Configurational Assignment to *N*-(1-Phenylalkyl)-substituted 2-Amino-1,2-diphenylethanols

Benito Alcaide, Carmen López-Mardomingo, Rafael Pérez-Ossorio,* and Joaquín Plumet
Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Compultense, Ciudad Universitaria, 28040 Madrid, Spain

Three-chiral centre aminoethanols are obtained by reduction of 1,2-imino ketones having a pre-existenting chiral centre. Assignment of configuration to the aminoethanols has been carried out on the basis of high-dilution i.r., ^{1}H n.m.r., and ^{13}C n.m.r. spectroscopic data.

The stereoselective synthesis of amino alcohols having two chiral centres has been achieved by reduction of 1,2-imino ketones.[1] Similarly, the reduction with various reagents of 1,2-imino ketones which possessed a pre-existing chiral centre allowed amino alcohols with three chiral centres to be obtained.[2] In the present paper the assignment of configuration to compounds (**1**)—(**7**) is reported. This type of compound can

$$\overset{1}{\text{Pr}}\text{–}\overset{2}{\text{CHOH}}\text{–}\overset{3}{\text{CHPh}}\text{–NH–CHPhR}$$

R = Me (**1**), Et (**2**), Pr (**3**)m Bu (**4**), Bu^i (**5**) Pr^i (**6**) Bu^t (**7**) †

exist as eight stereoisomers forming four racemates. The complete configurational assignment is based on the spectroscopic data reported below.

Results and Discussion

I.r. and ^{1}H *N.m.r. Spectrocopy.*—The possibility of the intramolecular association O–H · · · N has a decisive influence on the relative conformational populations ‡ of the amino alcohols.[1,2b,3] The study of this intramolecular association was carried out in the case of diastereoisomers of (**1**) and (**2**) by variable-dilution i.r. spectroscopy. Data are gathered in Table 1 in which values of the coupling constants $J_{1,2}$ are also given.

From the values of $\Delta\nu$§ ($\nu_{OH\ free} - \nu_{OH\ assoc.}$) a high degree of intramolecular association is deduced for these compounds.¶

Assignment of configuration of the chiral centres 1 and 2 of aminoethanols (**1**) and (**2**) is based on the following considerations. Since the values of $J_{1,2}$ are nearly equal for the α and β isomers and fairly close for the γ and ε isomers, the configuration of chiral centres 1 and 2 is expected to be the same for α and β isomers as for γ and ε isomers. This conclusion is in agreement with the chemical evidence, since α and β isomers are the major products in the direct lithium aluminium hydride (LAH) reduction of α-imino ketones, and γ and ε isomers are the only products obtained in the LAH reduction of the α-amino ketones prepared in turn by catalytic hydrogenation of α-imino ketones.[2] The mechanistic implications of this process point to this pairing of isomers (α and β, γ and ε) regarding the configurations of C-1 and C-2.

The conformational possibilities for all diastereoisomers of chiral centres 1 and 2 were then examined. They are shown in the diagram in which the (1*S*,2*S*) and (1*R*,2*S*) isomers are taken as examples.

For the (1*S*,2*S*) isomers, conformation (**III**) is sterically the most unstable and the only one incapable of intramolecular association; its contribution will then be negligible. According to Munk *et al.*,[6,7] the steric requirements for the (Ph · · · NR_2) interaction are large. This leads, for amino alcohols similar to ours but with a tertiary amino group, to $J_{1,2}$ values of 10—10.5 Hz. This value is accounted for by the larger population of conformation type (**II**) as compared to type (**I**). In our case, the less bulky NHR group would allow a larger relative population of (**I**) and a corresponding decrease in $J_{1,2}$. Values for α and β isomers in our compounds are of the order of 8 Hz, close to those of pseudoephedrine [with (*RR*,*SS*) configuration] which has also a secondary amino group.

For the (1*R*,2*S*) isomer, conformation (**IV**) will be less favoured on account of the lack of intramolecular association but it may be still significant since it is sterically less hindered than (**III**). The experimental values for the vicinal coupling constants $J_{1,2}$ for the γ and ε isomers are in agreement with the larger contributions of the conformers having 1-H and 2-H in a sinclinal arrangement.[6] Conformation (**VI**) is possibly the most populated.

