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A NEW SYNTHESIS OF BOTH THE ENANTIOMERS OF 4-AMINO-3-HYDROXYBUTANOIC ACID (GABOB) AND MM2 CALCULATIONS FOR ROTAMERS OF THE INTERMEDIATE OXAZOLIDIN-2-ONES

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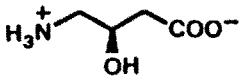
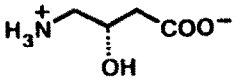
Abstract The easy chromatographic separation of the diastereomeric mixture of oxazolidin-2-ones 4a and 4b allows to synthesize pure R-(-)- 1a and (S)-(+)-GABOB 1b. The ^{1}H NMR pattern of 4a and 4b can be correlated with the configuration at C-5 and this relationship is confirmed by MM2 calculations for rotamers of 5-substituted oxazolidin-2-ones.

We have previously reported [1] that the iodocyclofunctionalization of allylic carbamates [2] containing as the chiral moiety the commercially available (S)-1-phenylethylamine, [3] allows to prepare diastereomeric mixtures of iodomethyloxazolidin-2-ones that may be easily separated by flash chromatography. In addition, on the basis of the ^{1}H NMR spectra, a conformational model has been proposed in order to attribute the configuration of the newly introduced stereogenic center in this class of compounds. In fact we have observed that the ^{1}H NMR chemical shifts at C-4 of these oxazolidin-2-ones strongly depend on the shielding of the phenyl group bonded to the stereogenic center on the nitrogen atom and on the substituent at C-5. [4] In this paper we confirm this structural assignment through the calculation of the conformational energies and describe an application of this methodology to a facile synthesis of the biologically active (R)- and (S)-4-amino-3-hydroxybutanoic acid (GABOB) 1a and 1b, [5] a 4-aminobutanoic acid derivative of great pharmacological importance because of its biological function as a neuromodulator in the mammalian central nervous system. Of particular interest is the (R)-(-)-isomer, as it has been shown to have greater biological activity than the (S)-(+)-isomer. [6]

