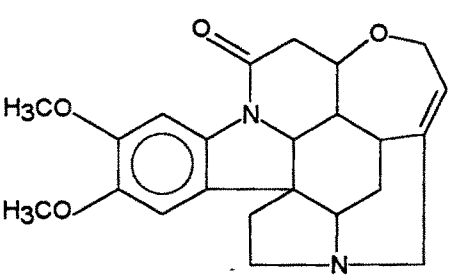
CHAPTER - 2

Synthesis of Chiral Secondary Alkanolamines

SYNTHESIS OF CHIRAL SECONDARY ALKANOLAMINES.

2.1 INTRODUCTION.

Chiral alkanolamines have wide applications in organic chemistry as resolving agents, chiral building blocks and chiral auxiliaries in stereo selective synthesis[1,2]. Naturally occurring amines such as brucine **(1)**, ephedrine **(2)** and aminoacids as well as synthetic amines such as α-methyl benzyl amine **(3)** and 2-amino-1-butanol **(4)** are frequently used.



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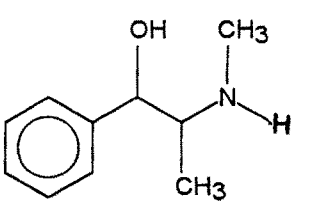

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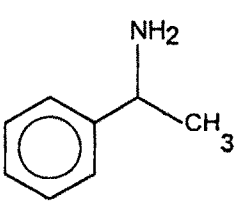

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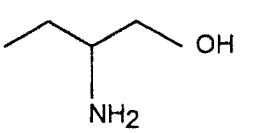


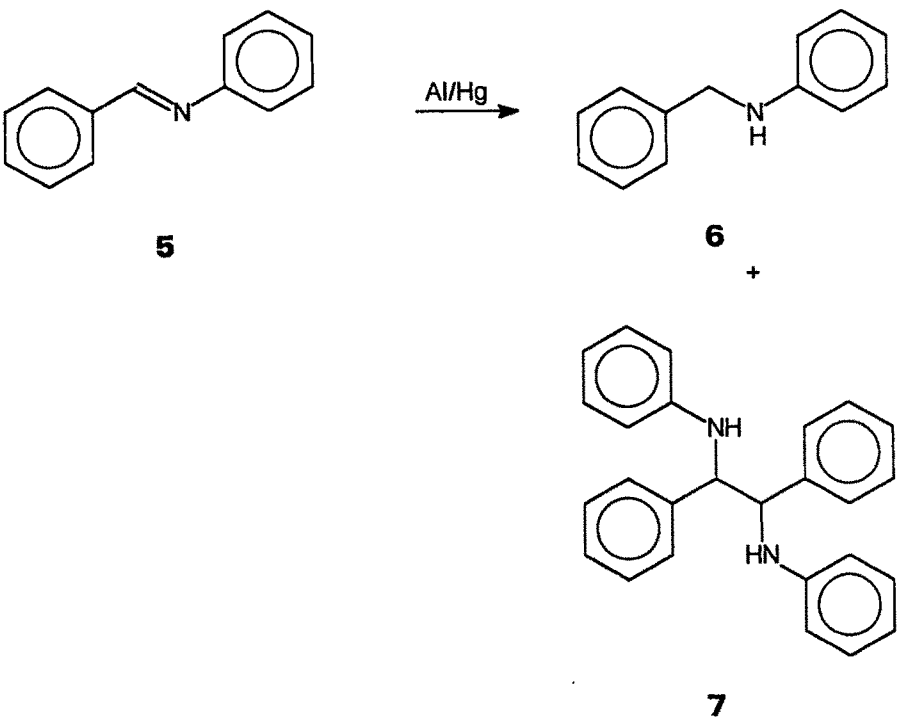
4

Naturally occurring chiral amines are available in enantiomerically pure form. But for the synthetic amines a resolution procedure or a stereoselective synthesis is needed for obtaining the enantiomers. In reactivity patterns chiral secondary alkanolamines combine the characteristics of amine and hydroxyl groups.

This combination of functionalities makes them versatile intermediates in countless industrial applications[3]. Alkyl alkanolamines are used as precursors for β-hydroxylated nitrosamines. These important compounds are used in the metabolic and carcinogenic studies.

N-substituted alkanolamines are reported to be bactereocidal, '*invitro*' against *mutans streptococii*, which form plaque on tooth surface[4]. Eckstein *etal*[5-7] have reported several derivatives of 2-amino-1-butanol which showed antiarrhythmic activity.

The most successful method for the synthesis of chiral amines involves hydrogenation of imines[1]. Imines can be reduced to the corresponding amines using a variety of reducing agents such as Na-EtOH, Al/Hg and Sn-HCl, but in most of the cases reductive dimerisation is observed[8]. For example, benzylidine aniline **(5)** undergoes reduction to form benzylaniline **(6)** and its dimer **(7)** **(Scheme II.1)** .



5 **6** + **7**

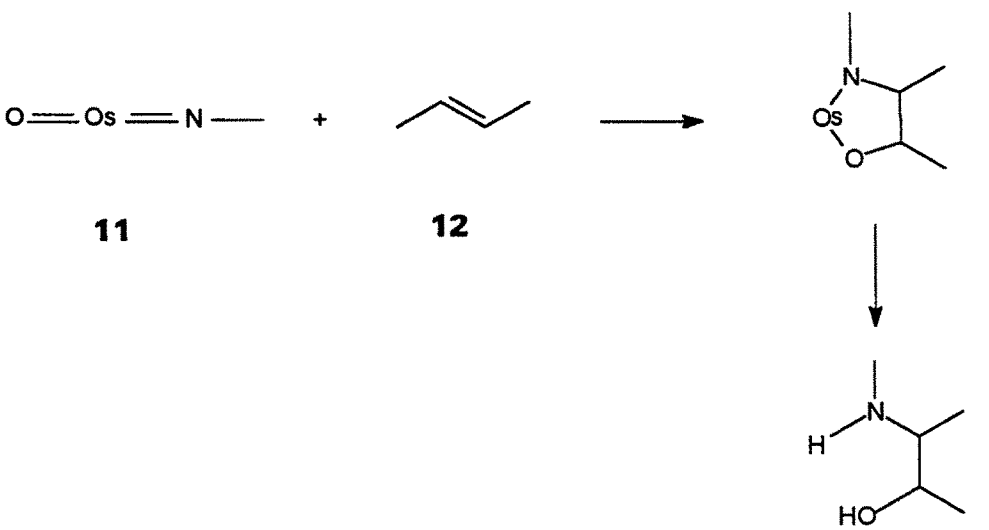
Scheme II.1

Alkyl alkanolamines can be prepared in several ways. Ethylene oxide **(8)** on treatment with methyl amine **(9)** furnished N-methyl aminoethanol[1] **(10)** **(Scheme II.2)**.

8 **9** **10**

Scheme II.2

Addition of imidoosmium reagent **(11)** to but-2-ene **(12)** is reported to give 4-(aminomethyl)-2,3-dimethyl ethanol amine[1] **(13) (Scheme II.3)**.

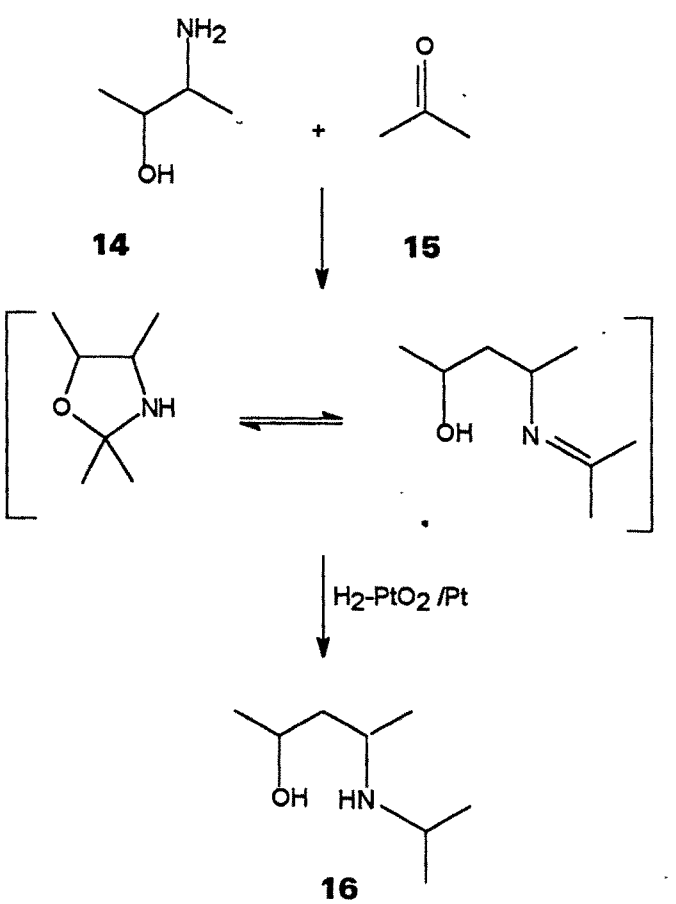


11 **12** **13**

Scheme II.3

Alkylation of primary amines with 2-bromoalcohols has been reported to give 2-alkyl alkanolamines[1]. A major limitation of this method is the possibility of further alkylation to tertiary amines and quarternary ammonium compounds.

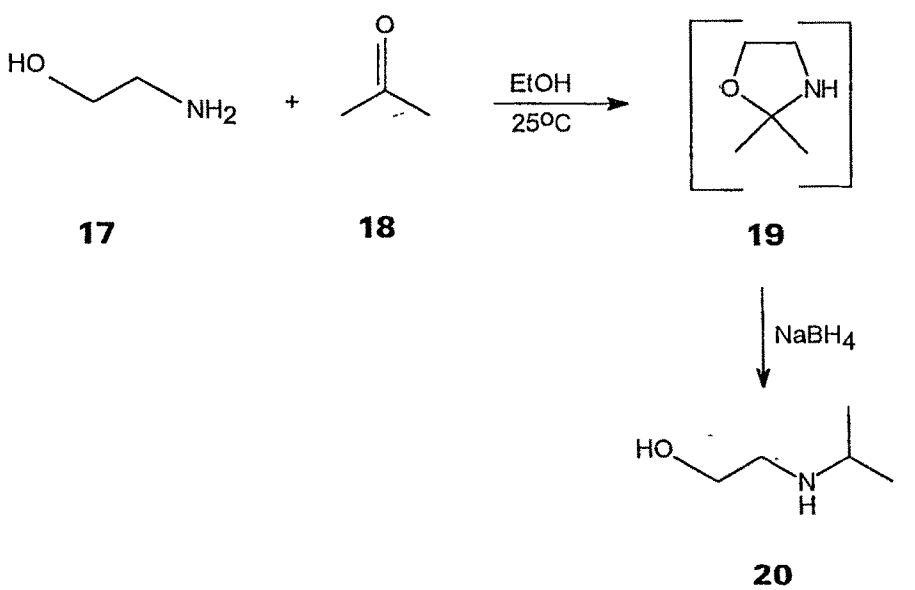
Cope and Hancock[9,10] successfully developed the catalytic reduction of the products formed *in situ,* by the reaction of ethanol amine and 2-amino-1-propanol with various aldehydes over PtO_2/ Pt catalyst at 1-2 atmospheric pressure of H_2. The reaction proceeded smoothly at room temperature via the oxazolidine intermediate to yield the corresponding 2-alkyl alkanolamine. At elevated temperature and pressure Raney Ni, Copperchromite also showed effective catalytic activity[9]. Englehardt *etal*[11] applied these findings to the reductive alkylation of alkanol amines. For example 2-amino-butan-3-ol **(14)** on treatment with acetone **(15)** followed by reduction furnished N-(isopropyl)-2-amino-butan-3-ol **(16). (Scheme II.4).**



Scheme II.4

The need for exogeneous source of hydrogen, the long reaction time and high temperature and pressures were some of the disadvantages of this method.