Table 1. Absorption frequencies for the free and associated hydroxy groups in three-chiral-centre aminoethanols, Ph–CHOH–CHPh–NH–CHPhR

Compd.	R	Isomer[a]	ν_{OH}^{free}/cm^{-1}	$\nu_{OH}^{assoc.}$/cm^{-1}	$\Delta\nu$/cm^{-1}	$J_{1,2}$ Hz
(**1**)[b]	Me	α	3 630	3 450	180	8.545
		β	3 630	3 450	180	8.056
		γ	3 630	3 470	160	4.883
		ε	3 630	3 470	160	6.347
(**2**)	Et	α	3 592	3 440	152	8.0
		β	3 604	3 440	164	8.0
		γ	3 608	3 448	160	5.0
		ε	3 600	3 448	152	6.5

[a] Isolation of isomers is described in ref. 2*c*. The isomers with the largest coupling constants are designated as α and β and those with the lowest values of $J_{1,2}$ as γ and ε. [b] Data from ref. 2*b*.

† The assignment of configuration to the amino alcohol (**1**) has been reported previously in ref. 2*b*. In the same paper, assignment of configuration to two stereoisomers of three amino alcohols ArCHOHCHArNHCHPhMe (with Ar = *p*-MeC_6H_4, *p*-ClC_6H_4, and *m*-MeC_6H_4) is also given.

‡ In the conformational analysis of certain 1,2-amino alcohols having a primary amino group only those conformations for which this type of association is allowed are considered as populated.[4]

§ The value of $\Delta\nu$ allows an estimation of the degree of perturbation of the O–H vibration frequency due to the presence of the hydrogen bond. The strength of this is proportional to the $\Delta\nu$ value.[5]

¶ For the remaining amino alcohols, the i.r. study could not be completed since not all the diastereoisomers could be isolated pure. Nevertheless, changes in R seem to have no decisive influence on the presence and intensity of intramolecular association. See ref. 1 for i.r. spectra of the *N*-benzyl and *N*-diphenylethyl derivatives similar to those reported in the present paper.

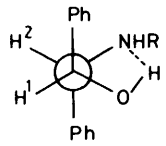
Table 2. ^{1}H N.m.r. parameters[a] of three-chiral-centre aminoethanols

Ph-$\overset{1}{C}$HOH-$\overset{2}{C}$HPh-NH-$\overset{3}{C}$HPhR

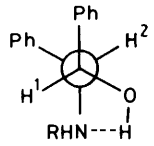
Compd.	R	Isomer	δ_1	δ_2	$J_{1,2}$	δ_3	δ_{Me}
(1)	Me	α[b]	4.612	3.424	8.545	3.631	1.360
		β[b]	4.644	3.905	8.056	3.772	1.501
		γ[b]	4.942	4.042	4.883	3.796	1.380
		ε[b]	4.699	3.666	6.347	3.538	1.274
(2)	Et[d]	α	4.43	3.26	8.0	3.1	0.73
		β	4.40	3.60	8.0	3.3	0.70
		γ	4.93	3.86	5.0	3.5	0.80
		ε	4.63	3.61	6.5	3.2	0.70
(3)	Pr[d]	α	4.63	3.37	8.0	3.4	
		β	4.60	3.73	7.5	3.5	
		γ	5.00	3.87	5.0	3.5	
		ε	4.66	3.57	6.5	3.3	
(4)	Bu[d]	α	4.53	3.33	8.5	3.4	
		β	4.63	3.70	7.5	3.4	
		γ	4.96	3.83	5.0	3.5	
		ε	4.66	3.57	6.0	3.3	
(5)	Bu^i[d]	α	4.57	3.33	8.5	3.4	
		β	4.55	3.70	7.5	3.4	
		γ	4.96	3.80	5.0	3.5	
		ε	4.60	3.57	6.5	3.6	
(6)	Pr^i[d]	α	4.42	3.25	8.0	2.90	0.90; 0.67
		β	4.48	3.55	6.3	3.11	0.97; 0.68
		γ	4.86	3.60	4.5	3.42	1.00; 0.73
		ε	4.50	3.40	6.5	2.90	0.88; 0.57
(7)	Bu^t	α	4.32	3.11	8.0	2.90	0.83
		β	4.38	3.42	5.5	2.90	0.90
		γ[c]	4.83	3.50	4.5	3.50	0.75
		ε[c]	4.50	3.50	6.5	2.91	0.75

