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PHENETHYLAMINE IN A RIGID FRAMEWORK : SYNTHESIS, STEREOCHEMISTRY AND REACTIONS OF CIS AND TRANS-4-AMINO-2,3,4,5-TETRAHYDRO-1-BENZOXEPIN-5-OLS AND THEIR DERIVATIVES

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Summary - cis- and trans- amino alcohols 1a and 2a and their derivatives have been synthesised and their stereochemistry studied. Stereochemical studies have shown that cis-isomer is thermodynamically more favoured than the trans-isomer.

Acylic compounds can assume a number of conformations, only one of which may fit the receptor best, but in cyclic systems the permissible conformations are limited. If these compounds are found to possess the activity of the prototype, such molecules will then provide useful information about the stereo-structure of the receptors.

In view of this, in a programme for the study of molecules which incorporate a 'Phenethylamino' group in a rigid framework, cis- and trans-6-Amino-6,7,8,9-tetrahydro-5H-benzocyclo-hepten-5-ols were synthesised and their pharmacological action studied.[1-3] The marked α-sympathomimetic activity exhibited by the cis-diastereoisomer prompted us to synthesise cis- and trans-4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ols and their methyl derivatives (1 and 2) and study their pharmacological activity.

Our methods of synthesis of 1 and 2 are different to method earlier reported by Lockhart et al[4] without giving any biological screening results.

3,4-Dihydro-1(2H)-benzoxepin-5-ones (4) needed as starting materials were prepared by cyclization of γ-phenoxybutyric acid 3 according to Scheme 1 by experimental modification of the known methods[4-7] which improved the yields.

4-Oximino-3,4-dihydro-1-(2H)-benzoxepin-5-ones 5, obtained by nitrosation of the ketones 4, on catalytic reduction in presence of 10% Pd/C gave 4-amino-3,4-dihydro-1-(2H)-benzoxepin-5-ones 6 (Scheme-2). Reduction of the Oximino ketones 5 with $LiAlH_4$; of the amino ketones 6 with $LiAlH_4$ or $NaBH_4$ or catalytic hydrogenation using 10% Pd/C gave a mixture of cis- and trans- aminoalcohols (1 and 2), the ratio of the two isomers varied with the method of reduction used and these results are summarised in Table-1.

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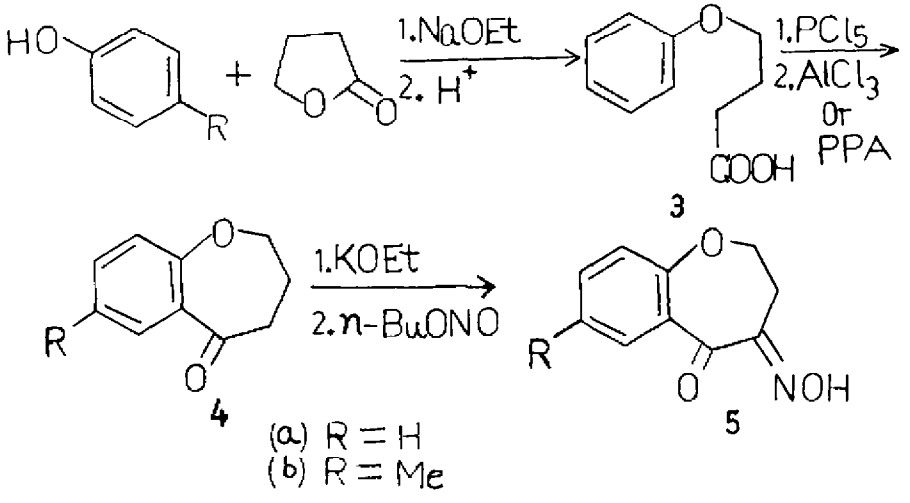
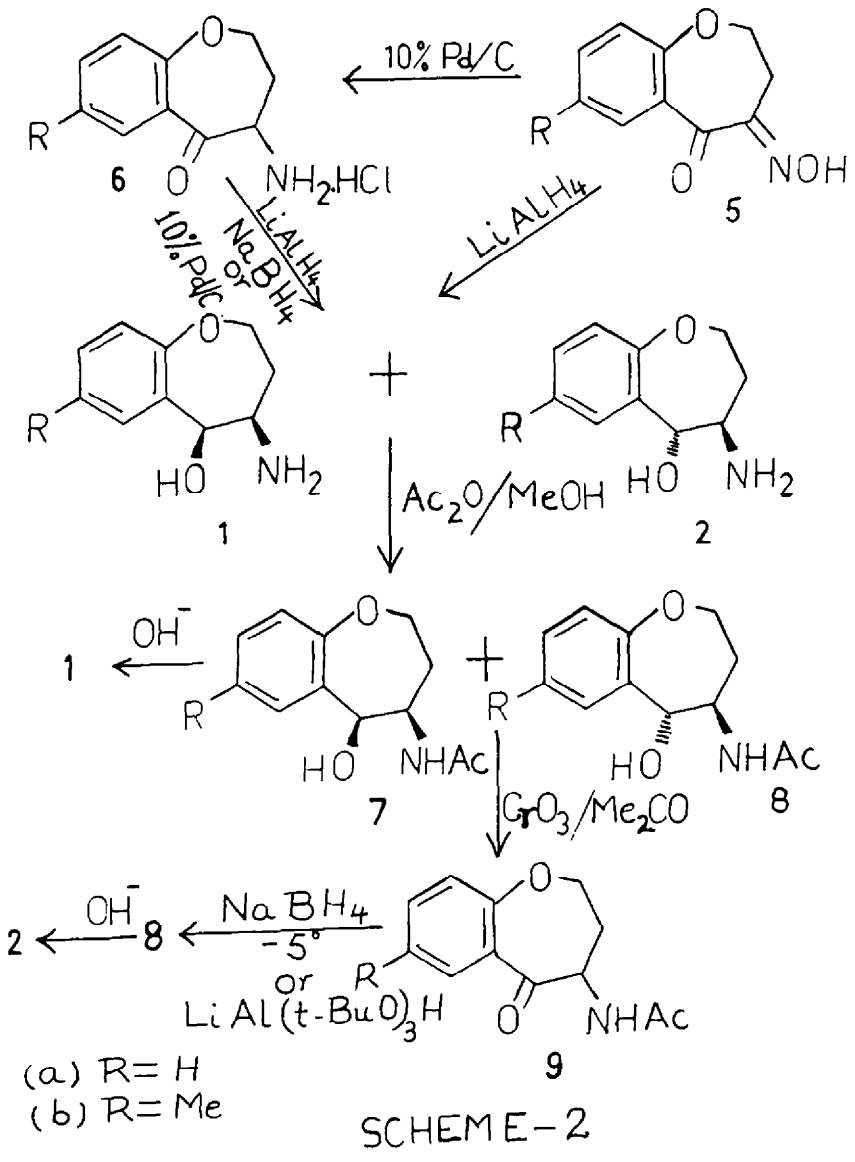