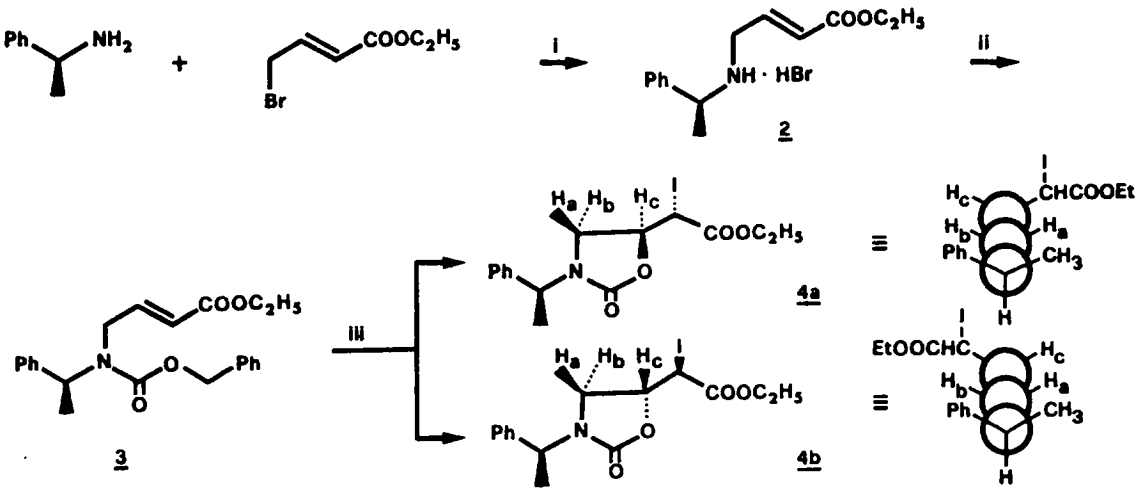


1a



1b

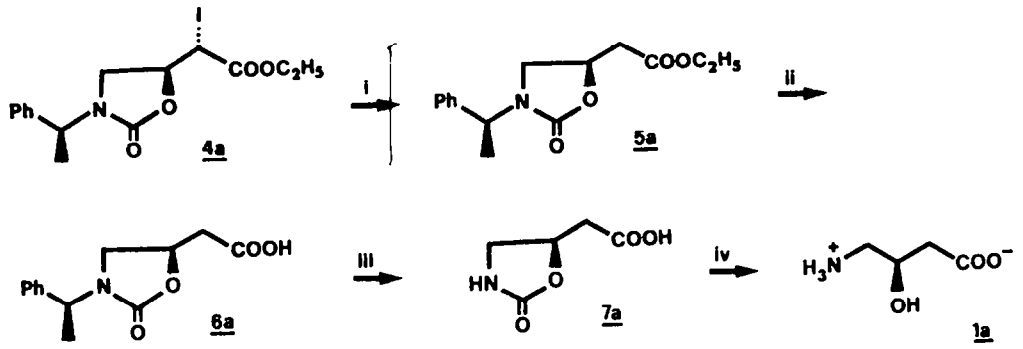
By treatment of ethyl 4-bromo-2(E)-butenoate with (S)-1-phenylethylamine, the corresponding hydrobromide 2 is quantitatively obtained and directly converted into the benzyloxycarbonylderivative 3 in 80% yield. The iodocyclization of 3, performed with iodine in $CHCl_3$ at r.t. gives a 1:1 diastereomeric mixture of oxazolidin-2-ones 4a and 4b, as determined by the ^{13}C NMR spectrum and g.l.c. analysis.



i. 1h at 0 °C, then at r.t ii. $PhCH_2O\overset{O}{\overset{\|}{C}}Cl$, $NaHCO_3$, acetone iii. column chromatography

Pure 4a and 4b are obtained by flash chromatography, and from the analysis of the ^1H NMR spectra the absolute configuration at C-5 is assigned. In fact the ^1H NMR spectra of diastereomers 4a and 4b show the non-equivalence of H_a and H_b and furthermore, owing to the phenyl group and CHRX shieldings, $\Delta\delta_{H_a,H_b}$ is larger in 4b than in 4a. In the ^1H NMR spectrum of 4b H_b resonates at 3.05 (dd, J_{ab} = 9 Hz and J_{bc} = 6.5 Hz), while H_a resonates at 3.7 δ (dd, $J_{ab} = J_{ac}$ = 9 Hz). On the contrary, 4a shows H_a resonating at 3.4 δ, upfield in respect to H_a in 4b and H_b at 3.40 δ, downfield in respect to H_b in 4b. These data agree with the extended Newman projection [1] where the phenyl ring preferentially eclipses an hydrogen that always resonates upfield in respect to the deshielded one. Thus we can attribute the R-configuration at C-5 of 4b, where a cis-relationship between H_a and H_c (J = 9 Hz) is observed; the R-configuration for the stereogenic center in the side chain is assigned from mechanistic considerations. On the contrary, the configuration for 4a is S at C-5 and S at the chain.

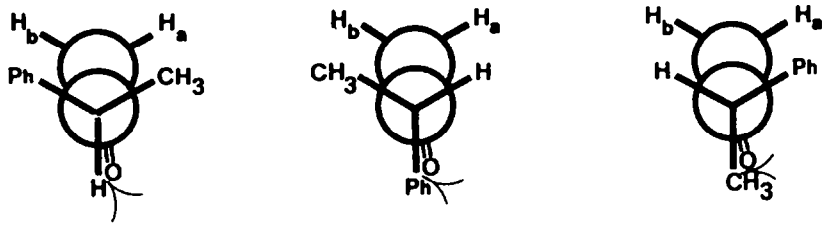
The cleavage of the C-I bond, performed on pure 4a with tri-n-butyltinhydride in refluxing benzene affords 5a in 85% yield, whereas pure 4b gives 5b. Either 5a and 5b show in the ^1H NMR spectrum the pattern of H_a and H_b identical with 4a and 4b. The oxazolidin-2-ones 5a and 5b are very unstable under basic conditions since they undergo a β-elimination to give the starting material 2; on the contrary, under mild acidic conditions, the corresponding acids 6a and 6b are obtained in a quantitative yield. When the cleavage is performed in refluxing 6M HCl, the GABOB hydrochloride is recovered, contamined by a 20% of N-phenylethyl derivative, as it is demonstrated by the ^1H NMR spectrum of the reaction mixture.