[a] All spectra were recorded in $CDCl_3$ at 60 MHz except those marked *b* and *c*. [b] In $CDCl_3$ at 360 MHz. Data at 60 MHz were published in ref. 2*b*. [c] In $CDCl_3$ at 90 MHz. [d] The remaining protons of alkyl residues appear as complex multiplets with imprecise chemical shifts. Correct integration was found throughout.

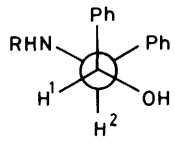
(1*S*,2*S*)



(I)

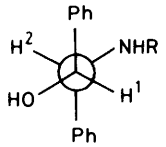


(II)

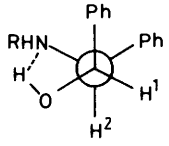


(III)

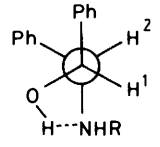
(1*R*,2*S*)



(IV)



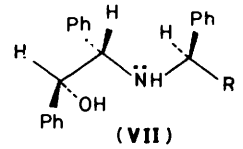
(V)



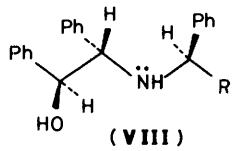
(VI)

In summary, the configuration (1*R*,2*R*/1*S*,2*S*) can be tentatively assigned to the α and β isomers. The important population of (**II**) accounts for the high values of $J_{1,2}$. The nearly exclusive population of (**I**) and (**II**) is in agreement with the higher degree of association (at least for the methyl derivative) deduced for the α and β isomers from i.r. data. The configuration (1*R*,2*S*/1*S*,2*R*) should then be assigned to the γ and ε isomers. The lower values of $J_{1,2}$ are expected since conformation (**IV**) is only of slight importance although perhaps not negligible. The degree of association for γ and ε isomers is lower due to this slight contribution of (**IV**).

(1*S*,2*S*,3*R*) (α)

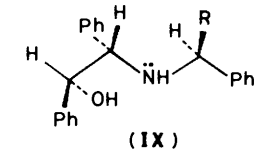


(VII)

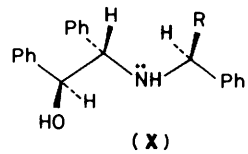


(VIII)

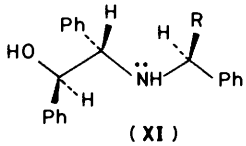
(1*S*,2*S*,3*S*) (β)



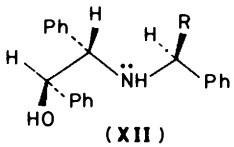
(IX)



(X)

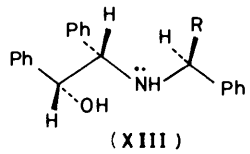


(XI)

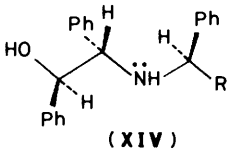


(XII)

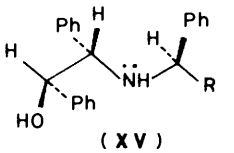
(1*R*,2*S*,3*S*) (γ)



(XIII)

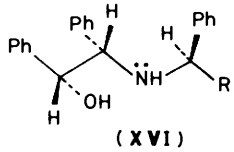


(XIV)



(XV)

(1*R*,2*S*,3*R*) (ε)



(XVI)

The extension of this configurational assignment to compounds (**3**)—(**7**) is based on the values of $J_{1,2}$ collected in Table 2 as well as on chemical evidence. Various methods for the assignment of configuration to amino alcohols though chemical reactions have been reported.[8] We have proceeded to the independent synthesis of the isomers with configurations (1*R*,2*S*/1*S*,2*R*) by opening of the *trans*-stilbene oxide ring by the appropriate racemic amine. This reaction, which occurs with inversion of configuration in the attacked carbon atom [9] led to the γ and ε isomers of (**1**), (**2**), (**6**), and (**7**). This fact, together with the constant values of $J_{1,2}$ (Table 2) for γ and ε isomers along the whole series ensures that in all cases the configuration is (1*R*,2*S*/1*S*,2*R*).