SCHEME-1

Table-1

Compound reduced	Reducing agent	Solvent	Composition of the amino alcohols	
			cis	trans
Oximino ketone 5a	$LiAlH_4$	THF-Et_2O	2	1
Amino ketone 6a	$LiAlH_4$	THF-Et_2O	1	2
Amino ketone 6a	$NaBH_4$	EtOH	2	1
Amino ketone 6a	10% Pd/C,H_2	MeOH-HCl	1	1

The composition of the reaction product was monitored by nmr spectroscopy. All attempts to separate the two isomers were unsuccessful and, therefore, the mixture of amino alcohols 1 and 2 was treated with Ac_2O-MeOH to form 4-acetamino derivatives 7 and 8. Lockhart et al[4] have reported that the mixture of the cis- and trans-acetamido alcohols 7a and 8a could be separated by treatment with 2N HCl when the trans-isomer goes into the the solution forming O-acetyl derivatives without inversion while the cis- isomer remains unchanged. In our hands Lockhart's[4] method of separation did not prove successful and the following procedure proved more convenient for preparing the cis- and trans-isomers. The pure cis- 4-acetamido-2,3,4,5-tetrahydro-1-benzoxepin-5-ol 7a was obtained as the less soluble product on crystallisation of the mixture of acetamido alcohols; the pure trans- compound could not be obtained from the mother liquor. For obtaining the trans compound, the mixture was oxidized with Jones[1] reagent to give the acetamido ketone 9a. The stereochemistry of the acetamido alcohols formed by the hydride reduction of ketone 9a was greatly affected by the reaction conditions.



SCHEME-2

Using $NaBH_4$ in a concentrated solution of the acetamido ketone 9a in EtOH, a mixture of cis- and trans- acetamido alcohols 7a and 8a was formed while at high dilution only the trans- isomer was formed. The striking selectivity introduced by high dilution may be due to the more favoured intramolecular delivery of the hydride from a N- complexed boro-hyride complex which would be sterically controlled. Using $LiAl(t\text{-}BuO)_3H$, a bulky hydride with sluggish reducing character instead of $NaBH_4$ under high dilution, the same stereo-selectivity was observed. This clearly indicates that high dilution is not required for high stereoselectivity when $LiAl(t\text{-}BuO)_3H$ is used as reducing agent. These results are summarised in Table 2.