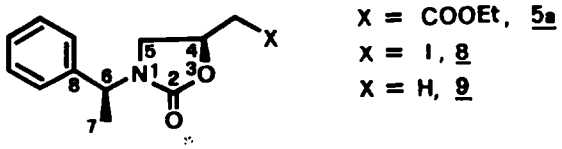
I. Bu_3SnH, refluxing benzene II. 6M HCl, at reflux III. Li/NH_3 IV. 6M HCl, at reflux, then Dowex 50W-X8

To avoid this troublesome separation, we exploited the reductive cleavage of the C-N bond of each diastereomer 6a and 6b with Li/NH_3 and 7a or 7b are obtained in good yield. The acidic hydrolysis of 7a or 7b affords eventually the GABOB hydrochloride (R)-1a or (S)-1b, respectively, confirming through the optical rotation the configurational assignment on the basis of the ^1H NMR spectral data.

An explanation of the observed ^1H NMR pattern, based on the conformational analysis, seems worth mentioning. In fact the relative equilibrium abundance of available conformers is the main factor which needs to be considered to account the ^1H NMR spectra. Among the three foreseen eclipsed conformations A, B, and C, the conformation A is considered to be most preferred since it is sterically least compressed owing to the interaction between the carbonyl group and the substituent.

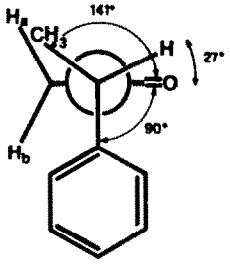


The conformational profile is calculated by molecular mechanics method [7] for 5-substituted oxazolidin-2-ones 5a, 8, and 9.

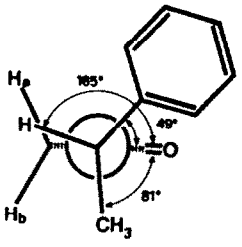


X = COOEt, 5a
X = I, 8
X = H, 9

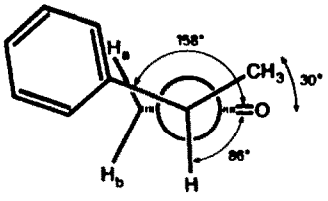
The plot obtained from a step-by-step full rotation around the N-C_6 bond exhibits only two minima and two maxima. In the calculated geometries of the two most stable forms, the C_6-C_7 or C_6- C_8 bonds are approximately perpendicular to the plane of the heterocyclic five-membered ring. The (2,1,6,7)-dihedral angle in the ground-state conformer A is calculated to be 141°, and the CH linkage is 27° out of the plane of the heterocyclic ring, while for B, that is 1.48 kcal/mol above the ground state conformer A, the phenyl ring is at 49° out of the plane and the (2,1,6,7) dihedral angle is 81°.



A



B



C

From the calculated energies it appears that of the possible conformers A, B and C of 5a, A is the more stable, while B is scarcely populated. From the A geometry it results that H_b, more than H_a, experiences the phenyl shielding. These results confirm the proposed model emploied to explain the ^1H NMR pattern. A similar conformational energy profile is observed for the oxazolidin-2-ones 7 and 8 (Table 1).