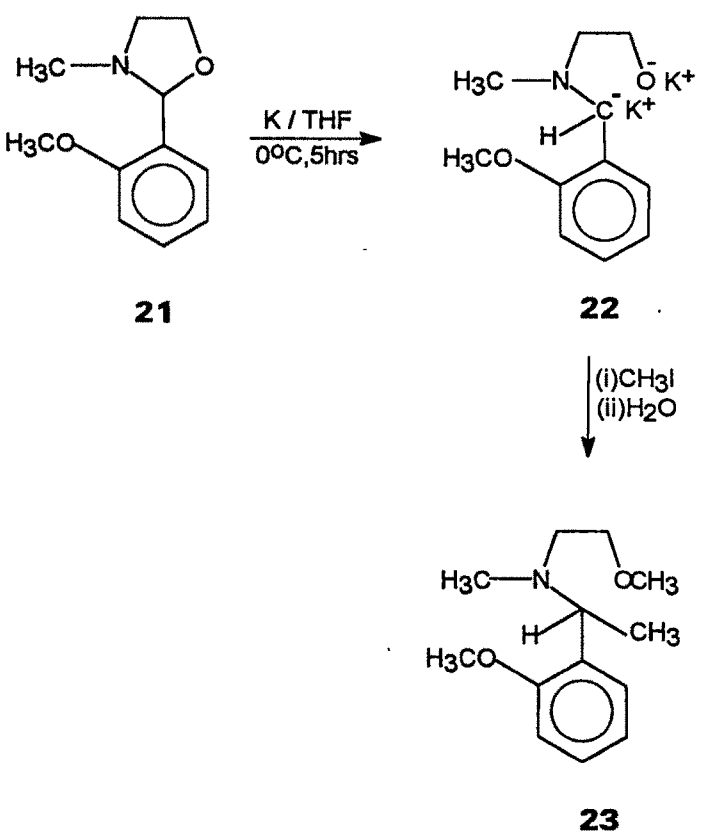
Saavedra[12] developed a simple, rapid and efficient method for the preparation of secondary alkyl alkanolamines uncontaminated by tertiary derivatives. This method combines the ease of formation of oxazolidines from alkanolamines and carbonyl compounds in absolute ethanol and the facile cleavage of the newly formed C-O bond of 1,3-oxazolidine *in situ* by sodiumborohydride. Ethanolamine on treatment **(17)** with acetone **(18)** produced 2,2-dimethyl-1,3-oxazolidine **(19)** which on reductive cleavage with sodium borohydride yielded N-(isopropyl)-2-amino-1-ethanol **(20)** **(Scheme II.5)**.



17 **18** **19** **20**

Scheme II.5

The reduction of a mixture of imine and 2-aryl-1,3-oxazlidine to the corresponding N-benzyl derivatives have been reported using hydrogen over Pd/C[1] and K/THF[13]. For example 2-(2-methoxyphenyl)-N-methyl-1,3-oxazolidine **(21)** is reduced with potassium in tetrahydrofuran, furnishing the potassium salt of N-methyl-(2-methoxy benzyl)-2-aminoethanol **(22)**, which on further treatment with methyl Iodide furnished the methyl derivative **(23) (Scheme II.6)**.



21 **22** **23**

Scheme II.6

This chapter describes our findings on the reaction of ***(R)*** and ***(S)*** 2-amino-1-butanol with benzaldehyde, 3-nitrobenzaldehyde, 4-chlorobenzaldehyde, 4-methylbenzaldehyde, 4-methoxybenzaldehyde and 3,4-dimethoxy benzaldehyde, which yielded a tautomeric mixture of the imine and the corresponding 1,3-oxazolidines, which on reduction with sodium borohydride in methanol, resulted in the formation of N-benzyl-2-amino-1-butanol, N-(3-nitrobenzyl)-2-amino-1-butanol, N-(4-Chlorobenzyl)-2-amino-1-butanol, N-(4-methoxybenzyl)-2-amino-1-butanol and N-(3,4-dimethoxybenzyl)-2-amino-1-butanol respectively.

2.2 RESULTS AND DISCUSSION

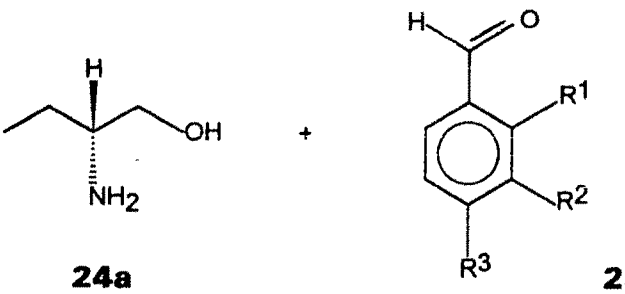
Condensation Of ***(R)*** or ***(S)*** 2-amino-1-butanol **(24a or 24b)** and benzaldehyde **(25c)** furnished the corresponding imines, namely ***(R)*** and ***(S)*** N-benzylidene-2-amino-1-butanol **(26a & 26b)** which was found to be in tautomeric equilibrium with 2-phenyl-4-ethyl-1,3-oxazolidine **(26a' & 26b')**, on reduction with sodium borohydride produced the ***(R)*** and ***(S)*** N-(benzyl)-2-amino-1-butanol **(32a & 32b)**. Similarly 3-nitrobenzaldehyde **(25d)**, 4-chlorobenzaldehyde **(25e)**, 4-methylbenzaldehyde **(25f)**, 4-methoxy benzaldehyde **(25g)** and 3,4-dimethoxybenzaldehyde **(25h)** on reaction with ***(R)*** or ***(S)***-2-amino-1-butanol **(24a & 24b)** yielded a tautomeric mixture of the imine and 1,3-oxazolidine, which on reduction with sodiumborohydride in methanol furnished ***(R)*** & ***(S)*** N-(3-nitrobenzyl)-2-amino-1-butanol **(33a & 33b)**, ***(R)*** & ***(S)*** N-(4-chlorobenzyl)-2-amino-1-butanol **(34a & 34b)**, ***(R)*** & ***(S)*** N-(4-methylbenzyl)-2-amino-1-butanol **(35a & 35b)**, ***(R)*** & ***(S)*** N-(4-methoxybenzyl)-2-amino-1-butanol **(36a & 36b)** and ***(R)*** & ***(S)*** N-(3,4-dimethoxybenzyl)-2-amino-1-butanol **(37a & 37b)** respectively **(Scheme II.7A & Scheme II.7B)**.

(R)-(-)-2-amino-1-butanol **(24a)** was reacted with benzaldehyde **(25c)**, in refluxing toluene with azeotropic removal of water, furnished ***(R)*** N-benzylidene-2-amino-1-butanol **(26a)**. The IR spectra of **26a** showed a sharp band at 1640 cm^{-1}, due to -C=N (Fig. 2.I). Similarly ***(S)***-(+)-2-amino-1-butanol **(24b)** was also reacted with benzaldehyde **(25c)** resulting in the formation of ***(S)*** N-benzylidene-2-amino-1-butanol **(26b)**. The IR spectra of **26b** has

shown similar spectral characteristics as that of **26a**.

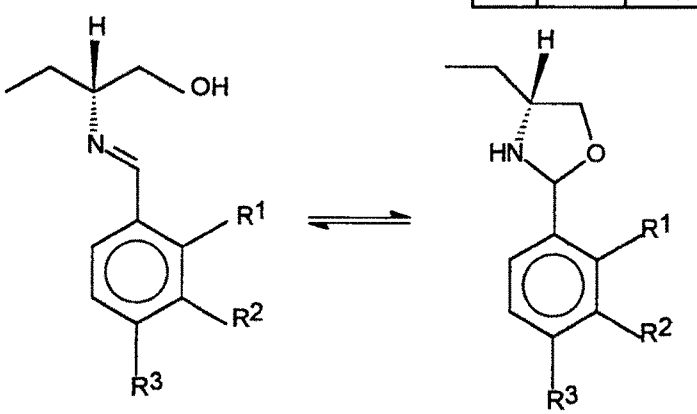
(R) N-benzylidene-2-amino-1-butanol **(26a)** and ***(S)*** N-benzylidene-2-amino-1-butanol **(26b)** showed approximately equal and opposite specific rotation indicating the formation of a single enantiomer.

^{1}H NMR spectrum of *(R)* N-benzylidene-2-amino-1-butanol (26a) (Fig. 2.II) showed a triplet at 0.85 which is assigned to the methyl protons of the imine formed. The multiplet at 1.60 is due to the methylene protons. A broad singlet at 2.45 accounted the hydroxyl proton. The -CH-N appeared at 3.20. A multiplet at 3.75 is exhibited for -CH_2-O. The aromatic protons appeared at 7.4-7.7 δ. The sharp singlet at 8.25 is assigned to the proton of -N=CH of the imine. The multiplet at 1.05 is assigned to the methyl proton of the 1,3-oxazolidine. The doublet at 5.45 was due to the -N-CH-O of the 1,3-oxazolidine. These signals in the ^{1}H NMR spectrum confirmed that **26a** is in tautomeric equilibrium with **26a´**.

