxypropyl)piperazine (*XV*). The compounds *VII*, *VIII*, *XI*, *XII* and *XIV* were unknown; compounds *I*, *IV*, *V*, *IX*, *X* and *XIII* were prepared by new procedures.

The derivatives *I* and *X* were synthesized by reaction of piperazine hexahydrate with two equivalents of allyl bromide and propyl bromide, respectively, in aqueous sodium hydroxide–dichloromethane in the presence of triethylbenzylammonium chloride. The compound *IV* was formed by the same method using a 1 : 1 molar ratio of the reactants; however, it could not be isolated by distillation. It was therefore converted into 1-benzoyl-4-propylpiperazine (*XVI*) by Schotten–Baumann

benzoylation of the reaction mixture. Subsequent hydrolysis of *XVI* with hydrochloric acid gave the compound *IV*.

The alcohol *V* was obtained by lithium aluminium hydride reduction of 1-(2-hydroxypropanoyl)piperazine (*XVII*) prepared from the compound *II* by reaction with ethyl 2-hydroxypropanoate. Similarly, 1-(4-allyl-1-piperazinyl)-2-propanone (*XVIII*), 1-(4-propanoyl-1-piperazinyl)-2-propanone (*XIX*), 3-(4-propanoyl-1-piperazinyl)propyl propanoate (*XX*), 1,4-bis(2,3-epoxypropyl)piperazine (*XXI*), 3-[4-(2-oxopropyl)-1--piperazinyl]-1-propanol (*XXII*) and 1,4-bis(2-methoxycarbonylethyl)piperazine were reduced to give compounds *VIII*, *XI*, *XII*, *XIII*, *XIV* and *XV*, respectively. The compounds *XVIII*, *XIX* and *XXII* were prepared by reaction of 1-chloro-2-propanone with compound *III*, 1-propanoylpiperazine (*XXIII*) and the alcohol *VI*, respectively, in the presence of potassium carbonate, the compound *XIX* being characterized only by its ^{1}H NMR spectrum. Reaction of *II* with methyl propanoate gave the derivative *XXIII*, the ester *XX* was formed by treatment of the alcohol *VI* with propanoic acid anhydride in methanol.

Compound *VII* was prepared by reaction of 1-allylpiperazine (*III*) with propyl bromide in the presence of potassium carbonate, the derivative *IX* was obtained analogously from the alcohol *VI* and allyl bromide.

The compounds *I*–*XV* were identified by gas–liquid chromatography and mass spectrometry. The pertinent retention indices are given in Table I. Mass spectra were measured using both direct inlet and the GC/MS technique. The spectra obtained in both ways were identical indicating that no decomposition of the compounds occurred during gas–liquid chromatography. The mass spectral data are given in Table II.

The cleavage of the side-chain between the α and β carbon atoms is characteristic of compounds with at least one 2-hydroxypropyl group but without 3-hydroxypropyl group as the second substituent (compounds *V*, *VIII*, *XI* and *XIII*). In these compounds the $(M-45)^+$ ion corresponds to the base peak. In the spectra of 3-hydroxy-

TABLE I
Retention indices (RI) of compounds *I*–*XV*

Compound	RI	Compound	RI	Compound	RI
II	1 190	*I*	1 360	*XII*	1 868
IV	1 264	*V*	1 630	*IX*	1 900
III	1 280	*XI*	1 669	*XIII*	2 092
X	1 313	*VIII*	1 689	*XIV*	2 318
VII	1 344	*VI*	1 816	*XV*	2 535