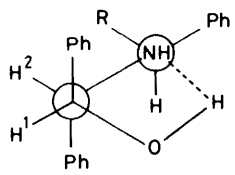
By exclusion all α and β isomers should have the (1*R*,2*R*/1*S*,2*S*) configuration although $J_{1,2}$ remains constant only for the α isomer. In the β isomers low values are obtained for (**6**) and (**7**). A tentative explanation is given below.

To deal with the more subtle problem of choosing the configuration for the third chiral centre in each diastereoisomer we take into consideration the significant magnetic parameters of amino alcohols (Table 2). We have simplified the conformational treatment of amino alcohols by considering that the preferred conformations for the (1*S*,2*S*,3*R*) isomer are (**VII**) and (**VIII**) which are derived from (**I**) and (**II**), respectively.

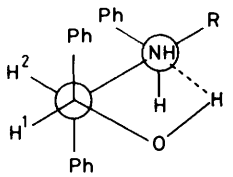
Table 3. Significant ^{13}C n.m.r. parameters for three-chiral-centre aminoethanols

$$\overset{1}{Ph}-\overset{2}{CHOH}-\overset{3}{CHPh}-NH-CHPhR$$

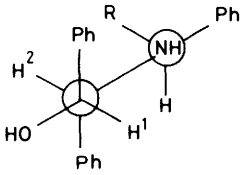
Compd.	Isomer	Confign.	δ C-1	C-2	C-3	C-4	C-5	C-6	C-7	$J_{H^1H^2}$
(1; R = Me)	α	(1*S*,2*S*,3*R*)	77.65	67.09	54.79	25.16				8.5
	β	(1*S*,2*S*,3*S*)	77.16	67.68	54.90	21.90				8.1
	γ	(1*R*,2*S*,3*S*)	75.37	65.62	54.52	22.77				4.9
	ε	(1*R*,2*S*,3*R*)	77.02	65.79	54.79	24.61				6.3
(2; R = Et)	α	(1*S*,2*S*,3*R*)	77.70	66.82	61.23	31.54	10.64			8.0
	β	(1*S*,2*S*,3*S*)	77.16	67.95	62.32	28.89	10.11			8.0
	γ	(1*R*,2*S*,3*S*)	75.16	66.00	61.72	29.98	10.42			5.0
	ε	(1*R*,2*S*,3*R*)	76.87	65.64	60.79	31.10	10.53			6.5
(4; R = Bu)	α	(1*S*,2*S*,3*R*)	77.40	66.50	59.25	38.10	28.03	22.21	13.57	8.5
	β	(1*S*,2*S*,3*S*)	76.73	67.72	60.77	35.71	27.86	22.46	13.78	7.5
	γ	(1*R*,2*S*,3*S*)	74.27	65.45	59.78	36.66	28.03	24.42	13.76	5.0
	ε	(1*R*,2*S*,3*R*)	77.12	65.29	59.53	38.84	28.33	22.41	13.73	6.0



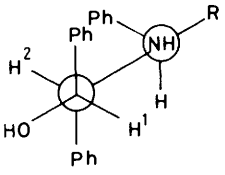
(IX)



(VII)



(XI)



(XIV)

Similarly, (**IX**) and (**X**) which also come from (**I**) and (**II**) are chosen for the (1*S*,2*S*,3*S*) isomer. For the (1*R*,2*S*,3*S*) and (1*R*,2*S*,3*R*) isomers three conformations were selected since (**IV**)—(**VI**) are all considered as populated. Examination of the appropriate Dreiding molecular models indicates that such a simplification may be acceptable, although with some reserve, for the (1*S*,2*S*,3*S*) and (1*R*,2*S*,3*S*) isomers for the most ramified alkyl groups.