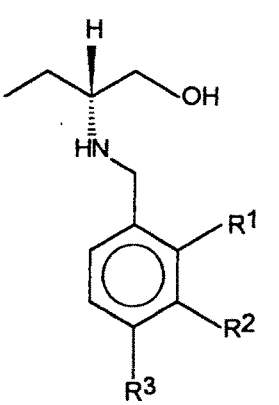


24a **25c-h**

25	R^1	R^2	R^3
c	H	H	H
d	H	NO_2	H
e	H	H	Cl
f	H	H	CH_3
g	H	H	OCH_3
h	H	OCH_3	OCH_3

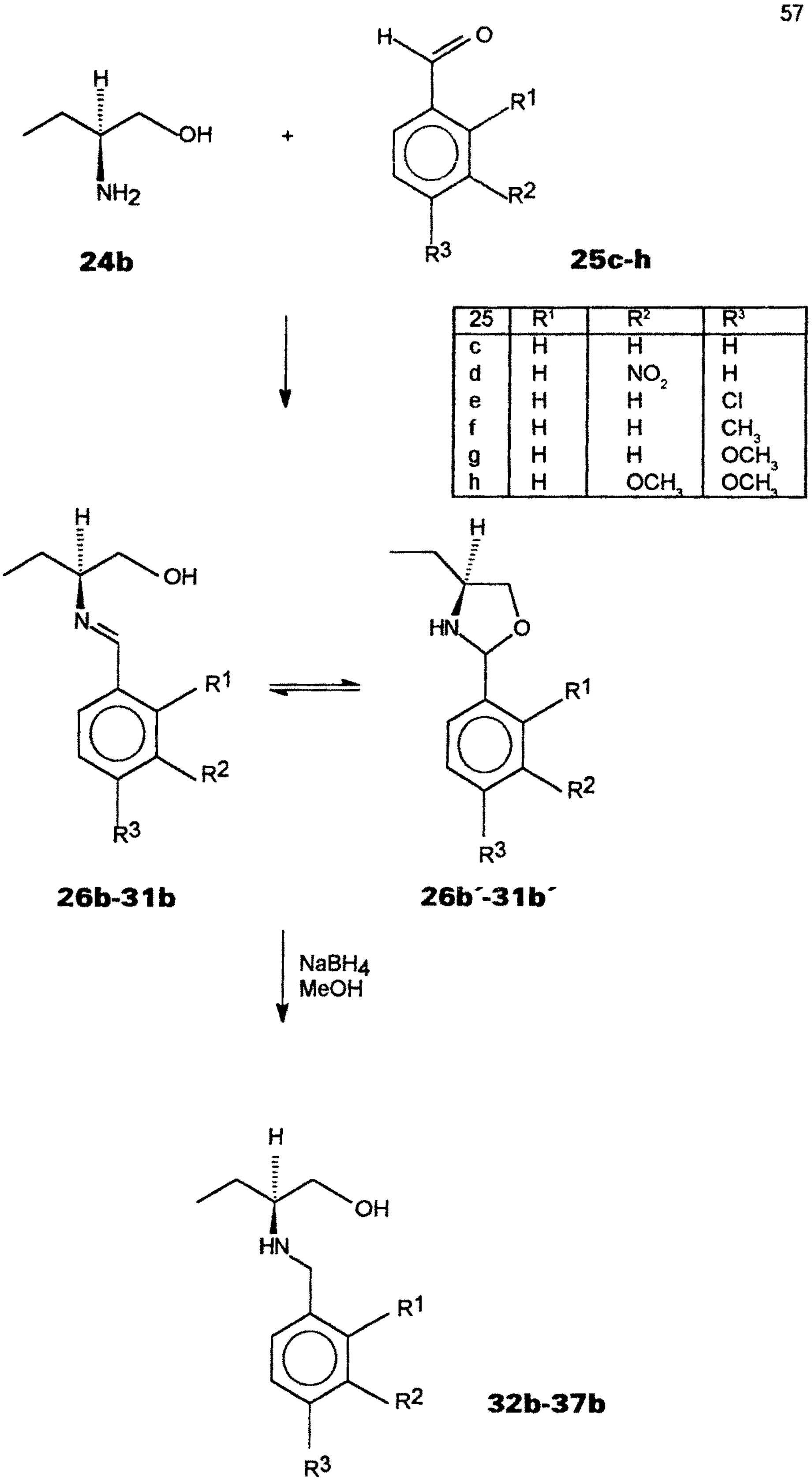


26a-31a **26a´-31a´**



32a-37a

Scheme II.7A



25	R^1	R^2	R^3
c	H	H	H
d	H	NO_2	H
e	H	H	Cl
f	H	H	CH_3
g	H	H	OCH_3
h	H	OCH_3	OCH_3

Scheme II.7B

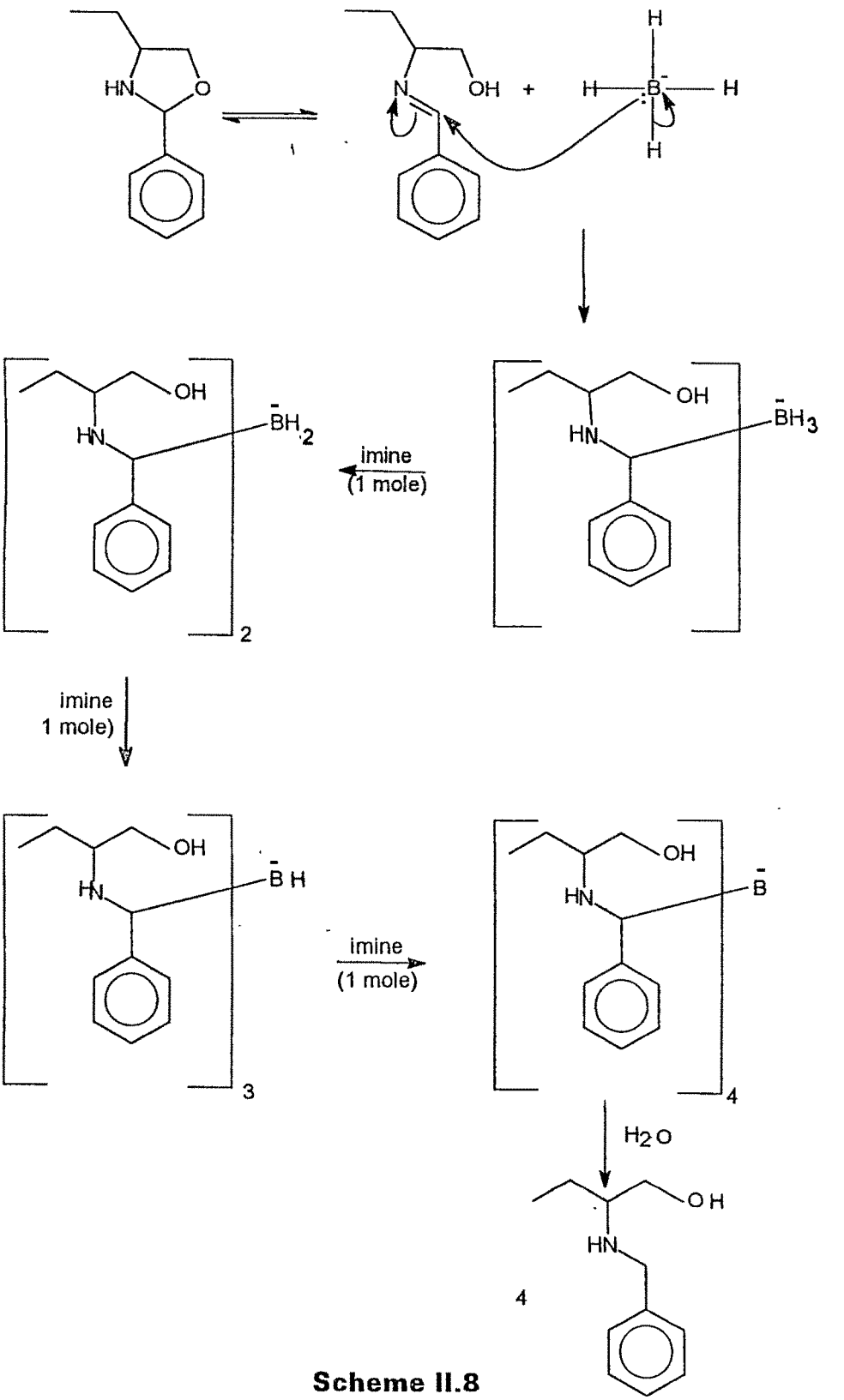
The ^{1}H NMR spectrum of ***(S)*** **N-benzylidene-2-amino-1-butanol (26b)** (Fig. 2.III) showed a triplet at 0.85 due to the methyl protons. The multiplet at 1.60 corresponds to the methylene protons. The broad singlet at 2.05 accounted for the hydroxyl proton. The multiplet at 3.20-3.40 is assigned to the -CH-N, and the multiplet at 3.75 is due to $-CH_2-O$. The aromatic protons appeared at 7.25 - 7.70 δ. The sharp singlet at 8.25 is assigned to the -N=CH proton. The signal appeared at 1.05 is assigned to the methyl protons of 1,3-oxazolidine. The doublet at 5.45 accounted for the -N-CH-O of the oxazolidine. The presence of these signals confirmed that **26b** is in tautomeric equilibrium with **26b´**.

From these spectral observations, it is confirmed that the product obtained by the reaction of ***(R)*** or ***(S)*** 2-amino-1-butanol **(24a or 24b)** with benzaldehyde **(25c)** exists as a tautomeric equilibrium of imine and the corresponding 1,3-oxazolidine, namely ***(R)*** or ***(S)*** N-benzylidene-2-amino-1-butanol **(26a & 26b)** with the corresponding tautomer 2-phenyl-4-ethyl-1,3-oxazolidines **(26a´ & 26b´)**. High resolution ^{1}H NMR studies of the compounds **(26a & 26b)** were carried out to find out the extent of formation of N-benzylidene-2-amino-1-butanol and 2-phenyl-4-ethyl-1,3-oxazolidine. It is found that the ratios of the mixtures **26a:26a´** is 84:16 and **26b:26b´** is 86:14. These calculations were done by the peak area measurement at 8.44 - 8.17 δ ppm (-N=CH) and 5.98 - 5.44 δ ppm (-N-CH-O)[14].

The ^1H NMR spectrum of ***(R)*** **N-(2-nitro benzylidene)-2-amino-1-butanol (27a)** (Fig 2.IV) has also shown signals at 5.5 δ ppm, accounted for a single proton, corresponds to the -N-CH-O, confirmed the formation of 1,3-oxazolidine. The sharp singlet appeared at 8.55 δ ppm, confirmed the formation of imine also. ***(R)*** & ***(S)*** N-(4-methylbenzylidene)-2-amino-1-butanol **(29a & 29b)**, ***(R)*** & ***(S)*** N-(4-methoxybenzylidene)-2-amino-1-butanol **(30a & 30b)**, and ***(R)*** N-(3,4-dimethoxybenzylidene)-2-amino-1-butanol **(31a)** also has shown similar spectral characteristics. The ratios of the extent of formation of the imine - 1,3-oxazolidine tautomer could not be determined in these cases due to the poorly resolved spectra.

The ^{13}C NMR spectrum (Fig. 2.V) of ***(R)*** **N-(4 - Chlorobenzylidene)-2-amino-1-butanol (28a)** showed a doublet at 10.61 due to methyl group. The triplet at 25.03 indicated the presence of a methylene group. A singlet appeared at 66.06 is assigned to the -CH group. The $-CH_2-O$ group appeared at 74.36 as a singlet. The multiplet at 128.56 - 129.46 is due to the aromatic ring. The -N=CH appeared as a singlet at 160.34 δ.

The products **26a - 31a** and **26b - 31b** were subjected to reduction with sodium borohydride in methanol. ***(R)*** & ***(S)*** N-benzylidene-2-amino-1-butanol **(26a & 26b)** which were found to be in equilibrium with the corresponding 2-phenyl-4-ethyl-1,3-oxazolidines **(26a´ & 26b´)** were treated with sodium borohydride in methanol resulting in the formation of ***(R)*** and ***(S)*** N-benzyl-2-amino-1-butanol **(32a & 32b)**. A plausible mechanism for reduction is given in **scheme II.8**.


HN
O
N
OH
+
H
B
H
H
H
OH
HN
BH2
2
imine
(1 mole)
OH
HN
BH3
imine
1 mole)
OH
HN
B H
3
imine
(1 mole)
OH
HN
B
4
H2O
OH
HN
4

Scheme II.8

Similarly ***(R)*** & ***(S)*** N-(3-nitrobenzylidene)-2-amino-1-butanol **(27a & 27b)**, ***(R)*** & ***(S)*** N-(4-chlorobenzylidene)-2-amino-1-butanol **(28a & 28b)**, ***(R)*** & ***(S)*** N-(4-methylbenzylidene)-2-amino-1-butanol **(29a & 29b)**, ***(R)*** & ***(S)*** N-(4-methoxybenzylidene)-2-amino-1-butanol **(30a & 30b)** and ***(R)*** & ***(S)*** N (3,4-dimethoxybenzylidene)-2-amino-1-butanol **(31a & 31b)** on sodium borohydride reduction produced ***(R)*** & ***(S)*** N-(3-nitrobenzyl)-2-amino-1-butanol **(33a & 33b)**, ***(R)*** & ***(S)*** N-(4-chlorobenzyl)-2-amino-1-butanol **(34a & 34b)**, ***(R)*** & ***(S)*** N-(4-methylbenzyl)-2-amino-1-butanol **(35a & 35b)**, ***(R)*** & ***(S)*** N-(4-methoxybenzyl)-2-amino-1-butanol **(36a & 36b)** and ***(R)*** & ***(S)*** N-(3,4-dimethoxybenzyl)-2-amino-1-butanol **(37a & 37b)** respectively.

High resolution ^{1}H NMR spectrum of **N-benzyl-2-amino-1-butanol (32a)** (Fig. 2.VI) showed a triplet at 0.9 δ ppm corresponds to the -CH_3 protons, a multiplet at 1.4 - 1.6 is assigned to -CH_2 protons, broad singlet at 2.64 is due to -N-CH_2 and the multiplet at 3.36 accounts the -N-CH proton. The multiplet at 3.7-3.9 corresponds to -CH_2-O protons. The aromatic protons appeared at 7.2-7.4 δ . ^{1}H NMR spectrum of ***(R)*-N-4-chlorobenzyl-2-amino-1-butanol (34a)** (Fig. 2 VII) showed a triplet at 0.95 accounted for methyl protons. The multiplet at 1.45 is assigned to the -CH_2 protons. A multiplet at 2.10 is due to the -N-CH_2 protons. Hydroxyl proton appeared at 2.62. The -CH proton was exhibited as a multiplet at 3.35. The multiplet at 3.75 corresponds to the -CH_2-O protons. The aromatic protons were appeared at 7.28 δ. The IR spectrum of **N-benzyl-2-amino-1-butanol (32a)** (Fig. 2.VIII) showed an absorption at 3300 cm^{-1} indicating the presence of a hydroxyl group.