Table 2

Solvent used per m.mole of 9a	Reducing agent (0.005 mole)	Temp. °C	%Composition of acetamido alcohols	
			cis	trans
MeOH (20 ml)	$NaBH_4$	0	10	90
EtOH (25 ml)	$NaBH_4$	-5	20	80
EtOH (5 ml)	$NaBH_4$	100	33	66
EtOH (100 ml)	$NaBH_4$	-5	0	100
RHF (5 ml)	$LiAl(t\text{-}BuO)_3H$	30	0	100

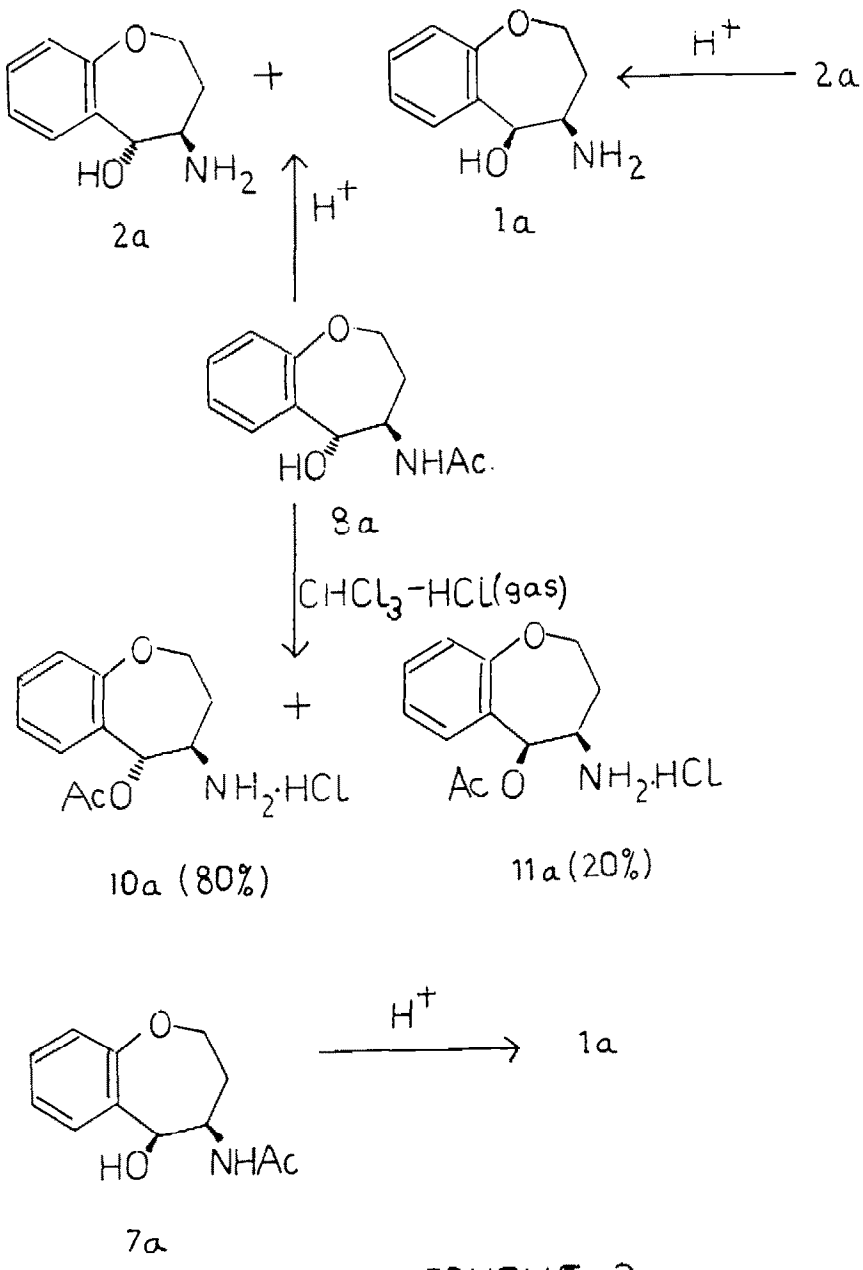
In case of the corresponding 7-methyl derivative, the two acetamido alcohols 7b and 8b were separated by fractional crystallisation from benzene.

Vicinal N-acylamino-alkanols undergo a proton catalysed N→O acyl migration[8-10] without inversion if the cyclic intermediate formation is sterically favoured and with inversion if the cyclic intermediate is sterically not favoured. In our case it was found that the cis-N-acetylamino derivative 7a remained unchanged on treatment with $CHCl_3$-HCl while the trans- N-acetylamino compound 8a on similar treatment gave the trans-O-acetyl cmpound 10a along with a small quantity (~20%) of the cis-O-acetyl compound 11a; the O-acetyl derivatives on treatment with $NaHCO_3$ regenerated the corresponding N-acetyl-amino compounds with inversion (Scheme-3).