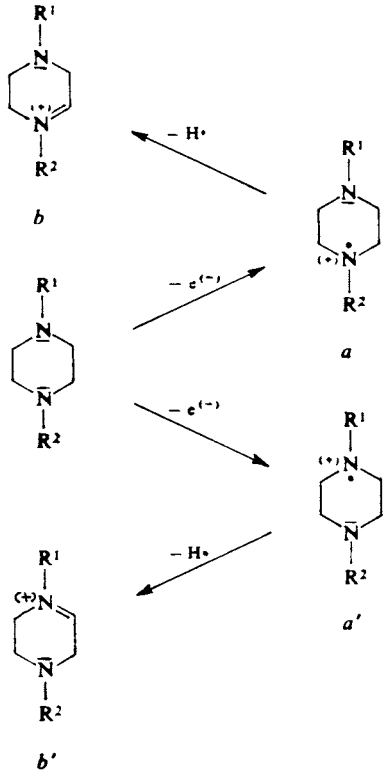
TABLE II

Mass spectra of compounds *I*—*XV*

Compound	M^+,%	*m*/*z*, %									
II	86(30)	44(100)	51(56)	29(52)	28(47)	43(45)	30(38)	56(36)	85(33)	41(31)	86(30)
III	126(18)	84(100)	41(48)	42(39)	56(38)	28(28)	126(18)	29(16)	30(14)	70(13)	51(13)
IV	128(25)	86(100)	99(91)[a]	56(63)	42(59)	44(38)	28(36)	70(32)	128(25)	30(21)	41(19)
V	144(0·5)	99(100)[b]	56(51)	44(28)	100(27)	70(26)	28(25)	42(33)	43(18)	58(13)	29(12)
VI	144(2·5)	58(100)	99(93)[b]	56(69)	43(68)	28(65)	42(56)	44(50)	29(43)	51(38)	31(38)
I	166(30)	41(100)	42(38)	70(63)	125(51)	56(45)	96(40)	28(30)	166(30)	68(25)	69(24)
VII	168(47)	42(100)	41(70)	70(67)	72(63)	139(63)[a]	56(63)	44(50)	158(47)	28(46)	43(40)
VIII	184(0)	139(100)[b]	42(64)	70(64)	41(48)	140(37)	96(34)	97(32)	56(30)	43(23)	28(21)
IX	184(25)	43(100)	42(69)	41(50)	70(50)	56(44)	58(38)	88(38)	139(35)[b]	44(33)	28(31)
X	170(33)	141(100)[a]	56(87)	42(70)	70(59)	98(47)	170(33)	72(33)	43(31)	41(25)	28(24)
XI	186(1·0)	141(100)[b]	70(59)	98(46)	42(44)	142(39)	56(33)	28(26)	43(25)	113(15)	41(15)
XII	186(49)	56(100)	70(86)	42(82)	141(64)[b]	43(72)	127(62)	28(57)	186(49)	98(40)	51(35)
XIII	202(0)	151(100)[b]	70(52)	42(49)	114(36)	43(36)	56(35)	98(34)	58(31)	28(29)	51(23)
XIV	202(0·2)	70(100)	127(79)	43(78)	42(65)	56(50)	51(50)	151(43)[b]	28(42)	98(36)	71(36)
XV	202(13)	43(100)	70(70)	51(63)	56(53)	42(51)	127(43)	71(34)	44(31)	31(30)	41(30)

[a] $(M-29)^+$; [b] $(M-45)^+$.

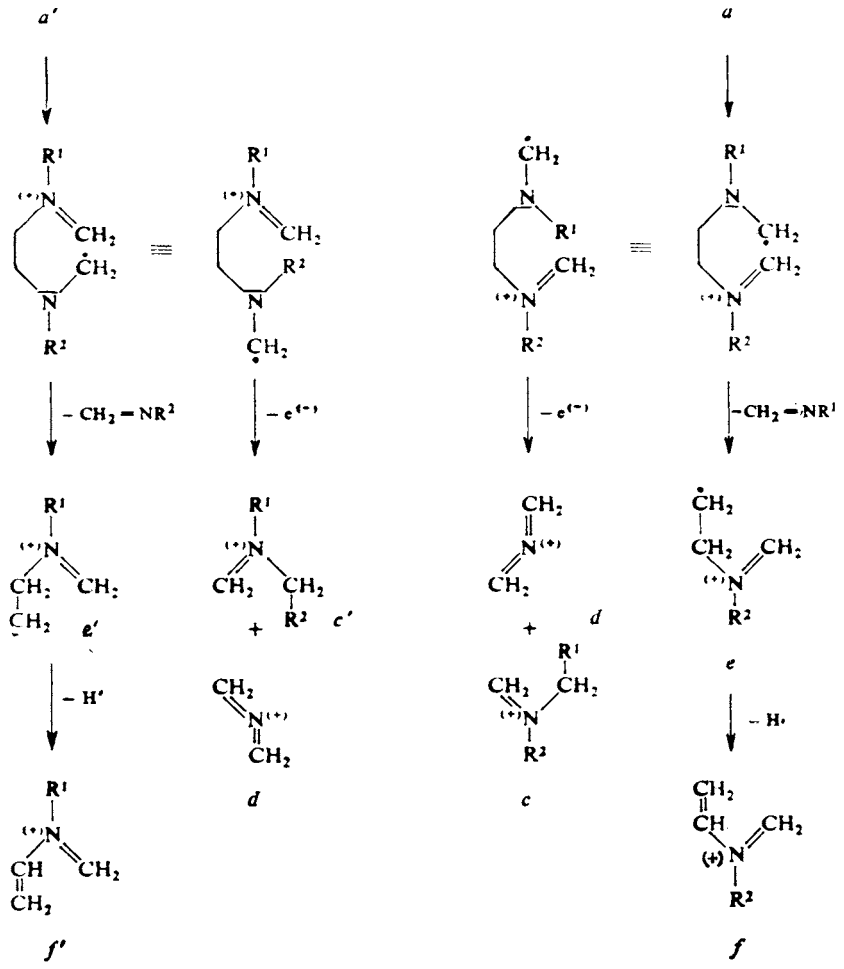
propyl derivatives the ion $(M-45)^+$ is less abundant (compounds *VI*, *IX*, *XII*, *XIV* and *XV*). A similar situation exists with compounds containing a propyl group (compounds *IV*, *VII*, *X*, *XI* and *XII*): the ion $(M-29)^+$ corresponds to the base peak only in the spectrum of compound *X* in which the second nitrogen bears also a propyl group. Still less abundant $(M-27)^+$ ions arise by cleavage of allyl groups (compounds *I*, *III*, *VII*, *VIII* and *IX*). The spectra of the 2-hydroxypropyl and 3-hydroxypropyl derivatives differ also in the abundance of the $(M-15)^+$ ion which for compounds *VI*, *IX*, *XII* and *XV* is negligible. Peaks due to molecular ions of significant intensity (25–50% of the base peak) occur in the spectra of all compounds containing allyl or propyl groups except compounds *VIII* and *XI* in which the second nitrogen atom bears a 2-hydroxypropyl group. The intensity of the molecular ion peak in the spectra of the 3-hydroxypropyl derivatives depends on the substituent at the second nitrogen atom and decreases in the order propyl (*XII*), allyl (*IX*), hydrogen (*VI*), 3-hydroxypropyl (*XV*) and 2-hydroxypropyl (*XIV*). The compound *XIII* gives no molecular ion at all.