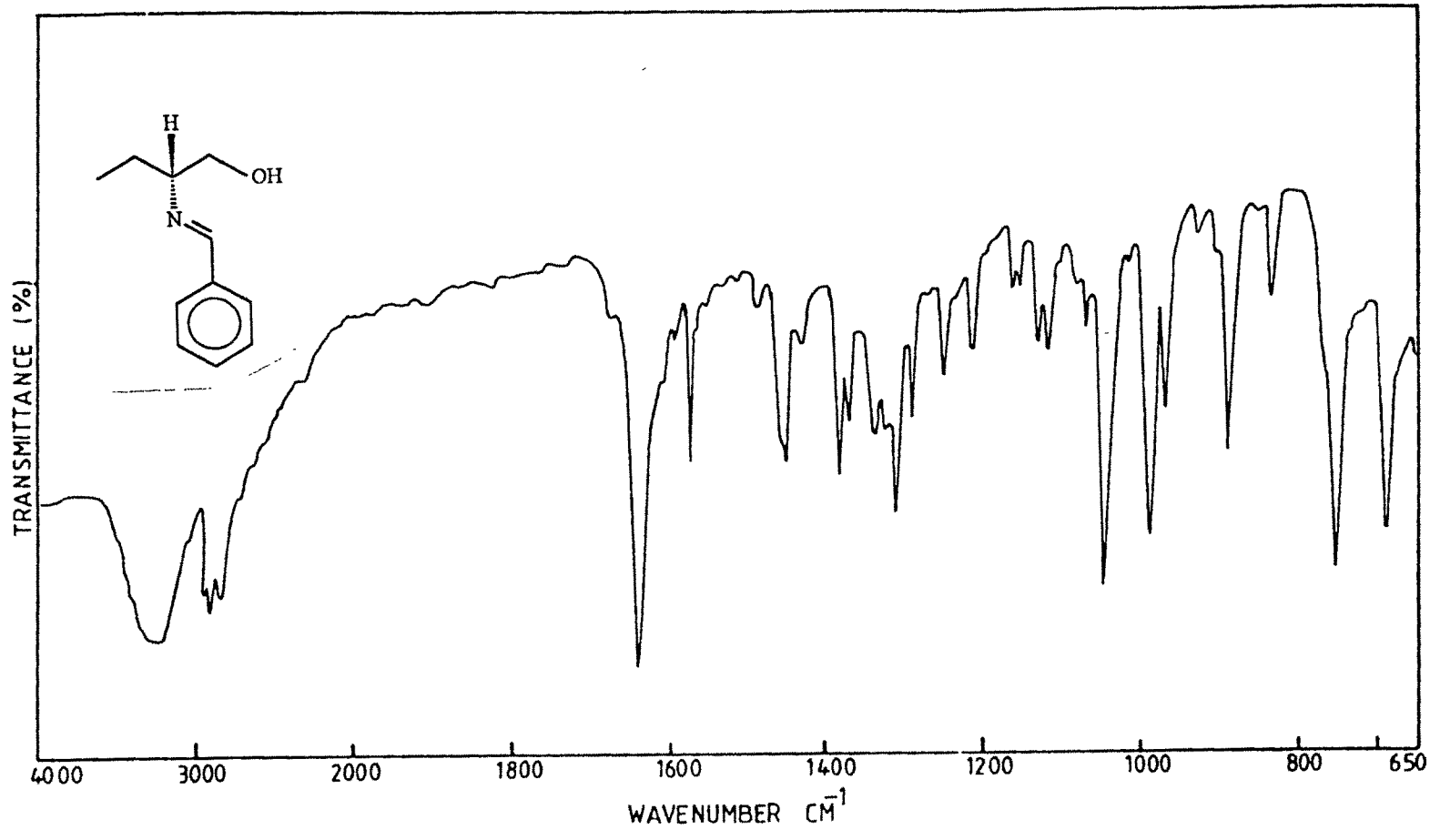


Fig. 2.1 IR (KBr) spectrum of ***(R)*** N-benzylidene-2-amino-1-butanol. **(26a)**

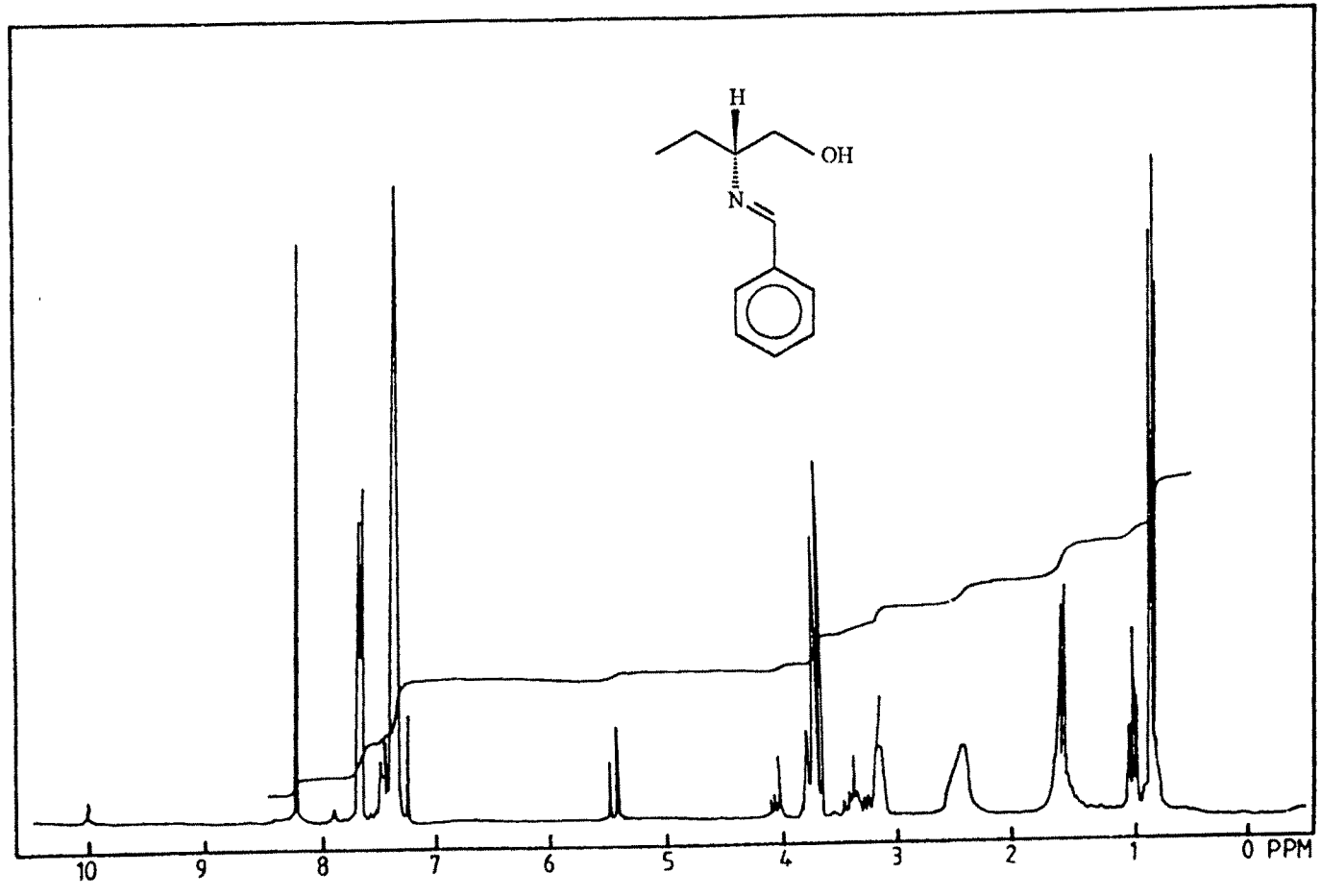


Fig 2.II ^1H NMR ($CDCl_3$) spectrum of ***(R)*** N-benzylidene-2-amino-1-butanol **(26a)**

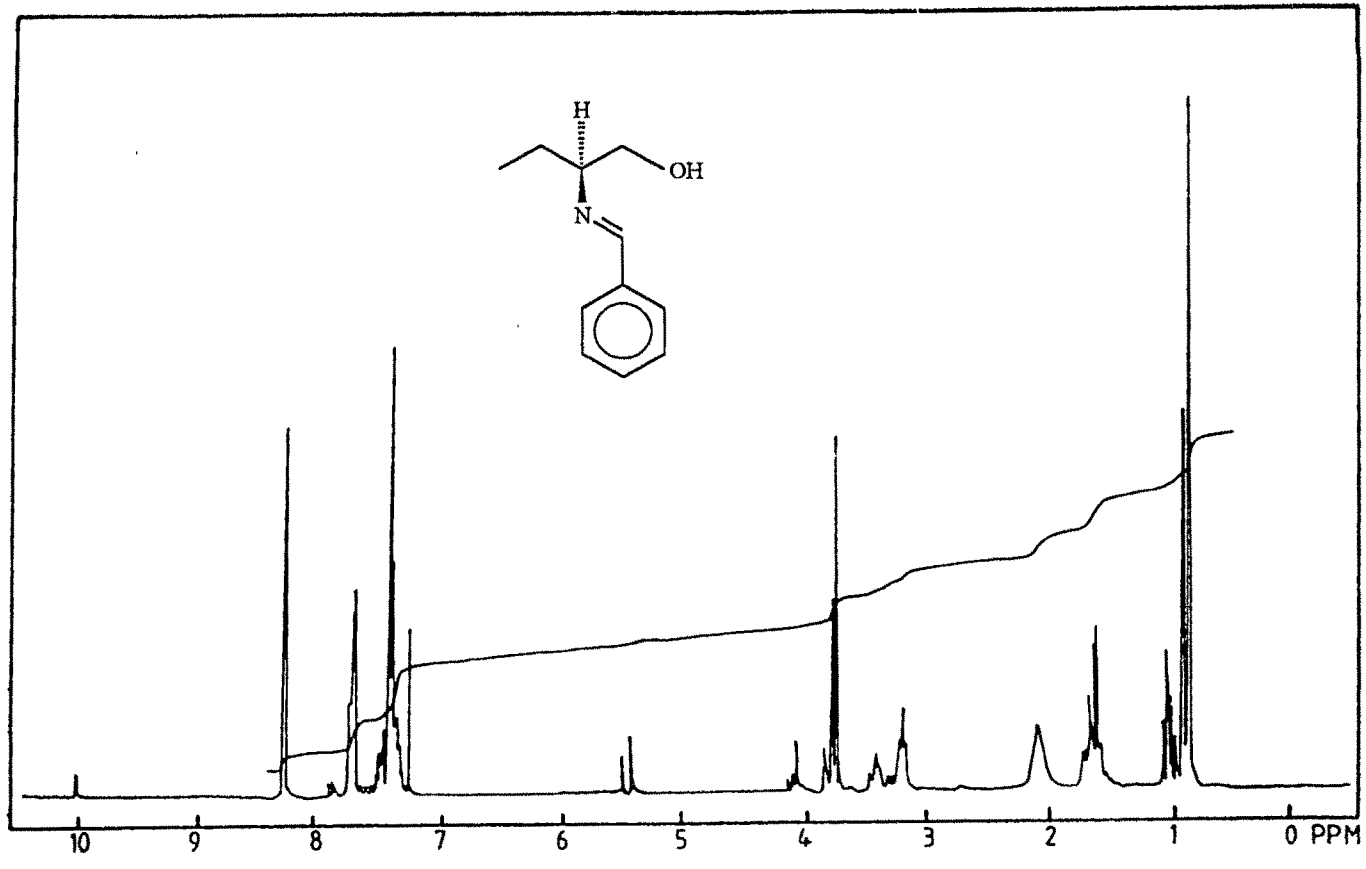


Fig. 2.III ^1H NMR ($CDCl_3$) spectrum of ***(S)*** N-benzylidene-2-amino-1-butanol **(26b)**