Treatment of cis-4-acetamido-2,3,4,5-tetrahydro-1-benzoxepin-5-ol 7a with 3N HCl for 2 h at 100°C gave cis- amino alcohol 1a; similar treatment of cis-4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ol did not cause epimerisation. However, treatment of trans -4-acetamido alcohol 8a or trans 4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ol 2a with 3N HCl for 6 h gave a mixture of cis- and trans- amino alcohols 1a and 2a in the ratio 1:4.

It would thus appear that in 4-amino-1-benzoxepin-5-ols, the cis-stereochemistry is thermodynamically more favoured as compared to the trans-stereochemistry. Base hydrolysis of both cis- and trans-N-acetylamino alcohols regenerated the corresponding amino alcohols.

Stereochemical Assignments :- Like Oxepanes, which are known to exist in boat, twist chair and chair conformations; 1-benzoxepins may also be expected to exist in the above three conformations. However, based on NMR studies (Table 3), it was found that 1a and 2a exist predominantly in boat and twist chair conformations. This is supported by the fact that rate of inversion of boat to chair in Oxepines is greatly reduced by aromatic ring annelation.[11] Table 3 gives the dihedral angle (ϕ) measurements for 4-H and 5-H as measured by examination on the Dreiding models.



SCHEME-3

The nmr spectra of cis- and trans-amino alcohols 1a and 2a are recorded in figure 1. In the nmr spectra of the cis-amino alcohol 1a, 5-H signal appeared at 4.82 δ (d, J = 1.5 Hz). This order of coupling could arise with seven membered ring

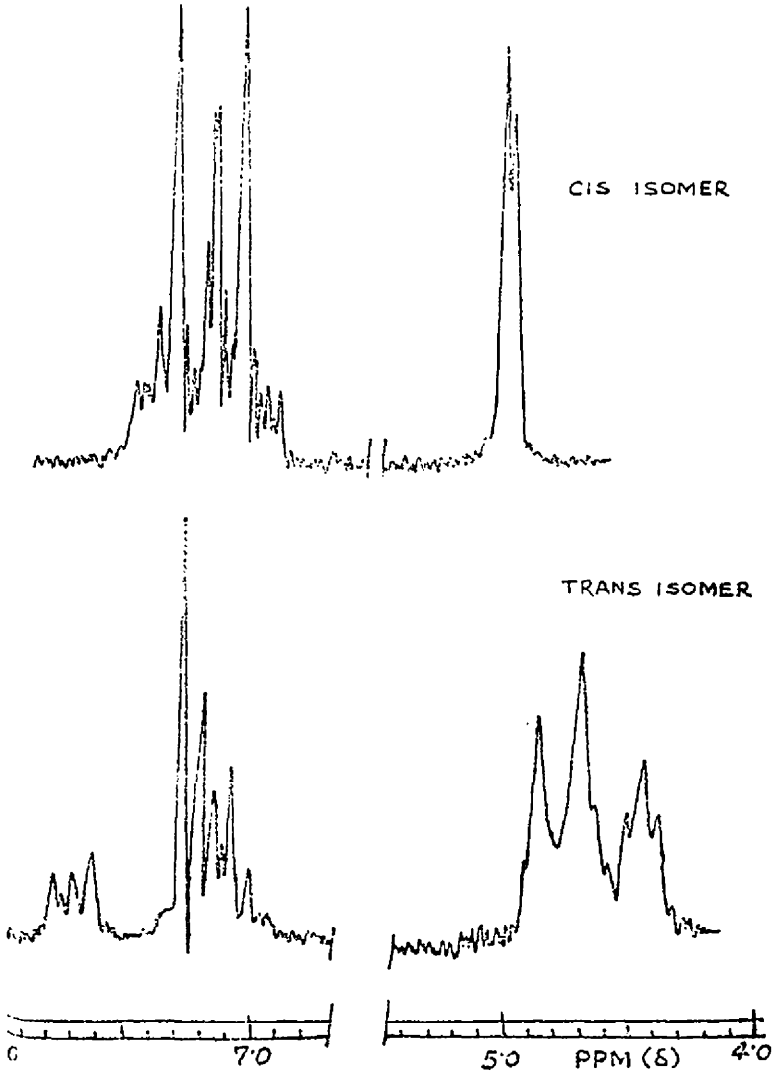


FIGURE 1

^{1}H NMR spectra of cis- and trans-amino alcohols 1a and 2a.