Together with the $J_{1,2}$ values, the chemical shifts are particularly suitable to confirm the configurational assignment. Thus, we assign configuration (1*S*,2*S*,3*R*) to the α isomer since it shows a large value of $J_{1,2}$ due to the predominance of (**VIII**), which is unchanged by changing R. This alkyl group is in such a position as to exert very little influence on the value of $J_{1,2}$. Also, the δ_2 value is relatively low compared with that found for the β isomer, showing a larger shielding of 2-H. Consequently, the β isomer will have the (1*S*,2*S*,3*S*) configuration with a high value of $J_{1,2}$ due to the contribution of (**X**) and a higher δ_2 since 2-H is less shielded.

The lack of constancy of $J_{1,2}$ in the β isomers is undoubtedly related to the position of R both in (**IX**) and (**X**). The significant decrease in $J_{1,2}$ for compounds (**6**) and (**7**) should mean that ramified R groups favour conformation (**IX**) over (**X**). A tentative explanation may be based on the increased *gauche* interaction (NHCHPhR ··· Ph^1) which will open the Ph^1–C^1–C^2–N dihedral angle, as favoured by the hydrogen bridge association. There will be no parallel effect for the (1*S*,2*S*,3*R*) isomer in which growing of the alkyl chain does not influence the (NHCHPhR ··· Ph^1) interaction.

Configuration (1*R*,2*S*,3*R*) can be assigned to the ε compound. Since (**XVI**) is possibly the most populated conformation, $J_{1,2}$ will be lower than in the two previous cases and unchanged on changing R. The values of δ_2 are comparatively low due to shielding.

The remaining (1*R*,2*S*,3*S*) configuration is assigned to the γ isomer for which a low $J_{1,2}$ and a fairly high δ_2 are expected. The very low value of $J_{1,2}$ could mean that (**XI**) is non-populated as compared with (**XIV**). This might be due to the fact that (**XI**) would be practically non-populated since besides being non-associated it has the important destabilizing interaction (NHCHPhR ··· Ph^1). A parallel situation does not occur for the ε (1*R*,2*S*,3*R*) isomer since R does not particularly affect the stability of (**XIV**).

^{13}C *N.m.r. Spectroscopy.*—Data from ^{13}C n.m.r. spectra are in agreement with the above conclusions. Spectra of all stereoisomers of amino alcohols (**1**), (**2**), and (**4**) have been recorded. Chemical shifts for the aliphatic carbon atoms and coupling constants $J_{H^1H^2}$ are collected in Table 3.

Comparison of the chemical shifts of the isomers of (**1**) with those of the related isomers of (**2**) and (**4**) shows that growing of the aliphatic chain does not significantly affect the chemical shifts of C-1 and C-2, but produces a deshielding β-effect on C-3 of *ca.* 5—7 p.p.m. and a deshielding α-effect on C-4. The nearly constant values of the chemical shifts for C-1 and C-2 show that conformational populations are unchanged for the three series compared; the constancy of the coupling constants $J_{H^1H^2}$ confirms this conclusion.

The values of the chemical shifts for C-1 and C-2 for the various isomers are related to the degree of steric crowding in the most populated conformations of these isomers. Thus, the lowest chemical shifts, at least for C-1, are obtained for the γ isomer. This can be related to the large crowding of the four bulkiest groups Ph^1, Ph^2, OH, and NHR in both conformations (**XII**) and (**XIII**) and to the fact that the most alleviated conformation (**XI**) is non-populated as stated before. The fact that the chemical shift for C-1 in the ε isomer has values close to those for the α and β isomers suggests that the population of (**XIV**) is not negligible, as was noted above.