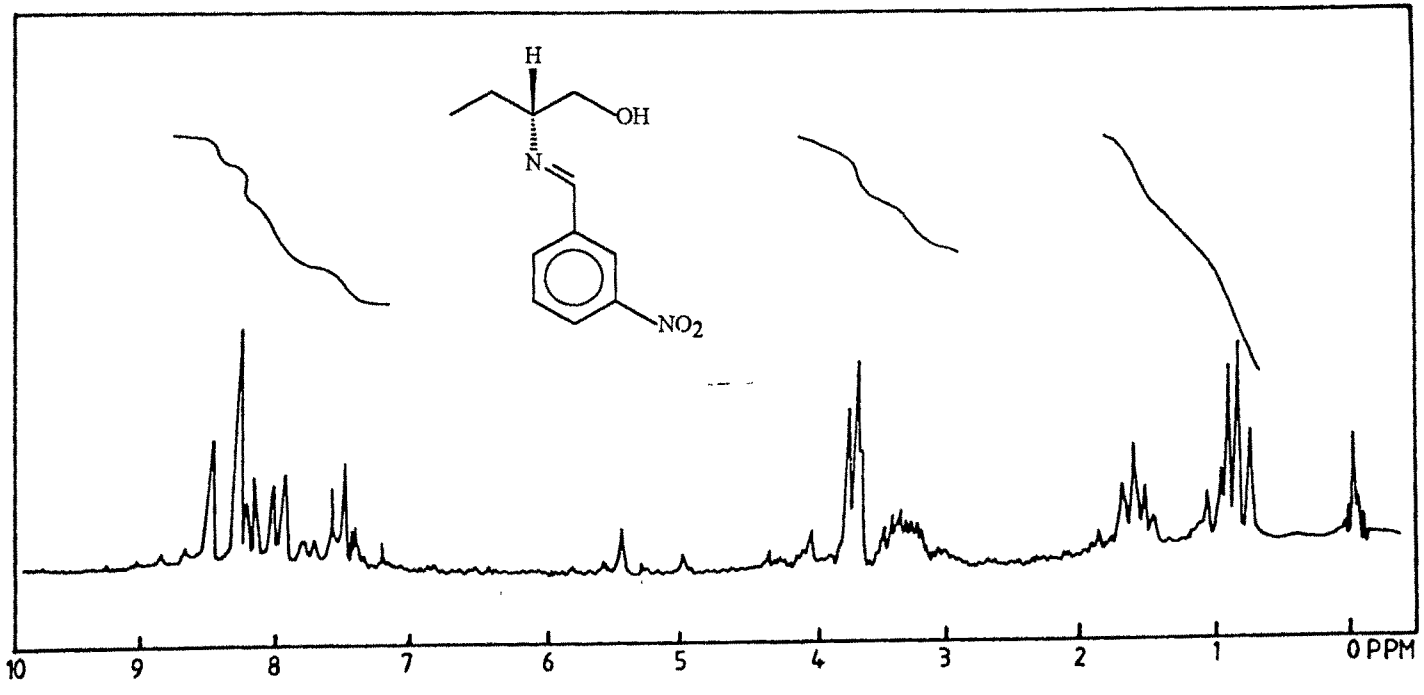


Fig. 2.IV ^1H NMR ($CDCl_3$) spectrum of ***(R)*** N-(2-nitrobenzylidene)-2-amino-1-butanol. **(27a)**

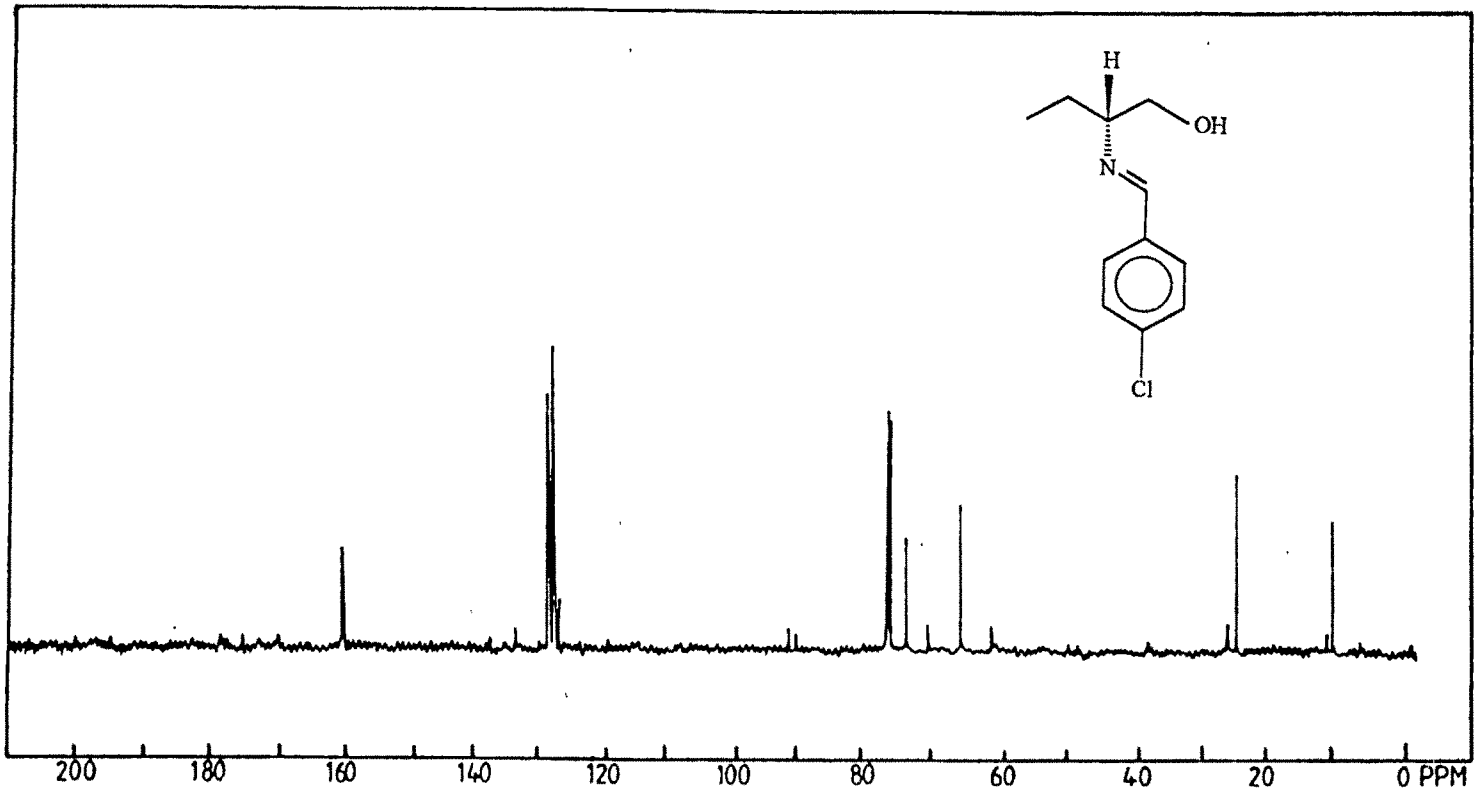


Fig. 2.V ^{13}C NMR ($CDCl_3$) spectrum of ***(R)*** N-(4-chlorobenzylidene)-2-amino-1-butanol. **(28a)**

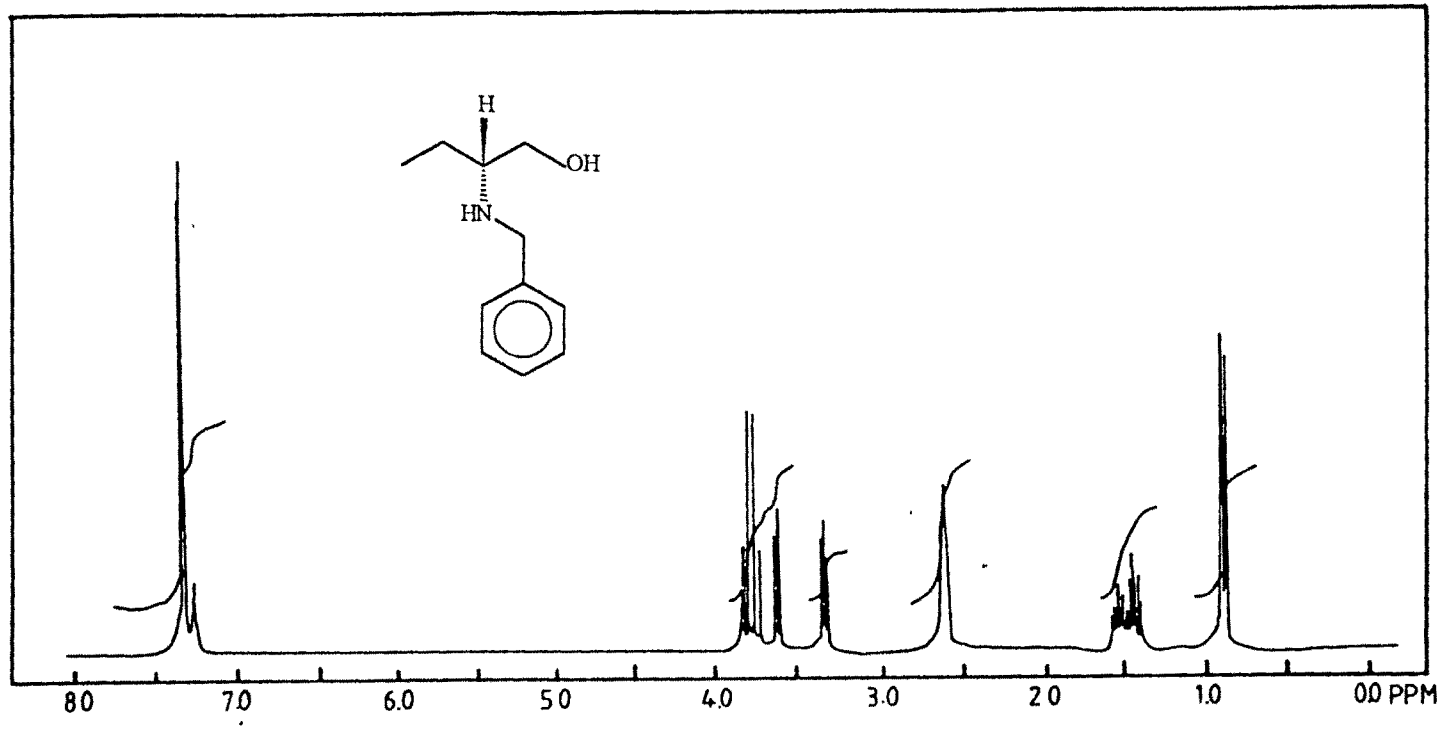


Fig. 2.VI ^1H NMR ($CDCl_3$) spectrum of ***(R)*** N-benzyl-2-amino-1-butanol. **(32a)**