in a boat conformation with 4,5-trans- stereochemistry or in a twist-chair conformation with 4,5-cis-stereochemistry. On the basis of previous work on amino benzocycloheptenols [1-3] and nmr data, this isomer has therefore been assigned 4,5-cis stereochemistry while the isomer 2a, in which 5-H signal appeared at 4.57 δ (d, J = 8.0 Hz), 4,5-trans-stereochemistry. This is further supported by the fact that aromatic 6-H, 7-H, 8-H and 9-H in the cis-isomer appeared as a multiplet centred at 7.1 δ, whereas in the trans-isomer 7-H, 8-H, and 9-H appeared as a multiplet at 7.1 δ but the 6-H signal appeared separately as a multiplet at 7.67 δ. This marked deshielding of the aromatic 6-H in the trans-isomer is caused by the field effect of 5-OH group, which would be quasi-equatorial in this isomer. This would also be consistent with the normal upfield position 4.57 δ of the axial 5-H in the trans-isomer relative to the equatorial 5-H at 4.82 δ in the cis-isomer. In all other cases the isomer having $J_{4,5}$ = 1.5 Hz has been assigned the cis- and the isomer with $J_{4,5}$ = 8.0 Hz a trans- conformation. The IR spectra of the two isomers did not show any marked difference in the OH stretching frequency, but there were significant differences in the fingerprint region.

Table 3

Conformation	Dihedral angle (ϕ)		J_{HH}, Hz for 1a	J_{HH}, Hz for 2a
	cis (1a)	trans (2b)		
Boat	4a,5a = 10°	4a,5a = 110°	8.0	2.0
Chair	4a,5a = 85°	4a,5a = 155°	0.0	9.0
Twist chair	4a,5a = 90°	4a,5a = 170°	0.0	10.0

Pharmacological Activity : The compounds in general exhibited a weak stimulant action and marked anorexigenic activity. The most marked anorexigenic activity was shown by cis- and trans-4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ols 1a and 2a. The LD_{50} in mice is 800 mg/kg and 500 mg/kg and ED_{50} is 75 mg/kg and 55 mg/kg respectively.

EXPERIMENTAL SECTION

General. Melting points were determined with a Townson and Mercer melting point apparatus IR spectra were recorded on a Perkin-Elmer model 137 spectrometer and ^{1}H NMR spectra on a 60 MHz Varian A-60D apparatus in δ units downfield from internal Me_4Si. Elemental microanalysis were carried out in Microanalysis Department of C.D.R.I., Lucknow.

3,4-Dihydro-1-(2H)-benzoxepin-5-one (4a) A mixture of γ-phenoxybutyric acid (1.8 g, 0.01 mol) and Polyphosphoric acid (110 g) was heated on a steam bath for 2 h with occasional shaking. The red coloured syrup thus obtained was poured onto crushed ice, extracted with Et_2O, the extract washed successively with 3N NaOH and H_2O, dried (Na_2SO_4) and.

concentrated under reduced pressure. The crude ketone thus obtained was distilled as a colourless oil; yield 0.9 g (55%); bp. 170-74°C (6 mm Hg) [lit[6] bp. 100-30°C (4 mm Hg)].

7-Methyl-3,4-dihydro-1(2H)-benzoxepin-5-one (4b) A mixture of γ-(4-methylphenoxy) butyric acid (3b: 1.94 g, 0.01 mol) and PCl_5 (2.1 g, 0.01 mol) in dry benzene (30 ml) was refluxed for 1 h and the solution concentrated under reduced pressure. The acid chloride thus obtained was dissolved in dry CS_2 (50 ml) and $AlCl_3$ (5.0 g) added under stirring. After complete addition the whole reaction mixture was refluxed for 3 h, decomposed with ice water and extracted with $CHCl_3$. The chloroform extract was washed with $NaHCO_3$ and H_2O, dried (Na_2SO_4) and concentrated under reduced pressure to give 1.0 g (58%) of 4b as a pale yellow oil; bp 105-8°C (0.5 mm Hg) [lit[6] bp. 114-16°C (0.9 mm Hg)].

4-Oximino-3,4-dihydro-1(2H)-benzoxepin-5-one (5a) A mixture of ketone (4a: 1.62 g, 0.01 mol) and n-butyl nitrite (1.03 g, 0.01 mol) in dry ether (40 ml) was added dropwise to a solution of KOEt [prepared from 0.7 g (0.02 g atom) potassium and 20 ml absolute EtOH] kept below 0°C. The mixture was allowed to stand overnight in a refrigerator, diluted with water and extracted with ether. The aqueous layer was separated, acidified and the crystalline product thus separated was filtered, pale yellow leaflets, yield 1.30 g (69%); mp 125-127°C; IR(KBr) 3200 (NOH), 1665 cm^{-1} (C=O).

7-Methyl-4-oximino-3,4-dihydro-1(2H)-benzoxepin-5-one (5b) was prepared analogously to 5a in 88% yield from 8b: mp 123-124°C.

For compoounds 5a and 5b no elemental analysis could be obtained as these were unstable at room temperature.