SCHEME 1

It is thus evident that, in comparison with piperazine (*II*), the molecular ion is stabilized by propyl and allyl groups bonded to the nitrogen atoms and destabilized by 3-hydroxypropyl and particularly 2-hydroxypropyl groups.

The mass spectrum of the unsubstituted piperazine (*II*) has already been interpreted[2]. We assume that the fragmentation pattern is analogous for all the compounds *I*–*XV* studied by us (Scheme 1, 2). The spectra of the monosubstituted piperazines *III*–*VI* contain the following most abundant ions (*m*/*z*): for compound *III* 126 (*a*, *a'*), 96 (*f*), 84 (*c*, *c'*) and 56 (*f'*); for compound *IV* 128 (*a*, *a'*), 99 (*e*), 86 (*c*, *c'*) and 56 (*f'*); for compounds *V* and *VI* 144 (*a*, *a'*), 143 (*b*, *b'*), 102 (*c*, *c'*) and 56 (*f'*).



SCHEME 2

In the case of the N,N′-disubstituted piperazines with different substituents (*VII* to *IX*, *XI*, *XII* and *XIV*) the situation is more complicated because in addition to the concurrent fragmentation at both nitrogen atoms also the difference between the substituents must be considered. Neither of the N,N′-disubstituted piperazines *I* and *VII*–*XV* gives rise to any *c* or *c′* ions which indicates that the ions at *m/z* 42 are not formed by the McLafferty rearrangement. The homologous series of ions at *m/z* (28 + 14n) present in the spectra of all the studied compounds (*I*–*XV*) is also of interest. The most abundant ions of this series are those at *m/z* 70 and 42. Similarly as in the case of aliphatic alcohols, the spectra of the 3-hydroxypropyl derivatives *VI*, *IX*, *XII* and *XV* show ions at *m/z* 31 and spectra of 2-hydroxypropyl derivatives *V*, *VIII*, *XI*, *XIII* and *XIV* ions at *m/z* 45.

I, $R^1 = R^2 = CH_2CH{=}CH_2$
II, $R^1 = R^2 = H$
III, $R^1 = H$, $R^2 = CH_2CH{=}CH_2$
IV, $R^1 = H$, $R^2 = CH_2CH_2CH_3$
V, $R^1 = H$, $R^2 = CH_2CH(OH)CH_3$
VI, $R^1 = H$, $R^2 = CH_2CH_2CH_2OH$
VII, $R^1 = CH_2CH{=}CH_2$, $R^2 = CH_2CH_2CH_3$
VIII, $R^1 = CH_2CH{=}CH_2$, $R^2 = CH_2CH(OH)CH_3$
IX, $R^1 = CH_2CH{=}CH_2$, $R^2 = CH_2CH_2CH_2OH$
X, $R^1 = R^2 = CH_2CH_2CH_3$
XI, $R^1 = CH_2CH_2CH_3$, $R^2 = CH_2CH(OH)CH_3$
XII, $R^1 = CH_2CH_2CH_3$, $R^2 = CH_2CH_2CH_2OH$
XIII, $R^1 = R^2 = CH_2CH(OH)CH_3$
XIV, $R^1 = CH_2CH(OH)CH_3$, $R^2 = CH_2CH_2CH_2OH$
XV, $R^1 = R^2 = CH_2CH_2CH_2OH$
XVI, $R^1 = COC_6H_5$, $R^2 = CH_2CH_2CH_3$
XVII, $R^1 = H$, $R^2 = COCH(OH)CH_3$
XVIII, $R^1 = CH_2CH{=}CH_2$, $R^2 = CH_2COCH_3$
XIX, $R^1 = COCH_2CH_3$, $R^2 = CH_2COCH_3$
XX, $R^1 = COCH_2CH_3$, $R^2 = CH_2CH_2CH_2OOCCH_2CH_3$
XXI, $R^1 = R^2 =$ 
XXII, $R^1 = CH_2COCH_3$, $R^2 = CH_2CH_2CH_2OH$
XXIII, $R^1 = H$, $R^2 = COCH_2CH_3$