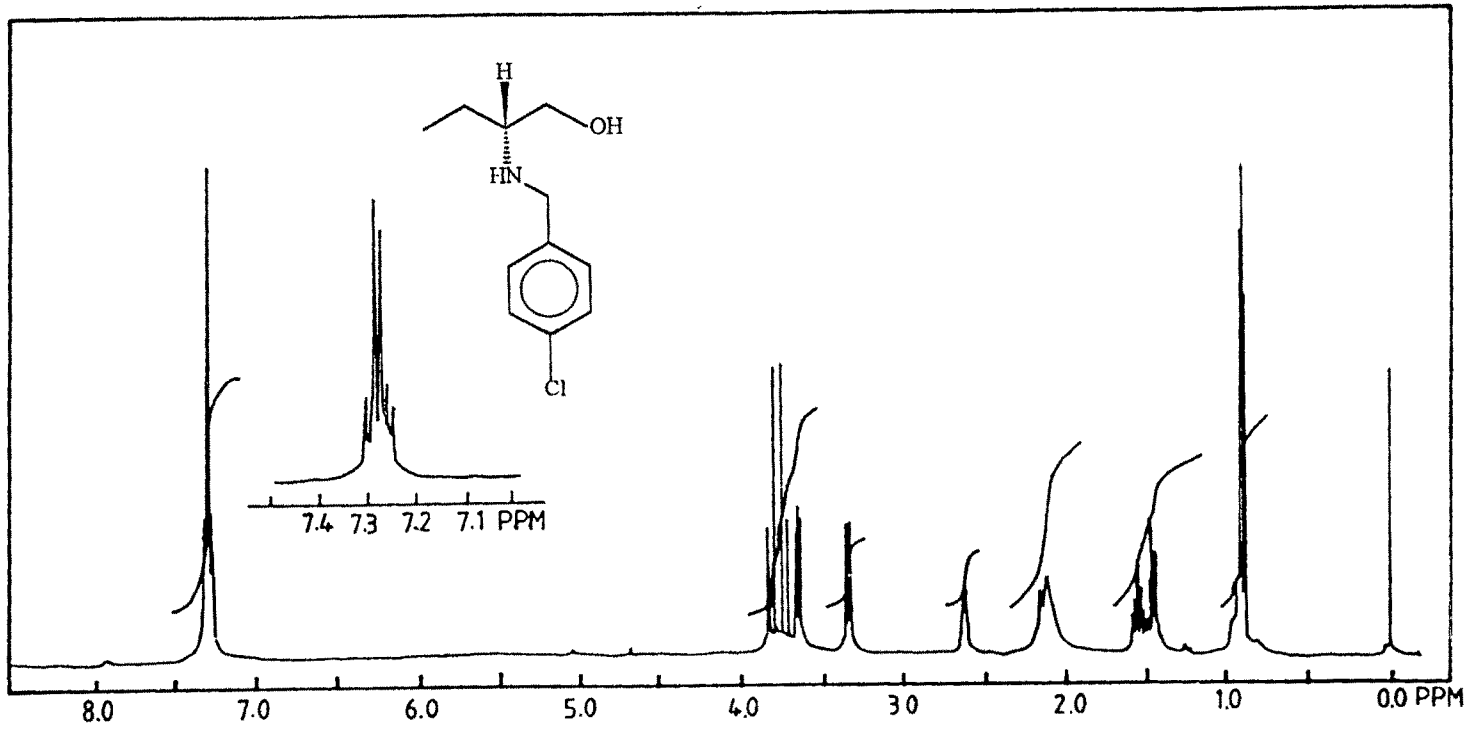


Fig. 2.VII ^1H NMR ($CDCl_3$) spectrum of ***(R)*** N-(4-chlorobenzyl)-2-amino-1-butanol. **(34a)**

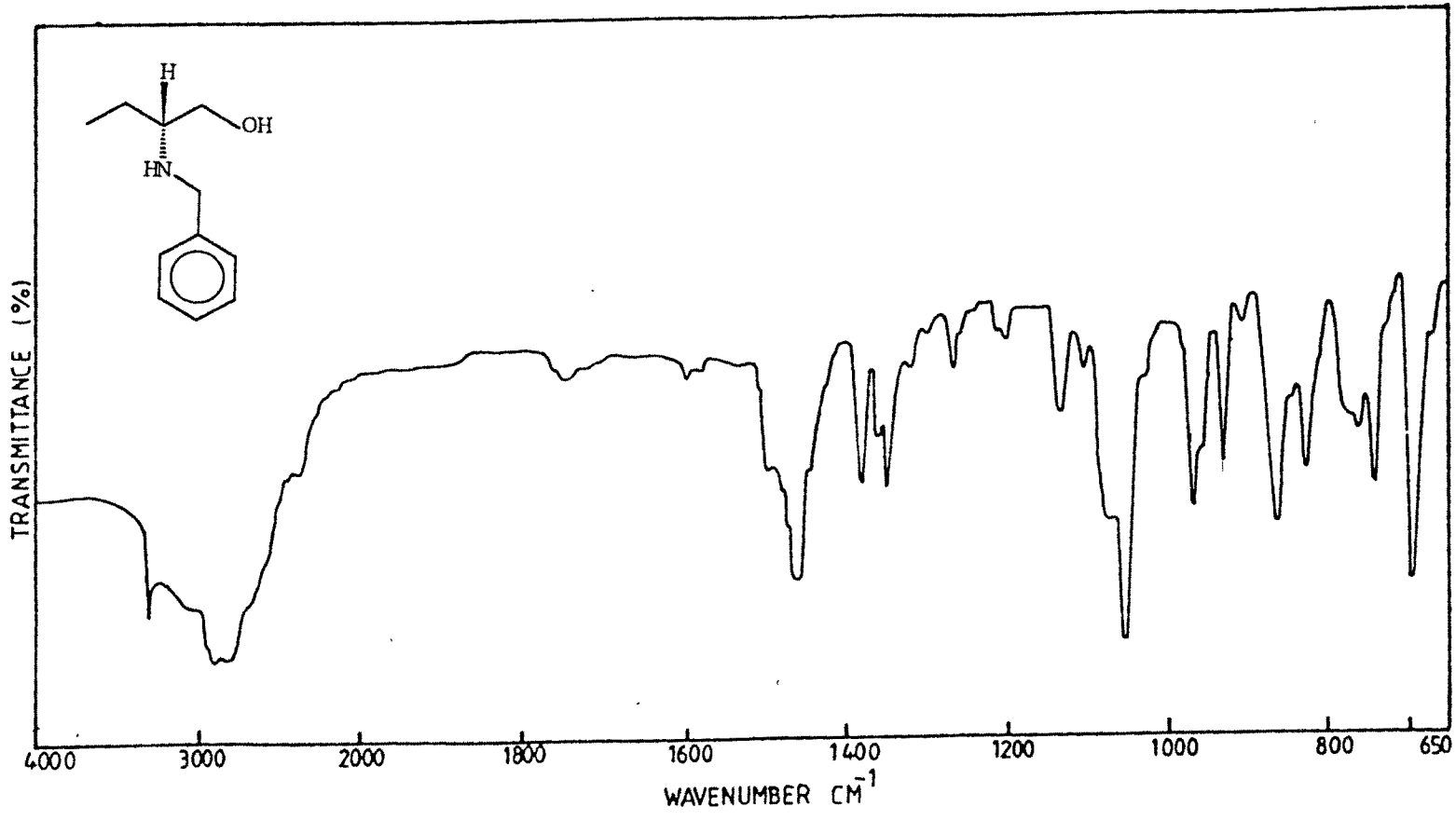


Fig. 2.VIII IR (KBr) spectrum of ***(R)*** N-benzyl-2-amino-1-butanol.
(32a)

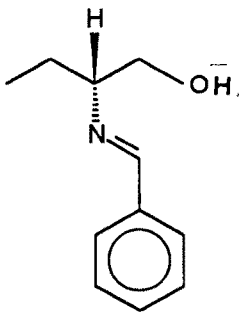
2.3 EXPERIMENTAL

Melting points were taken on a Gallenkamp. 350 micro melting apparatus by open capillary method, and are uncorrected. Optical rotations were measured on a Jasco-Dip 370 polarimeter at 25°C, in chloroform or methanol. Infrared spectra were recorded on a Shimadzu IR-408 and NMR spectra on JEOL-270FX, Perkin Elmer R-32 and Bruker UM-400 spectrometers.

2.3.1 Chiral Imines from (R) & (S) -2-amino-1-butanol. 26a-31a & 26b-31b.

To a solution of aromatic aldehyde **(25c-h)** (0.02 mole) in toluene was added, a solution of ***(R)*** or ***(S)*** 2-amino-1-butanol **(24a or 24b)** (0.02 mole) in toluene at 10°C. The reaction mixture was brought to room temperature and azeotropically distilled for 2 hrs. The water collected in the Dean-Stark apparatus was removed from time to rime. To remove the traces of water, the reaction mixture was refluxed for additional one hour, with a bypassed dropping funnel with 4A° molecular sieves placed between the flask and the reflux condenser. The completion of the reaction was monitored by TLC. After the completion of the reaction toluene was removed on a rotary evaporator under reduced pressure. The solid obtained was recrystallized from petroleum ether (60-80°C) - Ethyl acetate (60:40) mixture, to furnish the imines **26a-31a** and **26b-31b.**

(R) N-(benzylidene)-2-amino-1-butanol (26a)



Yield : 83% M.P. : 55-56° C.

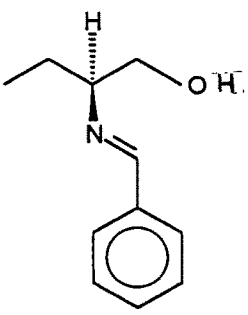
CHN found (calculated) : C - 74.20 (74.50), H - 8.03 (8.47), N - 7.58 (7.91).

$[\alpha]_D^{25}$: +39.30° (*c* 1.0 in $CHCl_3$).

ν_{max} (KBr)/cm^{-1} : 3250, 1640, 1450.

δ ppm ($CDCl_3$) : 0.85 (3H,t,-CH_3), 1.05 (-CH_3 of the corresponding 1,3-oxazolidine), 1.60 (2H,m,-CH_2), 2.45 (1H,br.s,-OH), 3.20 (1H,m,-CH), 3.75 (2H,m,-CH_2-O), 5.40, 5.50 (1H, -N-CH-O of 1,3-oxazolidine), 7.40, 7.70 (5H,m,-C_6H_5), 8.25 (1H,s,-N=CH).

(S) N-(benzylidene)-2-amino-1-butanol (26b)



Yield : 84% M.P. : 55° C.

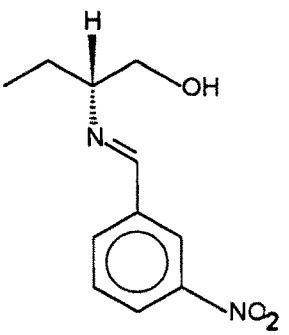
CHN found (calculated) : C - 73.99 (74.50), H - 7.79 (8.47), N - 7.52 (7.91).

$[\alpha]_D^{25}$: -35.99° (*c* 1.0 in $CHCl_3$).

ν_{max} (KBr)/cm^{-1} : 3250, 1645, 1580.

δ ppm ($CDCl_3$) : 0.85 (3H,t,-CH_3), 1.05 (-CH_3 of the corresponding 1,3-oxazolidine), 1.60 (2H,m,-CH_2), 2.05 (1H,br.s,-OH), 3.20, 3.40 (1H,m,-CH), 3.75 (2H,m,-CH_2-O), 5.40, 5.50 (1H, -N-CH-O of 1,3-oxazolidine), 7.25, 7.40, 7.70 (5H,m,-C_6H_5), 8.25 (1H,s,-N=CH).

(R) N-(3-nitrobenzylidene)-2-amino-1-butanol (27a)



Yield : 83%. M.P. : 121-23° C.

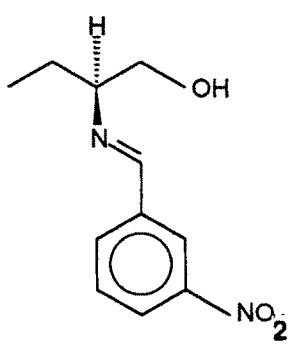
CHN found (calculated) : C - 59.63 (59.45), H - 6.34 (6.31), N - 12.38 (12.61).

$[\alpha]_D^{25}$: +18.13° (*c* 1.0 in $CHCl_3$).

ν_{max} (KBr)/cm^{-1} : 3250, 1635, 1520.

δ ppm ($CDCl_3$) : 0.85 (3H,t,-CH_3), 1.65 (2H,m,-CH_2), 3.40 (1H,m,-CH), 3.75 (2H,t,-CH_2-O), 5.50 (1H, -N-CH-O of 1,3-oxazolidine), 7.55, 8.00, 8.35 (4H,m,-C_6H_4), 8.55 (1H,s,-N=CH).