4-Amino-3,4-dihydro-1(2H)-benzoxepin-5-one hydrochloride (6a) A solution of oximino ketone (9a; 1.91 g, 0.01 mol), MeOH (40 ml) and conc. HCl (6 ml) was hydrogenated in the presence of 10% Pd/C (0.4 g) at room temperature and atmospheric pressure. After 24 h when the absorption of hydrogen had ceased, the catalyst was filtered off and the filtrate evaporated to dryness under reduced pressure. The residue on crystallization from abs. EtOH-Et_2O gave 6a as colourless crystals, yield 1.1 g (62%); mp 208-210°C (lit[4] mp. 209-212°C); IR(KBr) 3350 (NH), 1680 cm^{-1} (C=O); Anal. Calcd. for $C_{10}H_{11}NO_2$.HCl : C, 56.26; H, 5.62; N, 6.56. Found: C, 56.40; H, 5.43; N, 6.38

7-Methyl-4-amino-3,4-dihydro-1(2H)-benzoxepin-5-one hydrochloride (6b) was prepared in a similar manner from 9b in 53% yield, mp. 198-200°C, IR(KBr) 3360 (NH), 1680 cm^{-1} (C=O); Anal. Calcd. for $C_{11}H_{13}HO_2$.HCl: C, 58.02; H, 6.15; N, 6.15. Found: C, 58.35; H, 6.30; N, 6.43.

cis- and trans-4-Amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ols (1a and 2a)

Method A : By $LiAlH_4$ reduction of 4-oximino-3,4-dihydro-1(2H)-benzoxepin-5-one (5a). A solution of (5a; 1.91 g, 0.01 mol) in dry Et_2O (75 ml) was added dropwise to a suspension

$LiAlH_4$ (1.52 g, 0.04 mol) in 25 ml dry THF. The mixture was stirred for 12 h at room temperature, the complex decomposed with 3N NaOH solution and the mixture was extracted with $CHCl_3$. The $CHCl_3$-extract was dried (Na_2SO_4) and concentrated to give colourless solid; yield 1.0 g (56%); mp. 115-135°C. The nmr spectrum of the crude product showed that the cis and trans isomers are present in equal proportions.

Method B: By $LiAlH_4$ reduction of 4-amino-3,4-dihydro-1(2H)-benzoxepin-5-one hydrochloride (6a). A suspension of (10a; 0.71 g, 0.003 mol) in dry THF (25 ml) was added to a stirred suspension of $LiAlH_4$ (0.76 g, 0.02 mol) in dry THF (25 ml) and the reaction mixture was worked up as described above; colourless product; yield 0.40 g (70%); mp. 108-115°C; NMR spectrum showed the product to be a mixture of cis- and trans- isomers in the ratio 1:2.

Method C: By catalytic reduction of 4-amino-3,4-dihydro-1(2H)-benzoxepin-5-one hydrochloride (6a). A mixture of (6a; 0.71 g, 0.003 mol), MeOH (40 ml) and 10% Pd/C (0.2 g) was hydrogenated at room temperature and atmospheric pressure. After 24 h, the absorption of hydrogen ceased and the catalyst was filtered off. The filtrate was evaporated under reduced pressure and the residue on crystallization from EtOH-H_2O gave colourless needles; yield 0.3 g (83%); mp. 190-200°C; NMR showed it to be mixture of cis- and trans- isomers in the ratio 1:1.

Method D : By $NaBH_4$ reduction of (6a), $NaBH_4$ (0.38 g, 0.01 mol) was added with stirring to a cooled solution of (6a; 0.71 g, 0.003 mol) in absolute EtOH (20 ml). The reaction mixture was stirred for 12 h at room temperature, concentrated under reduced pressure, diluted with water, extracted with $CHCl_3$ and dried (Na_2SO_4). A pale yellow solid was obtained after removing the solvent under reduced pressure, yield 0.5 g (84%); mp. 108-115°C; NMR spectrum showed the product to be a mixture of cis and trans isomers in a ratio of 2:1.

cis-4-Acetamido-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (7a) A mixture of cis- and trans- amino alcohols (1a and 2a; 1.79 g, 0.01 mol), Ac_2O (3.5 ml) and MeOH (50 ml), were refluxed on a steam bath for 4-6 h, cooled and concentrated under reduced pressure. A yellow syrup thus obtained on purification by column chromatography followed by crystallisation from benzene gave cis- acetamido alcohol 7a as colourless needles, yield 0.8 g: mp. 152-153°C; IR(KBr) 3260 (OH), 3160 (NH), 1640 cm^{-1} ($NHCOCH_3$); ^1H NMR ($CDCl_3$) δ 1.95 (s, 3), 4.88 (d,1, $J_{4a,5e}$ 1.5 Hz); Anal. Calcd. for $C_{12}H_{15}NO_3$; C, 65.15; H, 6.79; N, 6.33, Found: C, 65.02; H, 6.99; N, 6.71.