EXPERIMENTAL

The temperature data are uncorrected. Gas–liquid chromatography (GLC) was performed on a Chrom 5 chromatograph (flame-ionization, 2 500 × 3 mm columns). The retention indices were determined (on-column injection) on a column packed with 3% OV-225 silicone elastomer

on Chromaton N-AW-DMCS (0·125—0·16 mm); programmed temperature 80—260°C, 5°C/min, nitrogen flow rate 30 ml/min. Purity of the prepared compounds was checked on a column packed with 10% silicon elastomer E 301 on Chromaton N-AW-DMCS (0·16—0·20 mm). Mass spectra were taken on a Gas Chromatograph — Mass Spectrometer LKB 9 000 (AB Stockholm) at 70 eV; direct inlet or after separation of the compounds by gas–liquid chromatography (the same conditions as for the determination of retention indices except that the carrier gas was helium). ^{1}H NMR Spectra were measured on Varian XL-100-15 (100·1 MHz) or Tesla BS-567 (100·1 MHz) instruments in deuteriochloroform at 31°C; internal standard tetramethylsilane. IR Spectra were recorded on a Perkin–Elmer 325 spectrophotometer.

1,4-Diallylpiperazine (*I*)

A solution of sodium hydroxide (60 g) in water (130 ml) was added to a mixture of dichloromethane (150 ml), piperazine hexahydrate (19·4 g; 100 mmol) and triethylbenzylammonium chloride (4·6 g; 20 mmol). Allyl bromide (24·2 g; 200 mmol) was added under stirring and the mixture was stirred at 40—45°C for 3 h. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 × 25 ml). The extract was combined with the original organic layer, dried over magnesium sulfate and the solvent distilled off through a column. The residue was cooled, the lower of the two layers extracted with ether (2 × 20 ml), the solvent evaporated and the residue added to the upper layer. Distillation afforded 9·1 g (55%) of *I*, b.p. 102—103°C/3·2 kPa (reported[3] b.p. 213°C/761 Torr). ^{1}H NMR Spectrum, ppm: 2·50 (8 H, s) $N(CH_2CH_2)_2N$; 3·02 (4 H, d, J = 6 Hz) 2 $N—CH_2—C$=; 5·04—5·32 (4 H, m) 2 =CH_2; 5·64—6·14 (2 H, m) 2 —CH=.

1-Benzoyl-4-propylpiperazine (*XVI*)

Piperazine hexahydrate (38·8 g; 200 mmol) was treated with propyl bromide (24·6 g; 200 mmol) as described for the preparation of *I*, affording 11·5 g of a mixture of piperazine, 1-propylpiperazine (*IV*) and 1,4-dipropylpiperazine (*X*), b.p. 68—71°C/1·9 kPa. A part of this product (8·5 g; 74%) was mixed with sodium hydroxide (6·6 g) in water (30 ml) and benzoyl chloride (10·2 g; 73 mmol) was added under stirring and cooling with ice. After stirring for 13 h at room temperature, the organic layer was separated and the aqueous one extracted with ether (2 × 25 ml). The extracts were combined with the original organic layer, dried over magnesium sulfate and evaporated to give 4·6 g (13%) of *XVI*, b.p. 116°C/4 Pa. For $C_{14}H_{20}N_2O$ (232·3) calculated: 72·38% C, 8·68% H, 12·06% N; found: 72·14% C, 8·86% H, 12·16% N. ^{1}H NMR Spectrum, ppm: 0·90 (3 H, t, J = 7 Hz) CH_3; 1·50 (2 H, m, $J_{\alpha,\beta} = J_{\beta,\gamma}$ = 7 Hz) C—CH_2—C; 2·20—2·58 (6 H, m) $CH_2—N(CH_2)_2$; 3·28—3·88 (4 H, m) $(CH_2)_2N—CO$; 7·20—7·48 (5 H, m) H_{arom}.