The largest values for the chemical shifts of C-1 and C-2 are found on the whole for the α and β isomers. This is related to the relative abundancy of conformations (**VIII**) and (**X**) both

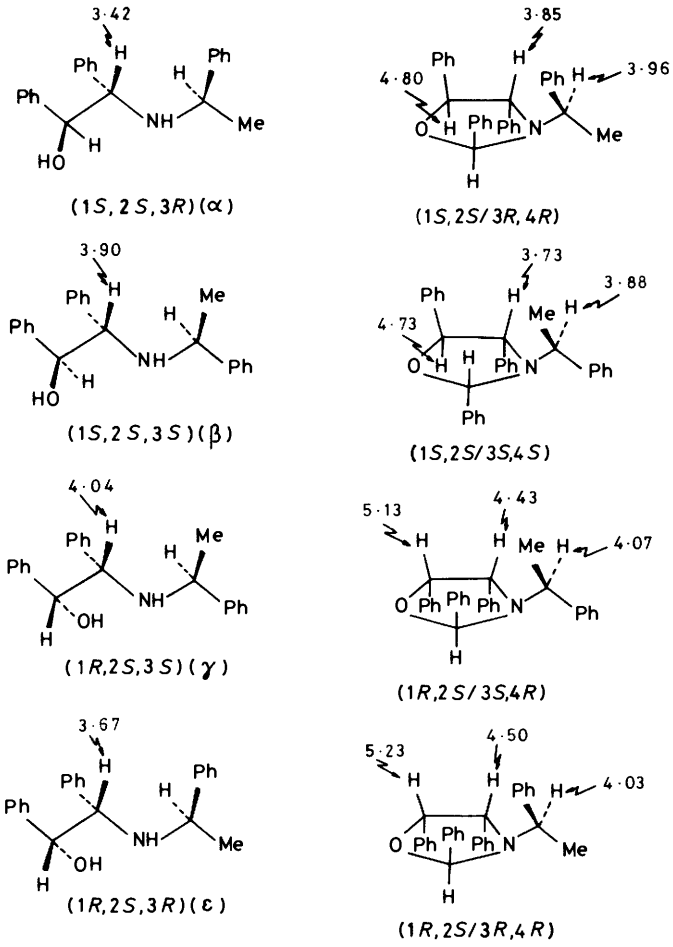


Figure. Numbering of chiral carbon atoms of amino alcohols (1, 2, 3) is maintained in the related oxazolidines. Thus the newly formed chiral centre is labelled as 4. This, of course, does not correspond with the accepted numbering of the oxazolidine ring

with an antiperiplanar 1-H–2-H arrangement and low steric crowding. The high value of $J_{H^1H^2}$ in these isomers confirms our conclusions.

^{13}C N.m.r. spectra then, although not particularly relevant to our problem, are in good agreement with the previous conclusions.

Comparison between ^1H *N.m.r. Chemical Shifts of the Aminoethanols and Related Oxazolidines.*—We have reported previously [10] the formation of oxazolidines with four chiral centres from resolved enantiomerically pure amino ethanols having three chiral centres. We pointed out that configurations of the chiral centres of starting amino ethanols are retained in the cyclic systems and that the newly formed chiral centre also has a definitive configuration.

In the Figure a comparison of the proton chemical shifts of the amino alcohols (**1**) with those of oxazolidines obtained from them is given. Since an oxazolidine ring is close to planarity,[11] any chemical shift of the 2-H would be influenced mainly by the aromatic ring attached to C-1. Thus in the α and β oxazolidines, 2-H lies within the shielding cone of Ph^1 and in the γ and ε oxazolidines it lies outside this cone. Then the 2-H chemical shifts for the α and β isomers (δ 3.85 and 3.73) are lower than for the γ and ε isomers (δ 4.43 and 4.50). This reasoning can be extended to the 1-H protons (δ 4.80 and 4.73 for the α and β isomers and δ 5.13 and 5.23 for the γ and ε). It may be noted that 2-H shows a fairly different degree of shielding in amino alcohols α and β, but shielding becomes very similar in the related oxazolidines. The same happens when amino alcohols γ and ε are compared with the oxazolidines obtained from them.

Finally, the relative constancy of the 3-H chemical shift in the oxazolidines may have its origin in the free rotation around the C-3–N bond.