cis-4-Amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (1a)

Method A: A mixture of cis- acetamido alcohol (7a; 0.55 g, 0.0025 mol); MeOH (30 ml) and 10% NaOH (20 ml) was refluxed on a steam bath for 12 h, cooled and MeOH removed under reduced pressure. The product which separated on cooling was filtered, washed with water, dried and crystallised from $CHCl_3$-hexane; yield 0.35 g (78%); mp. 145-146°C;

IR(KBr) 3350 (OH), 3300 cm^{-1} (NH); NMR ($CDCl_3$) δ 3.22 (b, 1), 4.02 (t, 2); 4.82 (d, 1, $J_{4a'5e}$ 1.5 Hz); 6.8-7.5 (m, 4). Hydrochloride crystallised from EtOH:Et_2O; mp. 260°C [lit[4] mp. 255°C); Anal. Calcd. for $C_{10}H_{13}NO_2$.HCl; C, 67.03; H, 7.27; N, 7.82. Found: C,66.70; H, 7.60; N, 7.54.

Method B : cis-Acetamido alcohol 7a (1.0 g) in 3N HCl (50 ml) was heated on a water bath for 3 h, concentrated under reduced pressure and the residue crystallized from EtOH-Et_2O, mp. 260°C; NMR spectra showed the compound to be 1a, identical to the product obtained by Method A.

4-Acetamido-3,4-dihydro-1(2H)-benzoxepin-5-one (9a) Jones reagent (10 ml) was added to a cooled mixture of the acetamido alcohols (7a and 8a; 1.1 g, 0.005 mol) in acetone (100 ml) and the mixture stirred for 2 h. MeOH (10 ml) was added to the mixture, concentrated and diluted with water. The colourless crystalline product thus separated was filtered and dried; yield 1.0 g (92%): ^1H NMR ($CDCl_3$) δ 2.03 (s, 3), 7.0-7.7 (m, 4), 7.83 (d, 1); Anal. Calcd. for $C_{12}H_{13}NO_3$. C, 65.75; H, 5.93; N, 6.39. Found: C, 65.70; H, 6.00, N, 6.03.

trans-4-Acetamido-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (8a)

Method A: $NaBH_4$ (0.38 g, 0.01 mol) was added with stirring at -5°C to a solution of (9a; 0.5 g, 0.0025 mol) in EtOH (250 ml). After 4 h, EtOH was removed under reduced pressure, the residue treated with water, extracted with $CHCl_3$. $CHCl_3$-extract was dried (Na_2SO_4) and concentrated. The residue on crystallization from benzene-hexane gave colourless needles, yield 0.35 g (70%); mp. 138°C (lit[4] mp. 138°C); IR(KBr) 3350 (OH), 3300 (NH) & 1650 cm^{-1} $NHCOCH_3$; ^1H NMR ($CDCl_3$) δ 1.88 (s, 3); 4.65 (d, 1, $J_{4a'5a}$ = 8 Hz); 6.80-7.40 (m, 4); Anal. Calcd. for $C_{12}H_{15}NO_3$; C, 65.15; H, 6.79; N, 6.33. Found: C, 65.34; H, 6.43; N, 6.35.

This reaction has been carried out at different dilutions and temperature and these results are summarised in table 2.

Method B: $LiAl(t\text{-}BuO)_3H$ (0.47 g, 0.0015 mol) was added to a solution of (9a; 218 mg, 0.001 mol) in dry THF (5 mol) with stirring at room temperature. The reaction mixture was stirred at 30°C for 12 h, diluted with water and extracted with $CHCl_3$. The $CHCl_3$-extract was dried (Na_2SO_4) and concentrated. The residue was crystallized from $CHCl_3$-Hexane to give colourless needles; yield 0.2 g (90%); mp. 138°C.

trans-4-Amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (2a)

8a (0.2 g) on base hydrolysis as described above for 1a, gave trans- isomer 2a. Crystallization from $CHCl_3$-hexane gave colourless solid; yield 0.15 g (83%); mp. 153-154°, IR(KBr) 3350 (OH), 3300 cm^{-1} (NH); NMR ($CDCl_3$) δ 4.47 (d, 1, $J_{4a'5a}$ = 8.0 Hz), (7.67, m, 1). Its hydrochloride was crystallized from EtOH-Et_2O; mp. 235°C (lit[4] 234°C); Anal. Calcd. for $C_{10}H_{13}NO_2$.HCl; C, 67.03; H, 7.27; N, 7.82. Found: C, 66.70; H, 7.34; N, 7.63.