1-Propylpiperazine (*IV*)

A stirred mixture of compound *XVI* (3·0 g; 13 mmol) and 17% hydrochloric acid (24 ml) was refluxed for 5 h. After cooling, the separated benzoic acid was filtered, the filtrate was made alkaline with 30% aqueous potassium hydroxide and extracted with chloroform (3 × 10 ml). The extract was dried over magnesium sulfate and the solvent evaporated, leaving 1·2 g (74%) of *IV*, b.p. 61°C/2·0 kPa (reported[4] b.p. 60—62°C/11 Torr).

1-(2-Hydroxypropanoyl)piperazine (*XVII*)

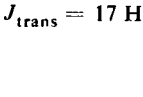
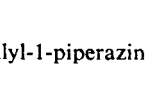
A suspension of compound *II* (8·6 g; 100 mmol) in ethyl 2-hydroxypropanoate (13·0 g; 110 mmol) was stirred at room temperature for 38 h. After 22 h the mixture turned into a clear solution which,

however, still contained the starting compound, as shown by GLC (E 301, 100°C for 6 min, then programme 100–220°C, 20°C/min). The mixture was therefore heated to 50°C for 150 h. Fractionation gave 5·1 g (32%) of *XVII*, b.p. 152–156°C/17 Pa. For $C_7H_{14}N_2O_2$ (158·2) calculated: 53·14% C, 8·92% H, 17·71% N; found: 53·13% C, 9·08% H, 17·65% N. ^{1}H NMR Spectrum, ppm: 1·31 (3 H, d, J = 7 Hz) CH_3; 2·73–3·03 (6 H, m) CH_2NHCH_2 and OH; 3·24 to 3·48 (2 H, m) and 3·48–3·73 (2 H, m) (at 60°C singlet at 3·48 ppm) $(CH_2)_2N$—CO; 4·41 (1 H, q) CH—O. IR Spectrum (CCl_4), cm^{-1}: 3 280–3 420 ν(OH); 1 640 ν(CO).

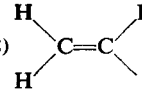
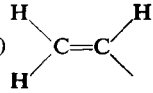
1-(1-Piperazinyl)-2-propanol (*V*)

A solution of compound *XVII* (4·3 g; 27 mmol) in tetrahydrofuran (25 ml) was added dropwise to a stirred suspension of 95% lithium aluminium hydride (1·6 g; 40 mmol) in ether (185 ml). The mixture was refluxed for 3 h with stirring, cooled and the excess hydride was decomposed with 4% sodium hydroxide (6·0 ml). The solid material was filtered and washed with tetrahydrofuran (40 ml). The filtrate was dried over potassium carbonate and the solvents were evaporated, affording 1·35 g (34%) of *V*, b.p. 108°C/1·3 kPa. ^{1}H NMR Spectrum, ppm: 1·11 (3 H, d, J = = 6 Hz) CH_3; 1·99–2·29 (8 H, m) $(CH_2)_2N$—CH_2, OH and NH; 2·85 (4 H, t, J = 5 Hz) CH_2NHCH_2; 3·60–3·94 (1 H, m) CH—O.

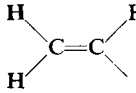
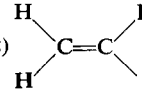
1-Allyl-4-propylpiperazine (*VII*)

Propyl bromide (4·9 g; 40 mmol) in acetone (4 ml) was added dropwise to a stirred mixture of potassium carbonate (6·1 g; 44 mmol), compound *III* (ref.[5,6]; 5·0 g; 40 mmol) and acetone (10 ml). After refluxing for 13 h with stirring, the solid was filtered and washed with ether. The filtrate was taken down affording 4·6 g (69%) of *VII*, b.p. 76°C/1·1 kPa. For $C_{10}H_{20}N_2$ (168·3) calculated: 71·37% C, 11·98% H, 16·65% N; found: 71·26% C, 12·02% H, 16·76% N. ^{1}H NMR Spectrum, ppm: 0·89 (3 H, t, J = 7·5 Hz) CH_3; 1·46 (2 H, m, $J_{\alpha',\beta'} = J_{\beta',\gamma'}$ = 7·5 Hz) C—CH_2—C; 2·30 (2 H, t, J = 7·5 Hz) N—CH_2—C—; 2·48 (8 H, bs) $N(CH_2CH_2)_2N$; 3·00 (2 H, d, J = 6 Hz) N—CH_2—C=; 5·11 (1 H, d, J_{cis} = 11 Hz)  ; 5·16 (1 H, d, J_{trans} = = 17 Hz)  ; 5·85 (1 H, m, J_{cis} = 11 Hz, J_{trans} = 17 Hz, $J_{\alpha,\beta}$ = 6 Hz) =CH—.