(S) N-(3-nitrobenzylidene)-2-amino-1-butanol (27b)



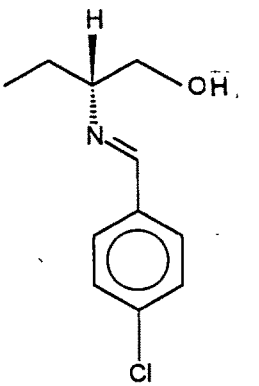
Yield : 83%. M.P. : 120°C.

CHN found (calculated) : C - 59.90 (59.45), H - 6.07 (6.31), N - 12.51 (12.61).

$[\alpha]_D^{25}$: -15.86° (*c* 1.0 in $CHCl_3$).

ν_{max} (KBr)/cm^{-1} : 3250, 1640, 1520.

(R) N-(4-chlorobenzylidene)-2-amino-1-butanol (28a)



Yield : 85%. M.P. : 65° C.

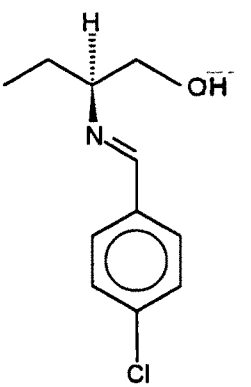
CHN found (calculated) : C - 61.94 (62.43), H - 6.42 (6.62), N - 6.49 (6.62).

$[\alpha]_D^{25}$: +18.66° (*c* 1.0 in MeOH).

ν_{max} (KBr)/cm^{-1} : 3250, 1640, 1590.

^{13}C NMR (δ / $CDCl_3$) : 10.61 ($-CH_3$), 25.03 ($-CH_2$), 66.06 (-CH), 74.36 ($-CH_2$-O), 128.56 - 129.46 (aromatic), 160.34 (-N=CH).

(S) N-(4-chlorobenzylidene)-2-amino-1-butanol (28b)



Yield : 81%. M.P. : 61° C.

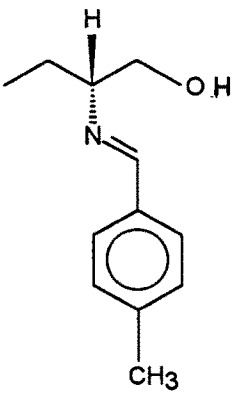
CHN found (calculated) : C - 62.70 (62.43), H - 6.45 (6.62), N - 6.73 (6.62).

$[\alpha]_D^{25}$: -21.70° (*c* 1.0 in MeOH).

ν_{max} (KBr)/cm^{-1} : 3250, 1645, 1590.

^{13}C NMR (δ / $CDCl_3$) : 10.52 ($-CH_3$), 24.91 ($-CH_2$), 65.78 (-CH), 74.50 ($-CH_2$-O), 127.37 - 129.39 (aromatic), 160.35 (-N=CH).

(R) N-(4-methylbenzylidene)-2-amino-1-butanol (29a)



Yield : 79%. M.P. : 51° C.

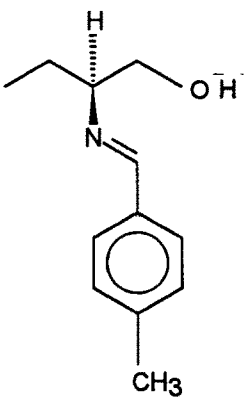
CHN found (calculated) : C - 75.00 (75.39), H - 8.49 (8.90), N - 7.21 (7.30).

$[\alpha]_D^{25}$: +31.86° (*c* 1.0 in $CHCl_3$).

ν_{max} (KBr)/cm^{-1} : 3200, 1640, 1520.

δ ppm ($CDCl_3$) : 0.85 (3H,t,-CH_3), 1.60 (2H,m,-CH_2), 2.30 (3H,s,-CH_3 on ring), 3.70 (2H,t,-CH_2-O), 7.10, 7.45 (4H,m,-C_6H_4), 8.10 (1H,s,-N=CH).

(S) N-(4-methylbenzylidene)-2-amino-1-butanol (29b)



Yield : 78%. M.P. : 53° C.

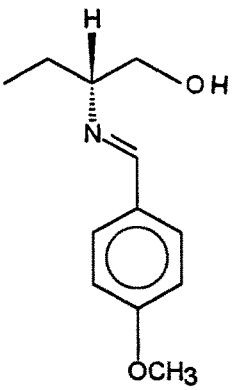
CHN found (calculated) : C - 74.90 (75.39), H - 8.57 (8.90), N - 7.21 (7.30).

$[\alpha]_D^{25}$: 29.70° (*c* 1.0 in $CHCl_3$).

ν_{max} (KBr)/cm^{-1} : 3200, 1630.

δ ppm ($CDCl_3$) : 0.80 (3H,t,-CH_3), 1.60 (2H,q,-CH_2), 2.35 (3H,s,-CH_3 on ring), 3.10 (1H,m,-CH), 3.70 (2H,d,-CH_2-O), 7.20, 7.60 (both 2H,d,-C_6H_4), 8.20 (1H,s,-N=CH).

(R) N-(4-methoxybenzylidene)-2-amino-1-butanol (30a)



Yield : 76%. M.P. : 54-55° C.

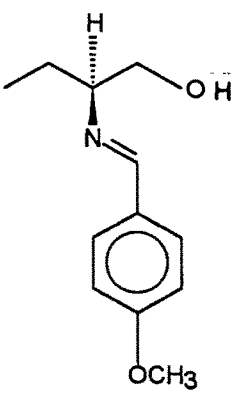
CHN found (calculated) : C - 68.94 (69.56), H - 8.72 (8.21), N - 6.37 (6.76).

$[\alpha]_D^{25}$: +62.60° (*c* 1.0 in $CHCl_3$).

ν_{max} (KBr)/cm^{-1} : 3250, 1630.

δ ppm ($CDCl_3$) : 0.85 (3H,t,-CH_3), 1.55 (2H,q,-CH_2), 2.80 (3H,s,-OCH_3), 3.10 (1H,m,-CH), 3.85 (2H,m,-CH_2-O), 6.95, 7.75 (m,d,4H,-C_6H_4), 8.15 (1H,s,-N=CH).

(S) N-(4-methoxybenzylidene)-2-amino-1-butanol (30b)



Yield : 77%. M.P. : 57° C.

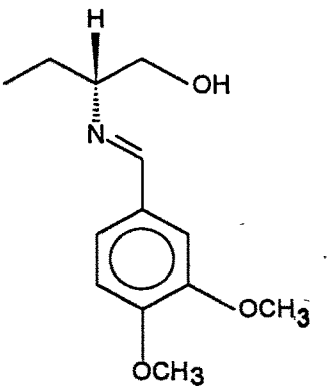
CHN found (calculated) : C - 68.94 (69.56), H - 8.50 (8.21), N - 6.89 (6.76).

$[\alpha]_D^{25}$: -59.30° (*c* 1.0 in $CHCl_3$).

ν_{max} (KBr)/cm^{-1} : 3250, 1640, 1520.

δ ppm ($CDCl_3$) : 0.85 (3H,t,-CH_3), 1.55 (2H,q,-CH_2), 3.30 (1H,m,-CH), 3.80 (2H,m,-CH_2-O), 6.90, 7.50 (4H,m,-C_6H_4), 8.10 (1H,s,-N=CH).

(R) N-(3,4-dimethoxybenzylidene)-2-amino-1-butanol (31a)



Yield : 85%. M.P. : 74° C.

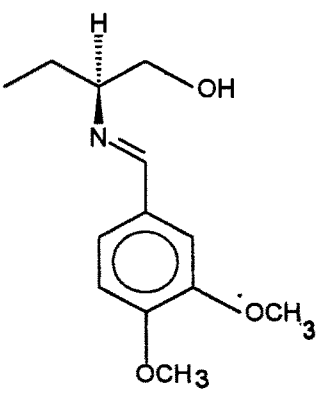
CHN found (calculated) : C - 65.90 (65.50), H - 7.95 (8.40), N - 5.64 (5.88).

$[\alpha]_D^{25}$: +17.98° (*c* 1.0 in MeOH).

ν_{max} (KBr)/cm^{-1} : 3250, 1630,1510.

δ ppm ($CDCl_3$) : 0.80 (3H,t,-CH_3), 1.60 (2H,q,-CH_2), 3.20 (1H,m,-CH), 3.70 (2H,d,-CH_2-O), 3.90 (6H,s,2-OCH_3), 7.00 (3H,m,-C_6H_3), 8.10 (1H,s,-N=CH).

(S) N-(3,4-dimethoxybenzylidene)-2-amino-1-butanol (31b)



Yield : 85%. M.P. : 73° C.

CHN found (calculated) : C - 66.00 (65.50), H - 8.90 (8.40), N - 5.76 (5.88).

$[\alpha]_D^{25}$: -16.60° (*c* 1.0 in MeOH).

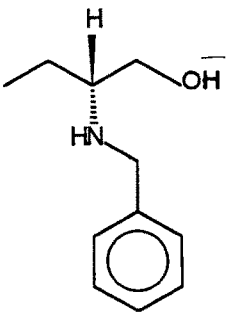
ν_{max} (KBr)/cm^{-1} : 3250, 1640,1520.

δ ppm ($CDCl_3$) : 0.80 (3H,t,-CH_3), 1.64 (2H,q,-CH_2), 3.20 (1H,m,-CH), 3.70 (2H,d,-CH_2-O), 3.90 (6H,s,2-OCH_3), 7.20 (3H,m,-C_6H_3), 8.20 (1H,s,-N=CH).

2.3.2 N-BENZYL DERIVATIVES OF *(R)* & *(S)* 2-AMINO-1-BUTANOL (32A-37A & 32B-37B)

The chiral imines **26a-31a** & **26b-31b** (0.01 mole) were dissolved separately in 25 ml of methanol. The solution was cooled at 0 °C in ice bath and sodium borohydride (0.012 mole) was added in small portions. The completion of the reaction was monitored by TLC. Addition of water (5 ml) and removal of the solvent under reduced pressure gave a residue which was extracted with dichloro methane. The dichloro methane extract was dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure furnished the product, which was crystallised from petroleum ether (60-80°c) - dichloromethane (50:50), to give the N-benzyl derivatives **(32a-37a)** and **(32b-37b)**.

(R) N-benzyl-2-amino-1-butanol (32a)



Yield : 91%. M.P. : 63-64° C.

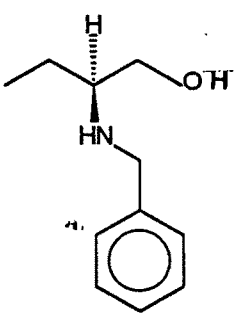
CHN found (calculated) : C - 73.36 (73.34), H - 9.09 (9.49), N - 7.46 (7.82).

$[\alpha]_D^{25}$: -21.31° (*c* 1.0 in $CHCl_3$).

ν_{max} (KBr)/cm^{-1} : 3300, 1450, 1250, 950.

δ ppm ($CDCl_3$) : 0.90 (3H,t,-CH_3), 1.40-1.60 (2H,m,-CH_2), 2.64 (3H,s,-NH,-N-CH_2), 3.36 (1H,m,-CH), 3.64 (1H,m,-OH), 3.70, 3.90 (2H,m,-CH_2-O), 7.20, 7.40 (5H,m,-C_6H_5).

(S) N-benzyl-2-amino-1-butanol (32b)



Yield : 92%. M.P. : 62° C.

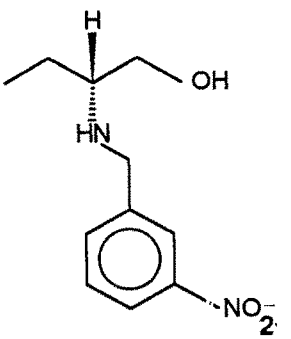
CHN found (calculated) : C - 74.01 (73.74), H - 8.95 (9.49), N - 7.40 (7.82).