Compound 2a or 8a on refluxing with 3N HCl for 3 h gave a mixture of cis- and trans-4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ols in 1:3 ratio.

cis- and trans-5-Acetoxy-4-amino-2,3,4,5-tetrahydro-1-benzoxepin hydrochloride (11a and 10a) A solution of (8a; 220 mg, 0.001 mol) in $CHCl_3$ was saturated with dry HCl gas. The reaction mixture was stirred for 12 h at room temperature, evaporated and the residue crystallized from MeOH-Et_2O; yield 197 mg (77%); mp. 145-152°C; IR(KBr) 3300 (NH), 1765 cm^{-1} (O-C=O); NMR (D_2O) δ 6.00 (d,1, $J_{4a,5a}$ 8.5 Hz), 6.10 (d, 1, $J_{4a,5e}$ 1.0 Hz). Anal. Calcd. for $C_{12}H_{15}NO_3$. HCl; C, 55.92; H, 6.22; N, 5.44. Found C, 55.55; H, 6.52; N, 5.64.

The cis-4-acetamido-2,3,4,5-tetrahydrol-1-benzoxepin-5-ol does not undergo N→O acetyl migration under these conditions.

cis- and trans-7-Methyl-4-acetamido-2,3,4,5-tetrahydro-1-benzoxepin-5-ols (7b and 8b). A solution of (5b; 2.05 g, 0.01 mol) in dry THF (50 ml) was added to a stirred suspension of $LiAlH_4$ (1.14 g, 0.03 mol) in dry Et_2O (50 ml) and the reaction mixture was worked up as described above for isolation of mixture of 1a and 2a. The nmr of the crude product showed it to be a mixture of cis-(60%) and trans- (40%) (1b and 2b) isomers. The crude mixture of amino alcohols was converted into their corresponding acetamido alcohols, as described above for 7a and 8a. Acetamido alcohols 7b and 8b were separated by fractional crystallization from benzene; (i) cis-4-acetamido-7-methyl-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (7b); mp. 153-154°C; ^1H NMR ($CDCl_3$) δ 1.88 (s,3), 2.28 (s,3), 4.75 (d,1,$J_{4a',5e}$ 1.0 Hz); Anal. Calcd. for $C_{13}H_{17}NO_3$; C, 66.38; H, 7.23; N, 5.96. Found : C, 65.98; H, 7.43; N, 5.63 and (ii) trans-4-Acetamido-7-methyl-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (8b); mp. 139-140°C; IR(KBr) 3350 (OH), 3200 (NH), 1650 cm^{-1} (NH $COCH_3$); ^1H NMR ($CDCl_3$) δ 2.02 (s, 3), 2.38 (s, 3), 4.85 (d, 1, $J_{4a',5a}$ 8 Hz); Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.38; H, 7.23; N, 5.96. Found: C, 66.50, H, 7.30, N, 5.88.

cis-7-Methyl-4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (1b). cis-Acetamido alcohol 7b on base hydrolysis (4N, NaOH, MeOH) gave the corresponding amino alcohols 1b in 73% yield; mp. 115-116°C. Hydrochloride was crystallized from abs. EtOH-Et_2O, mp. 252°C; ^1H NMR (free base $CDCl_3$) δ 2.30 (s, 3), 3.97 (t, 2), 4.77 (d, 1, $J_{4a',5e}$ 1.5 Hz); Anal. Calcd. for $C_{11}H_{15}NO_2$.HCl: C, 57.51; H, 6.57; N, 6.10. Found: C, 57.32; H, 6.81; N, 6.23.

trans-7-Methyl-4-amino-2,3,4,5-tetrahydro-1-benzoxepin-5-ol (2b). It was obtained in 83% yield by base hydrolysis of 8b; mp. 148-149°C (lit[4] mp. 151-153°C); IR(KBr) 3350 (OH), 3300 cm^{-1} (NH); ^1H NMR ($CDCl_3$)δ 2.37 (s, 3), 4.78 (d,1,$J_{4a',5a}$ 8.5 Hz), 7.48 (d, 1); Hydrochloride was crystallized from abs. EtOH-Et_2O mp. 260°C (lit[4] mp. 250°C); Anal. Calcd. for $C_{11}H_{15}NO_2$.HCl: C, 57.51; H, 6.97; N, 6.10. Found: C, 57.81; H, 6.61; N, 6.23.

7-Methyl-4-acetamido-3,4-dihydro-1-(2H)-benzoxepin-5-one (9b). It was obtained in 77% yield by Jones oxidation of acetamido alcohols 7b and 8b as described for 9a; 156-157°C (lit[4] mp. 159-160°C); IR(KBr) 3350 (NH), 1700 (C=O), 1600 cm^{-1} ($NHCOCH_3$); ^1H NMR ($CDCl_3$):δ 2.02 (s, 3), 2.29 (s, 3), 7.60 (d, 1); Anal. Calcd. for $C_{13}H_{15}NO_2$; C, 66.95; H, 6.43; N, 6.00, Found: C, 66.83; H, 6.80; N, 6.22.

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