Table — Conformational energies and relative abundances of (R)-5-substituted oxazolidin-2-ones

MOLECULE	CONFORMER A			CONFORMER B		
	angle[a]	Energy	population %[c]	angle[a]	Energy[b]	population %[c]
5a	141°	0	92.4	-81°	1.48	7.6
8	141°	0	87.2	-83°	1.14	12.8
9	141°	0	77	-78°	0.74	23

[a] Dihedral angle $-\overset{\overset{O}{\|}}{C}-\overset{|}{N}-\overset{|}{C}-CH_3$ (2,1,6,7) [b] Relative energy (kcal/mole) respect to the ground-state

[c] Relative abundance calculated as exp(-E/RT) for T = 300 °K

From the analysis of the contributions to the total energy, we can mainly attribute the difference on energy to the increased long-range interactions between the oxygen and hydrogen, phenyl or methyl, respectively. A further destabilizing interaction between the phenyl and the H_a is present in the conformation C, so this structure gets the top of the energetic profile.

EXPERIMENTAL SECTION

General data Melting points (Pyrex capillary) were determined on a Buchi 510 hot stage apparatus and are uncorrected. ^{1}H NMR (90 MHz) spectra were taken with a Varian EM 390 instrument, and ^{13}C NMR spectra (20 MHz) with a Varian XL 100. IR spectra were recorded on a Perkin-Elmer Model 682 instrument. Optical rotation data were taken with a Perkin-Elmer 241 digital polarimeter.

(S)-N-(1-Phenylethyl)-N-3-(ethoxycarbonyl-2(E)-propen-1-yl)amine hydrobromide 2

A mixture of (S)-1-phenylethylamine (14.1 g; 116 mmol) and ethyl 4-bromo-2(E)-butenoate (25 g; 104 mmol) was stirred for 1 h at 0 °C and 3 h at r.t. The resulting oil was chromatographed on silica gel using ethyl acetate:methanol (95:5) as the eluting solvent, to yield 2 (25 g; 80%) as an oil; I.R. (neat) 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.1 - 1.6 (m, 6H), 3.25 (d, 2H), 3.8 (q, 1H), 4.15 (q, 2H), 5.85 - 7.2 (m, 2H), 7.3 - 7.8 (m, 5 ArH), 8.7 (bs, 2H, NH, HBr).

(S)-N-(1-Phenylethyl)-N-(3-ethoxycarbonyl-2(E)-propen-1-yl)-N-(benzyloxycarbonyl)amine 3

To a solution of the hydrobromide 2 (31.4 g; 100 mmol) in water:acetone (4:1) (100 ml), were sequentially added at 0 °C $NaHCO_3$ (16.8 g; 200 mmol) and benzyloxycarbonyl chloride (19.8 g; 116 mmol) in acetone (30 ml). After 1 h ether (300 ml) was added and the organic layer was washed with 10% aqueous $NaHSO_4$ (100 ml) and then with 10% aqueous Na_2CO_3, dried (Na_2SO_4) and concentrated in vacuo to give an oil which was purified by silica gel chromatography using cyclohexane:ethyl acetate (9:1) as the eluting solvent, to afford 3 (33.1 g; 90%) as a colorless oil; I.R. (neat) 1720 and 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.2 (t, 3H), 1.5 (d, 3H; J = 6Hz), 3.4 - 3.9 (m, 2H), 4.1 (q, 2H), 4.8 (q, 1H; J = 6 Hz), 5.2 (s, 2H), 5.4 - 6.8 (m, 2H), 7.25 (bs, 10 ArH).

(5S,R)-3-[(1S)-phenylethyl]-5-[(1S,R)-ethoxycarbonyl-iodomethyl] oxazolidin-2-one 4a,b