$[\alpha]_D^{25}$: +20.52° (*c* 1.0 in $CHCl_3$).

ν_{max} (KBr)/cm^{-1} : 3300, 1450, 1240, 930.

δ ppm ($CDCl_3$) : 0.96 (3H,t,-CH_3), 1.40-1.60 (2H,m,-CH_2), 2.64 (3H,s,-NH,-N-CH_2), 3.36 (1H,m,-CH), 3.64 (1H,m,-OH), 3.70, 3.90 (2H,m,-CH_2-O), 7.20, 7.40 (5H,m,-C_6H_5).

(R) N-(3-nitrobenzyl)-2-amino-1-butanol (33a)



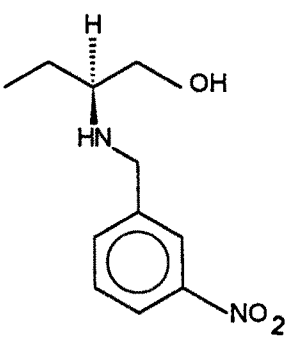
Yield : 92%. M.P. : 92-94° C.

CHN found (calculated) : C - 58.21 (58.93), H - 7.47 (7.14), N - 12.31 (12.50).

$[\alpha]_D^{25}$: -23.90° (*c* 1.0 in $CHCl_3$).

ν_{max} (KBr)/cm^{-1} : 3250, 1520, 1450, 1270.

(S) N-(3-nitrobenzyl)-2-amino-1-butanol (33b)



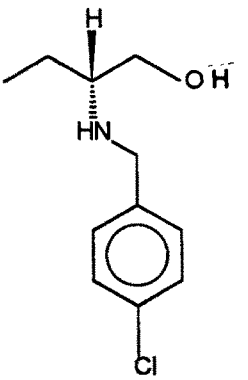
Yield : 92%. M.P. : 93° C.

CHN found (calculated) : C - 58.65 (58.93), H - 7.41 (7.14), N - 12.61 (12.50).

$[\alpha]_D^{25}$: +24.90° (*c* 1.0 in $CHCl_3$).

ν_{max} (KBr)/cm^{-1} : 3250, 1520, 1460, 1270.

(R) N-(4-chlorobenzyl)-2-amino-1-butanol (34a)



Yield : 81%. M.P. : 81° C.

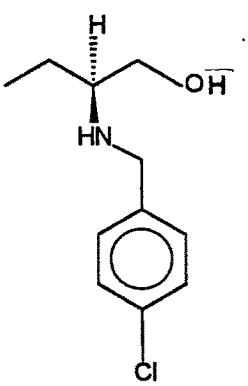
CHN found (calculated) : C - 62.20 (61.80), H - 7.80 (7.49), N - 6.47 (6.55).

$[\alpha]_D^{25}$: -12.91° (*c* 1.0 in $CHCl_3$).

ν_{max} (KBr)/cm^{-1} : 3300, 1490, 1450, 1370, 950.

δ ppm ($CDCl_3$) : 0.95 (3H,t,-CH_3), 1.45 (2H,m,-CH_2), 2.10 (3H,m,-NH,-N-CH_2), 2.62 (1H,m,-OH), 3.35 (1H,m,-CH), 3.75 (2H,m,-CH_2-O), 7.28 (4H,m,C_6H_4).

(S) N-(4-chlorobenzyl)-2-amino-1-butanol (34b)



Yield : 81%. M.P. : 72° C.

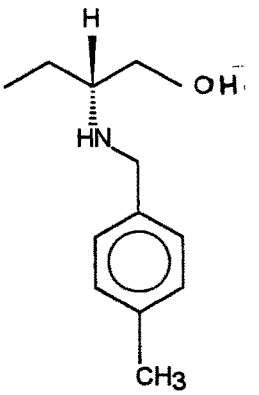
CHN found (calculated) : C - 62.20 (61.80), H - 7.80 (7.49), N - 6.47 (6.55).

$[\alpha]_D^{25}$: +13.91° (*c* 1.0 in $CHCl_3$).

ν_{max} (KBr)/cm^{-1} : 3300, 1490, 1450, 1370, 950.

δ ppm ($CDCl_3$) : 0.92 (3H,t,-CH_3), 1.45 (2H,m,-CH_2), 2.26 (3H,br.s,-NH,-N-CH_2), 2.60 (1H,m,-OH), 3.36 (1H,q,-CH), 3.60-3.90 (2H,m,-CH_2-O), 7.30 (4H,q,-C_6H_4).

(R) N-(4-methylbenzyl)-2-amino-1-butanol (35a)



Yield : 83%. M.P. : 63° C.

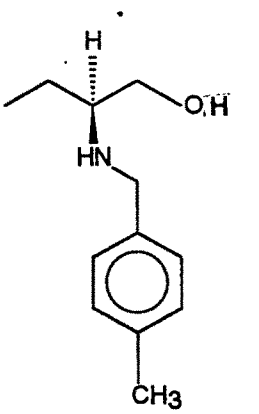
CHN found (calculated) : C - 75.01 (74.61), H - 9.23 (9.84), N - 7.45 (7.25).

$[\alpha]_D^{25}$: 11.42° (*c* 1.0 in MeOH).

ν_{max} (KBr)/cm^{-1} : 3200, 1520, 1350, 1270.

δ ppm ($CDCl_3$) : 0.90 (3H,t,-CH_3), 1.50 (2H,q,-CH_2), 2.25(3H,s,-CH_3 on ring), 2.40 (1H,s,-OH), 3.40 (1H,m,-CH), 3.80 (2H,m,-CH_2-O), 7.20 (4H,br.s,-C_6H_4).

(S) N-(4-methylbenzyl)-2-amino-1-butanol (35b)



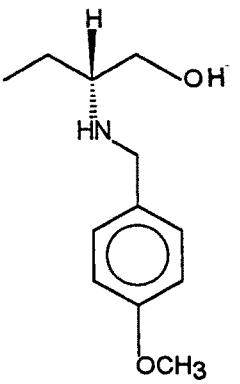
Yield : 81%. M.P. : 64° C.

CHN found (calculated) : C - 74.31 (74.61), H - 9.76 (9.84), N - 7.45 (7.25).

$[\alpha]_D^{25}$: +12.70° (*c* 1.0 in MeOH).

ν_{max} (KBr)/cm^{-1} : 3200, 1520, 1350, 1270.

(R) N-(4-methoxybenzyl)-2-amino-1-butanol (36a)



Yield : 89%. M.P. : 62 - 63° C.

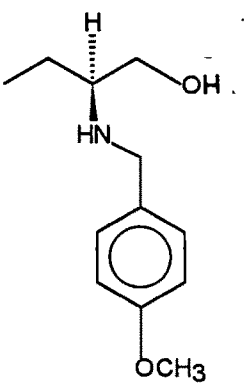
CHN found (calculated) : C - 69.02 (68.89), H - 9.30 (9.09), N - 6.78 (6.69).

$[\alpha]_D^{25}$: -35.60° (*c* 1.0 in $CHCl_3$).

ν_{max} (KBr)/cm^{-1} : 3250, 1510, 1350, 1270.

δ ppm ($CDCl_3$) : 0.90 (3H,t,-CH_3), 1.50 (2H,q,-CH_2), 2.40(3H,m,-NH, -N-CH_2), 3.30 (1H,m,CH), 3.60 (2H,m,-CH_2-O), 3.80 (2H,s,-OCH_3 on ring), 6.90, 7.20 (both 2H,d,-C_6H_4).

(S) N-(4-methoxybenzyl)-2-amino-1-butanol (36b)



Yield : 91%. M.P. : 61° C.

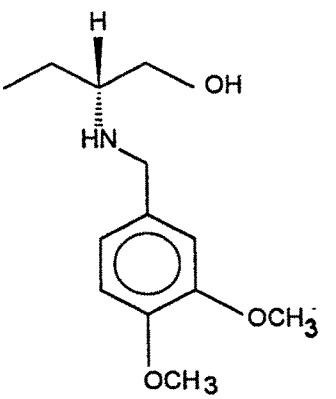
CHN found (calculated) : C - 68.40 (68.89), H - 9.54 (9.09), N - 6.86 (6.69).

$[\alpha]_D^{25}$: +33.30° (*c* 1.0 in $CHCl_3$).

ν_{max} (KBr)/cm^{-1} : 3250, 1520, 1350, 1270.

δ ppm ($CDCl_3$) : 0.90 (3H,t,-CH_3), 1.50 (2H,q,-CH_2), 2.40(3H,m,-NH, -N-CH_2), 3.34 (1H,m,CH), 3.60 (2H,m,-CH_2-O), 3.80 (3H,s,-OCH_3 on ring), 6.90, 7.20 (4H,dd,-C_6H_4).

(R) N-(3,4-dimethoxybenzyl)-2-amino-1-butanol (37a)

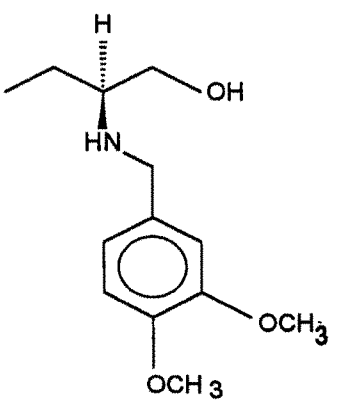


Yield : 86%. M.P. : 81°C.

CHN found (calculated): C - 65.01 (65.27), H - 8.90 (8.78), N - 5.56 (5.85).

ν_{max} (KBr)/cm^{-1} : 3250, 1510, 1450, 1370.

(S) N-(3,4-dimethoxybenzyl)-2-amino-1-butanol (37b)



Yield : 89%. M.P. : 82°C.

CHN found (calculated): C - 65.46 (65.27), H - 8.96 (8.78), N - 6.02 (5.85).

ν_{max} (KBr)/cm-1 : 3250, 1520, 1450, 1370.

2.4 REFERENCES

1. M.B. Eleveld, H. Hogeveen & E.P. Schudde, ***J. Org. Chem.***, **51** (1986) 3635.
2. K. Drausz, K. Kleeman & J. Martens, ***Angew. Chem. Int. Ed. Engl.***, **21** (1982) 1982.
3. '***The Alkanolamines hand book***', 1981, The Dow Chemical Co.
4. Yoshifumi Murata, Etsuko Miyamoto, Michihiro Ueda & Suserma Kawashima, ***J. Antibact. Antifung. Agents.***, **19** (1991) 343.
5. Eckstein Marian, Tobiasz Otrebska Kazimeira, Kadlubowska, Szklarr Barbara, Wyoke Malgorzata, Czerny Boguslaw & Juzwiak Stefanic, ***Pol. J. pharmacol pharma.***, **39** (1987) 309; ***CA*** **108** (1988) 68571 r.
6. Eckstein Marian & Cegla Marek, ***Acta. Pol pharm.***, **44** (1987) 12; ***CA*** **108** (1988) 6573 q.
7. Eckstein Marian & Cegla Marek, Krupinska Jolanta, Cebo Barbara & Michna Maria, ***Pol J. pharmacol pharm.***, **39** (1987) 317.
8. Reduction, Ed. by Robert L. Augustine (1968) p. 319, Marcel Dekker Inc., New York.
9. A.C. Cope & E.M. Hancock, ***J. Am. Chem. Soc.***, **64** (1942) 1503.
10. A.C. Cope & E.M. Hancock, ***J. Am. Chem. Soc.***, **66** (1944) 1453.
11. E.L. Englehardt, F.S. Crossley & J.M. Spargue, ***J. Am. Chem. Soc.***, **72** (1950) 2718.
12. Joseph E. Saavedra, ***J. Org. Chem.***, **50** (1985) 2271.

13. Ugo Azzena, Giovanni Melloni & Cristina Nigra, ***J. Org. Chem.***, 58 (1993) 6707.

14. Kimio Higashiyama, Hiroaki Inoue & Hiroshi Takahashi, ***Tetrahedron lett.***, (1992) 235.