Table 4. Opening of *trans*-stilbene oxide with amines Ph–$CHRNH_2$

R	Epoxide (mmol)	Amine (mmol)	Reaction time (h)	Yield (%)[a]
Me	6.6	66.3	4	52
Et	6.6	66.3	4	51
Pr^i	2.5	25.5	5	50
Bu^t	2.5	25.5	6	45

[a] Of pure isolated product.

Experimental

Variable-dilution i.r. spectra were recorded on a Beckmann 1240 spectrophotometer in CCl_4. ^1H N.m.r. spectra were recorded with a Varian T 60-A (60 MHz), a Varian En-360 (90 MHz), and a Bruker WN 360 (360 MHz) apparatus. ^{13}C N.m.r. spectra were taken with a Varian FT-80 apparatus. The synthesis and isolation of diastereoisomeric amino alcohols are reported elsewhere.[2c] Preparation of oxazolidines has already been reported.[10]

Ring Opening of trans-*Stilbene Oxide.*[3b]—This was carried out in a nitrogen atmosphere with an epoxide:amine ratio of 1:10. Refluxing was continued until the disappearance of the epoxide spot on t.l.c. Then the excess of amine was distilled off at reduced pressure and the residue was chromatographed on a silica gel column using benzene–diethyl ether (9:1) as eluant. Separation of the aminoethanol fraction gave a 1:1 mixture of the γ and ε isomers throughout. Reaction times and yields are collected in Table 4.

References

1 For the synthesis and configurational assignment of this type of compound see B. Alcaide, C. López-Mardomingo, R. Pérez-Ossorio, and J. Plumet, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1649, and references therein.
2 For the synthesis and structure of this type of compounds see: (*a*) R. Haro, C. Jimenez Tebar, R. Pérez-Ossorio, and J. Plumet, *Tetrahedron Lett.*, 1979, 1355; (*b*) B. Alcaide, R. Fernández de la Pradilla, C. López-Mardomingo, R. Pérez-Ossorio, and J. Plumet, *J. Org. Chem.*, 1981, **46**, 3234; (*c*) B. Alcaide, G. Domínguez, C. López-Mardomingo, R. Pérez-Ossorio, and J. Plumet, following paper.
3 (*a*) T. Kanzawa, *Bull. Chem. Soc. Jpn.*, 1956, **29**, 398, 479, and 604; (*b*) R. Mathis, M. T. Maurette, Ch. Godechot, and A. Lattes, *Bull. Soc. Chim. Fr.*, 1970, 3047.
4 D. Seeback, A. K. Beck, T. Mukhopadhyay, and E. Thomas, *Helv. Chim. Acta*, 1982, **65**, 1101.
5 A. Chabaud, M. Fetizon, and M. Golfier, *Bull. Soc. Chim. Fr.*, 1966, 252, and references therein.
6 M. E. Munk, M. K. Meilahn, and P. Franklin, *J. Org. Chem.*, 1968, **33**, 3480.
7 M. K. Meilahn, M. Statham, and M. E. Munk, *J. Org. Chem.*, 1975, **40**, 3551.
8 See for example B. R. Gunther and W. Kirmse, *Liebigs Ann. Chem.*, 1980, 518.

9 (*a*) D. Swern, *Chem. Rev.*, 1959, **59**, 737; (*b*) R. M. Laid and R. E. Parker, *J. Am. Chem. Soc.*, 1961, **83**, 4277; (*c*) L. E. Overman and L. A. Flippin, *Tetrahedron Lett.*, 1981, **22**, 195; (*d*) E. Epifani, A. Lupucci, B. Macchia, P. Tognetti, M. C. Breschi, M. de Tacca, E. Martinotti, and L. Giovannini, *J. Med. Chem.*, 1983, **26**, 254.
10 B. Alcaide, C. López-Mardomingo, R. Pérez-Ossorio, and J. Plumet, *J. Heterocycl. Chem.*, 1982, **19**, 45.
11 M. Hotokka and P. Pyyko, *J. Mol. Struct.*, 1979, **51**, 133.

Received 25*th October* 1984; *Paper* 4/1827