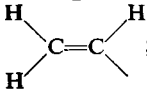
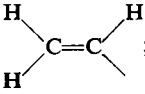
1-(4-Allyl-1-piperazinyl)-2-propanone (*XVIII*)

This compound was prepared by reaction of the compound *III* (ref.[6]; 12·6 g; 100 mmol) with 1-chloro-2-propanone (ref.[7]; 10·2 g; 110 mmol) in the presence of potassium carbonate similarly as the compound *VII*, except that the mixture was stirred for 12 h at room temperature. Yield 9·1 g (50%) of *XVIII*, b.p. 111–112·5°C/1·3 kPa. For $C_{10}H_{18}N_2O$ (182·3) calculated: 65·90% C, 9·95% H, 15·37% N; found: 65·78% C, 9·83% H, 15·57% N. ^{1}H NMR Spectrum, ppm: 2·16 (3 H, s) CH_3; 2·52 (8 H, bs) $N(CH_2CH_2)_2N$; 3·01 (2 H, d, J = 6 Hz) CH_2—C=; 3·19 (2 H, s) CH_2—CO; 5·13 (1 H, d, J_{cis} = 10 Hz)  ; 5·16 (1 H, d, J_{trans} = 17 Hz)  ; 5·84 (1 H, $J_{\alpha,\beta}$ = 6 Hz) J_{cis} = 10 Hz, J_{trans} = 17 Hz) =CH—. IR Spectrum (CCl_4), cm^{-1}: 1 635 (w) ν(C=C); 1 710 (s) ν(C=O).

1-(4-Allyl-1-piperazinyl)-2-propanol (*VIII*)

The title compound was obtained by reduction of the compound *XVIII* (2·0 g; 11 mmol) with lithium aluminium hydride (0·2 g; 5 mmol) in ether as described for the preparation of *V*; yield 1·6 g (79%) of *VIII*, b.p. 105°C/1·3 kPa. For $C_{10}H_{20}N_2O$ (184·3) calculated: 65·18% C, 10·94% H, 15·20% N; found: 65·36% C, 10·94% H, 15·94% N. ^{1}H NMR Spectrum, ppm: 1·11 (3 H, d, J = 6 Hz) CH_3; 1·92–2·84 (10 H, m) $N(CH_2CH_2)_2N—CH_2—C—O$; 2·40 (1 H, s) OH; 2·99 (2 H, d, J = 6 Hz) $CH_2—C=$; 3·60–4·02 (1 H, m) CH—O; 5·12 (1 H, d, J_{cis} = 11 Hz)  ; 5·16 (1 H, d, J_{trans} = 17 Hz)  ; 5·84 (1 H, m, $J_{\alpha,\beta}$ = 6 Hz, J_{cis} = = 11 Hz, J_{trans} = 17 Hz).

3-(4-Allyl-1-piperazinyl)-1-propanol (*IX*)

This compound was prepared by reaction of the alcohol *VI* (5·0 g; 35 mmol) with allyl bromide (4·2 g; 35 mmol) in acetone (12·5 ml) in the presence of potassium carbonate (5·4 g; 39 mmol) analogously as described for compound *VII*; yield 3·1 g (49%) of *IX*, b.p. 130–132°C/1·5 kPa (reported[8] b.p. 120–124°C/3 Torr). ^{1}H NMR Spectrum, ppm: 1·72 (2 H, m, J = 6 Hz) C—CH_2—C; 2·24–2·94 (10 H, m) $N(CH_2CH_2)_2NCH_2—C$; 3·00 (2 H, d, $J_{\alpha,\beta}$ = 6 Hz) $CH_2—C=$; 3·77 (2 H, t, J = 4·5 Hz) $CH_2—O$; 4·88 (1 H, s) OH; 5·13 (1 H, d, J_{cis} = 11 Hz)  ; 5·16 (1 H, s, J_{trans} = 17 Hz)  ; 5·84 (1 H, m, $J_{\alpha,\beta}$ = 6 Hz, J_{cis} = 11 Hz, J_{trans} = = 17 Hz) —CH=.

1,4-Dipropylpiperazine (*X*)

The compound was obtained from piperazine hexahydrate (19·4 g; 100 mmol) and propyl bromide (24·6 g; 200 mmol) as described for compound *I* except that the reaction time was 6 h. The product (8·15 g; 48%) boiled at 101–102°C/5·3 kPa or at 86°C/1·6 kPa (reported[9] b.p. 84°C/10 Torr). ^{1}H NMR Spectrum, ppm: 0·90 (6 H, t, J = 7·5 Hz) 2 CH_3; 1·51 (4 H, m, $J_{\alpha,\beta}$ = = $J_{\beta,\gamma}$ = 7·5 Hz) 2 C—CH_2—C; 2·31 (4 H, t, J = 7·5 Hz) 2 N—CH_2—C—C; 2·48 (4 H, bs) $N(CH_2CH_2)_2N$.