To a solution of 3 (7.34 g; 20 mmol) in $CHCl_3$ (100 ml), I_2 (10 g; 40 mmol) was added at r.t. After 5 h, the reaction was diluted with $CHCl_3$ (100 ml), the organic phase washed with 10% aqueous $Na_2S_2O_3$ (100 ml) and dried (Na_2SO_4). The solvent was then removed in vacuo to give a 6.65 g of a mixture 1:1 of diastereomers 4a and 4b in 90% yield. The separation of diastereomers was achieved by silica gel chromatography with cyclohexane:ethyl acetate (7:3) as the eluting solvent, to yield first the less polar (5S)-isomer 4a (3.2 g; 48%) in pure form as an oil. Further elution gave the more polar (5R)-isomer 4b in pure form (3.1 g; 47%), as an oil. (5S)-3-[(1S)-Phenylethyl]-5-[(1S)-ethoxycarbonyl-iodomethyl] -oxazolidin-2-one 4a: R_f = 0.52 (cyclohexane:ethyl acetate 7:3); I.R. (neat) 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.2 (t, 3H), 1.6 (d, 3H, J = 6Hz), 3.4 (m, 2H), 4.2 (q, 2H), 4.5 (m, 2H), 5.25 (q, 1H; J = 6Hz), 7.3 (m, 5 ArH); ^{13}C NMR ($CDCl_3$): δ 13.7, 16.2, 23.6, 46.0, 51.7, 62.4, 72.0, 127.1, 128.1, 128.8, 139.2, 168.6. (5R)-3-[(1S)-Phenylethyl]-5-[(1R)-ethoxycarbonyl-iodomethyl]oxazolidin-2-one 4b: R_f = 0.43 (cyclohexane:ethyl acetate 7:3); I.R. (neat): 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.2 (t, 3H), 1.55 (d, 3H, J = 6 Hz), 3.05 (dd, 1H, H_b, J_{ab} = 9 Hz, J_{bc} = 6.5 Hz), 3.7 (dd, 1H, H_a, $J_{ab} = J_{ac}$ = 9 Hz), 4.2 (q, 2H), 4.60 (m, 2H), 5.25 (q, 1H, J = 6 Hz), 7.3 (m, 5 ArH); ^{13}C NMR ($CDCl_3$): δ 13.6, 16.4, 22.9, 45.9, 51.7, 62.4, 72.4, 127.2, 128.1, 128.8, 139.2, 168.6.

(5R)-3-[(1S)-Phenylethyl]-5-(ethoxycarbonylmethyl)oxazolidin-2-one 5a

To a solution of 4a (8.6 g; 21 mmol) and ABIN (3.45 g; 21 mmol) in benzene (25 ml), was added dropwise tri-n-butyltinhydride (11.13 ml; 42 mmol) and was refluxed for 5 h. The solvent was removed under vacuum and the residue chromatographed on a silica gel column (hexane:ethyl acetate 6:4) to give 5a (4.8 g; 85%) as a white solid that was successively crystallized from

cyclohexane:ether 1:1; m.p. 58 °C; I.R. (nujol) 1750 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.2 (t, 3H), 1.55 (d, 3H, J = 6 Hz), 2.75 (m, 2H), 3.3 (m, 2H), 4.15 (q, 2H), 4.75 (m, 1H), 5.25 (q, 1H, J = 6 Hz), 7.3 (m, 5 ArH); ^{13}C NMR ($CDCl_3$): δ 14.1, 16.3, 39.4, 45.4, 51.5, 61.1, 69.5, 127.0, 127.9, 128.8, 139.5, 157.0, 169.3; $[\alpha]_D$ -37.3° (c = 5.12; $CHCl_3$).

(5R)-3-[(1S)-Phenylethyl]-5-(carboxymethyl)oxazolidin-2-one 6a

To a solution of 5a (5.1 g; 18.4 mmol) in acetone (10 ml), 6 M HCl (5 ml) was added and the mixture refluxed for 3 h. After evaporation in vacuo and silica gel chromatography (cyclohexane:ethyl acetate 1:1) 6a (4.2 g; 92%) was obtained as a white solid; m.p. 146 - 148 °C; I.R. (nujol) 1750 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.55 (d, 3H, J = 6 Hz), 2.75 (m, 2H), 3.3 (m, 2H), 4.75 (m, 1H), 5.25 (q, 1H, J = 6 Hz), 7.3 (m, 5 ArH); $[\alpha]_D$ -46.6° (c = 1.63; $CHCl_3$).

(3R)-4-Amino-3-hydroxybutanoic acid 1a

A solution of lithium metal (490 mg; 70 mmol) in anhydrous ammonia (150 ml) was stirred at -60 °C and 6a (2.49 g; 10 mmol) was added all at once, dissolved in THF/t-BuOH (55 ml; 10:1). After 3' the reaction was quenched by addition of solid NH_4Cl (3.8 g; 70 mmol), the ammonia was allowed to evaporate and the volatiles were removed in vacuo. The I.R. and the ^1H NMR spectra of the product were recorded in the presence of inorganic salts: I.R. (nujol) 1750 cm^{-1}; ^1H NMR (D_2O): δ 2.70 (d, 2H; J = 6 Hz), 3.4 (dd, 1H, H_a, J_{ab} = 9 Hz, J_{ac} = 6.5 Hz), 3.85 (dd, 1H, H_b, J_{ab} = J_{bc} = 9 Hz), 4.85 (m, 1H). The compound 7a was directly hydrolyzed by dissolving in 6 M HCl (50 ml) and refluxing the mixture for 7 h. After removal of the solvent, the residue is purified by ion-exchange chromatography on Dowex 50W-X8 (200-400 mesh H^+ form), eluting first with water and then with 2N NH_4OH, to yield 1a (0.83 g; 70%) as a white solid that was successively crystallized from H_2O: ethanol 1:1; m.p. 213 °C; I.R. (KBr) 3450, 3100-2500, 2150, 1665 cm^{-1}; ^1H NMR (D_2O): δ 2.3 (bd, 2H; J = 6 Hz), 3.0 (m, 2H), 4.1 (m, 1H); $[\alpha]_D$ -19.8° (c = 0.84; H_2O). Anal. Calcd for $C_4H_9NO_3$: C, 40.34; H, 7.56, N, 11.77. Found: C, 40.34; H, 7.66, N, 11.68.

(5S)-3-[(1S)-Phenylethyl]-5-(ethoxycarbonylmethyl)oxazolidin-2-one 5b

Prepared as 5a: colorless oil; I.R. (neat) 1750 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.2 (t, 3H, J = 6 Hz), 1.55 (d, 3H, J = 6 Hz), 2.6 (m, 2H), 2.85 (dd, 1H, H_b, J_{ab} = 9 Hz, J_{bc} = 6.5 Hz), 3.7 (dd, 1H, H_a, J_{ab} = J_{ac} = 9 Hz), 4.1 (q, 2H, J = 6 Hz), 4.85 (m, 1H), 5.25 (q, 1H, J = 6 Hz), 7.3 (m, 5 ArH); ^{13}C NMR ($CDCl_3$): δ 14.1, 16.5, 39.3, 45.3, 51.4, 60.9, 69.7, 127.0, 127.9, 128.7, 139.5, 157.0, 169.2; $[\alpha]_D$ -58.5° (c = 5.21; $CHCl_3$).

(5S)-3-[(1S)-Phenylethyl]-5-(carboxymethyl)oxazolidin-2-one 6b

Prepared as 6a; white solid; m.p. 112 - 114 °C; I.R. (nujol) 1750 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.55 (d, 3H, J = 6 Hz), 2.70 (m, 2H), 2.85 (dd, 1H, H_b, J_{ab} = 9 Hz, J_{bc} = 6.5 Hz), 3.7 (t, 1H, H_a, J_{ab} = J_{ac} = 9 Hz), 4.85 (m, 1H), 5.25 (q, 1H, J = 6 Hz), 7.3 (m, 5 ArH); $[\alpha]_D$ -73.8° (c = 3.37; $CHCl_3$).

(3S)-4-Amino-3-hydroxybutanoic acid 1b

Prepared as 1a; $[\alpha]_D$ +19.7° (c = 1.05; H_2O).

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