1-Propanoylpiperazine (*XXIII*)

A solution of compound *II* (5·0 g; 58 mmol) in methyl propanoate (70 ml) was refluxed for 45 h, the unreacted compounds were evaporated and the product was distilled, giving 2·5 g (30%) of *XXIII*, b.p. 135–138°C/1·9 kPa; 98–100°C/8 Pa. For $C_7H_{14}N_2O$ (142·2) calculated: 59·12% C, 9·92% H, 19·70% N; found: 59·19% C, 10·01% H, 19·60% N. ^{1}H NMR Spectrum, ppm: 1·14 (3 H, t, J = 7 Hz) CH_3; 2·43 (2 H, q, J = 7 Hz) $COCH_2$; 2·76–3·20 (5 H, m) CH_2NHCH_2; 3·40–3·82 (4 H, m) $(CH_2)_2N—CO$.

1-(4-Propyl-1-piperazinyl)-2-propanol (*XI*)

A solution of 1-chloro-2-propanone[10] (1·0 g; 11 mmol) in 2-butanone (1 ml) was added to a mixture of *XXIII* (1·6 g; 11 mmol), potassium carbonate (1·7 g; 12 mmol) and 2-butanone (8·5 ml)

After stirring for 45 min at room temperature, the solid was filtered off and washed with chloroform. The filtrate was taken down, leaving a crystalline material, melting at 55–62°C. According to ^{1}H NMR spectrum, the product corresponded to the desired 1-(4-propanoyl-1-piperazinyl)--2-propanone (*XIX*) containing about 25% (mol) of compound *XXIII*. ^{1}H NMR Spectrum, ppm: 1·13 (3 H, t, J = 7 Hz) CH_3—C—CO; 2·13 (3 H, s) CH_3CO; 2·19–2·59 (6 H, m) CH_2CON and $(CH_2)_2N$—C—CO; 3·19 (2 H, m) N—CH_2—CO; 3·37—3·86 (4 H, m) $(CH_2)_2NCO$.

This product (1·7 g; 85%) was reduced with 70% lithium aluminium hydride (1·0 g; 18 mmol) in tetrahydrofuran as described for the preparation of *V*, affording 0·9 g (51%) of *XI*, b.p. 110°C/1·5 kPa. For $C_{10}H_{22}N_2O$ (186·3) calculated: 64·47% C, 11·90% H, 15·04% N; found: 64·37% C, 11·98% H, 14·94% N. ^{1}H NMR Spectrum, ppm: 0·89 (3 H, t, J = 7 Hz) CH_3CH_2; 1·12 (3 H, d, J = 6 Hz) CH_3—C—O; 1·49 (2 H, m, $J_{\alpha,\beta} = J_{\beta,\gamma}$ = 7 Hz) C—CH_2—C; 2·17 to 2·80 (12 H, m) CH_2—N$(CH_2CH_2)_2$N—CH_2; 3·33 (1 H, s) OH; 3·58–4·00 (1 H, m) CH—O.

3-(4-Propanoyl-1-piperazinyl)propyl Propanoate (*XX*)

Propanoic acid anhydride (8·2 g; 63 mmol) was added at −70°C to a solution of the alcohol *VI* (1·3 g; 9·0 mmol) in methanol (4·0 ml). The mixture was briefly shaken and allowed to stand overnight. Distillation afforded 2·0 g (87%) of *XX*, b.p. 139–142°C/3 Pa. For $C_{13}H_{24}N_2O_3$ (256·4) calculated: 10·93% N; found: 11·06% N. ^{1}H NMR Spectrum, ppm: 1·13 (6 H, t, J = = 7·5 Hz) 2 CH_3; 1·80 (2 H, m, $J_{\alpha,\beta} = J_{\beta,\gamma}$ = 6·5 Hz) N—C—CH_2—C—O; 2·17–2·60 (10 H, m) $CH_2N(CH_2CH_2)_2N$; 3·31–3·76 (4 H, m) 2 CH_2—C=O; 4·09 (2 H, t, J = 6·5 Hz) CH_2—O. IR Spectrum (CCl_4), cm^{-1}: 1 653 ν(CO) in N—CO—C; 1 740 ν(CO) in C—CO—O.

3-(4-Propyl-1-piperazinyl)-1-propanol (*XII*)

Prepared by reduction of compound *XX* (1·3 g; 5·1 mmol) with 70% lithium aluminium hydride (0·6 g; 10 mmol) in ether as described for the compound *V*. Yield 0·6 g (64%) of *XII*, b.p. 125°C / 1·5 kPa. For $C_{10}H_{22}N_2O$ (186·3) calculated :64·47% C, 11·90% H, 15·04% N; found: 64·63% C, 12·02% H, 14·89% N. ^{1}H NMR Spectrum, ppm: 0·88 (3 H, t, J = 7·5 Hz) CH_3; 1·23–1·83 (5 H, m) 2 C—CH_2—C and OH; 2·14–2·72 (12 H, m) $CH_2N(CH_2CH_2)_2NCH_2$; 3·77 (2 H, t, J = 5 Hz) CH_2—O.

1,4-Bis(2-hydroxypropyl)piperazine (*XIII*)

Prepared by reduction of *XXI* (ref.[10]; 0·95 g; 4·8 mmol) with 95% lithium aluminium hydride (0·4 g; 10 mmol) in tetrahydrofuran as described for the preparation of *V* except that the reaction was carried out at room temperature. Yield 0·58 g (60%) of *XIII*, m.p. 110°C (cyclohexane) (reported[5] m.p. 115–116°C). ^{1}H NMR Spectrum, ppm: 1·11 (6 H, d, J = 6 Hz) 2 CH_3; 2·14 to 2·79 (12 H, m) $CH_2N(CH_2CH_2)_2NCH_2$; 3·29 (2H , s) 2 OH; 3·61 to 3·96 (2 H, m) 2 CH—O.

3-[4-(2-Oxopropyl)-1-piperazinyl]-1-propanol (*XXII*)

This compound was obtained by reaction of the alcohol *VI* (4·9 g; 34 mmol) with 1-chloro-2-propanone[7] (3·4 g; 37 mmol) in the presence of potassium carbonate (5·7 g; 41 mmol) in 2-butanone similarly as described for the preparation of *XVIII*. Yield of *XXII* 4·0 g (59%) b.p. 114–115°C/ 1 Pa. For $C_{10}H_{20}N_2O_2$ (200·3) calculated: 59·97% C, 10·07% H, 13·99% N; found: 60·12% C, 10·53% H, 13·96% N. ^{1}H NMR Spectrum, ppm: 1·21 (2 H, m, $J_{\alpha,\beta} = J_{\beta,\gamma}$ = 5·2 Hz) CH_2— —C—O; 2·13 (3 H, s) CH_3; 2·36–2·75 (10 H, m) CO—C—N$(CH_2CH_2)_2NCH_2$; 3·17 (2 H, s) CO—CH_2—N; 3·76 (2 H, t, J = 5·2 Hz) CH_2—O; 4·63 (1 H, s) OH.

3-[4-(2-Hydroxypropyl)-1-piperazinyl]-1-propanol (*XIV*)

Compound *XXII* (3·7 g; 18 mmol) was reduced with lithium aluminium hydride as described for the preparation of *V*; yield 2·7 g (72%) of the product, b.p. 122–124°C/3 Pa. For $C_{10}H_{22}N_2O_2$ (202·3) calculated: 59·37% C, 10·96% H, 13·85% N; found: 59·02% C, 10·69% H, 14·21% N. ^{1}H NMR Spectrum, ppm: 1·11 (3 H, d, $J = 6$ Hz) CH_3; 1·70 (2 H, m, $J_{\alpha,\beta} = J_{\beta,\gamma} = 5{\cdot}5$ Hz) C—CH_2—C; 2·05–2·30 (2 H, m) N—CH_2—C—C—O; 2·30–2·93 (10 H, m) $N(CH_2CH_2)_2$.NCH_2—C—O; 3·61–3·95 (3 H, m) CH_2—O and CH—O; 3·98 (2 H, s) 2 OH.

1,4-Bis(3-hydroxypropyl)piperazine (*XV*)

1,4-Bis(2-methoxycarbonylethyl)piperazine[11] (12·9 g; 50 mmol) was reduced with 50% lithium aluminium hydride (3·8 g; 50 mmol) in ether as described for the preparation of *V*. Solid matter obtained from quenched reaction mixture on filtration was extracted with boiling methanol (100 ml). The extract was taken down affording 7·3 g (72%) of *XV*, m.p. 142–144°C (ethanol, reported[12] m.p. 143–144°C). ^{1}H NMR Spectrum, ppm: 1·72 (4 H, m, $J_{\alpha,\beta} = J_{\beta,\gamma} = 6$ Hz), 2 C—CH_2—C; 2·54 (12 H, bs) $CH_2N(CH_2CH_2)_2NCH_2$; 3·74 (4 H, t, $J = 6$ Hz) 2 CH_2—O; 4·80 (2 H, s) 2 OH.

The elemental analyses were carried out under supervision of Dr L. Helešic, NMR *spectra were taken under supervision of Dr P. Trška,* IR *spectra were measured by Dr E. Janečková and Dr A. Kohoutová in the Central Laboratories of this Institute.*

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