SYNTHESIS OF OPTICALLY ACTIVE 1-AZA-4-OXABICYCLO[4.1.0]-HEPTAN-5-ONES

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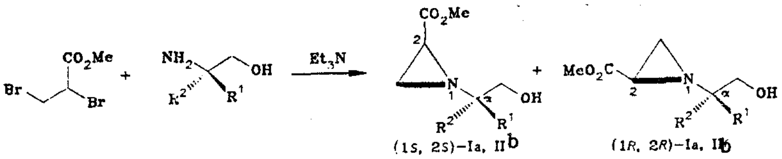
UDC 547.717'867'464.07:541.632'634:543.422

The reaction of the methyl ester of 1,2-dibromopropionic acid with chiral β-aminoalcohols under the conditions of the Gabriel-Cromwell reaction gave epimers of methyl 1-(β-hydroxyalkyl)aziridine-2-carboxylates, which were separated by liquid chromatography. NMR spectroscopy and CD were used to determine the absolute configuration of these products. The relative rate of conversion of epimeric esters of trans-1-(β-hydroxyalkyl)aziridine-2-carboxylic acids to 1-aza-4-oxabicyclo[4.1.0]heptan-5-ones is a function of the intramolecular contacts of the reacting OH and CO_2Me groups in the lactonization of the cis isomers. The most favorable conformation of the six-membered ring in 1-aza-4-oxabicyclo[4,1,0]heptan-5-ones in solution is a distorted boat.

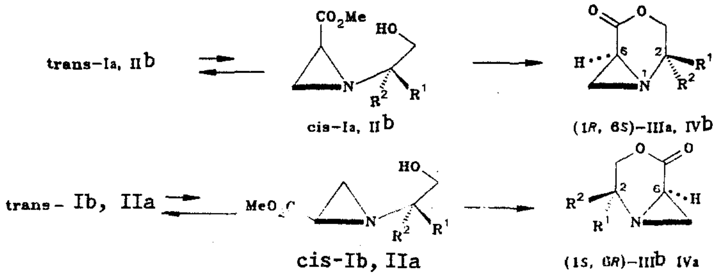
In previous work [1, 2], we synthesized new heterocycles, namely, 1-aza-4-oxabicyclo[4.1.0]heptan-5-ones, from esters of 1-(β-hydroxyalkyl)aziridine-2-carboxylic acids.

In the present work, the reaction of the methyl ester of 1,2-dibromopropionic acid with optically active aminoalcohols, namely, (R)-2-amino-1-butanol and (S)-2-amino-3-methyl-1-butanol [(S)-valinol], gave mixtures of epimers of methyl 1-(β-hydroxyalkyl)aziridine-2-carboxylates, which were separated using high efficiency liquid chromatography (HELC).



I a,b R^1=Et, R^2=H, α-(*R*); II a,b R^1=H, R^2=*i*-Pr, α-(*S*)

The closeness of the existing chiral center and the chiral center formed provide for stereoselectivity in this synthesis, especially in the case of hindered (S)-valinol. Analytical HELC data indicated that the Ia:Ib diastereomer ratio was 1.4, while the IIa:IIb ratio was 0.3. The difference in the intramolecular distances between the chiral centers in diastereomers Ia and Ib and in diastereomers IIa and IIb apparently have a major effect on their chromatographic mobility and rate of lactonization. Thus, these pairs are readily separated by liquid chromatography (see R_f values in Table 1) and differ significantly in the lactonization rate in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene: the conversion of Ib and IIb after 3 h is about 90% but the conversion of their isomers is less than 5%.



IIIa.,b R^1=Et, R^2=H, (2*R*); IV a,b R^1=H, R^2=*i*-Pr, (2*S*)

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0009-3122/89/2507-0818$12.50

TABLE 1. Characteristics of Ia,b-IVa,b

Compound	R_f	ν, cm⁻¹			$[\alpha]_D^{20}$, deg (c, %, in ethanol)	CD spectrum (MeOH), λ max,nm ($[\theta]_{max}$,deg·cm²/mole)	Yield, %
		aziridine CH	C=O	OH			
Ia	0,42	3060	1740	3370	−73,8 (4,3)	220 (−4080)	85
Ib	0,31				88,6 (0,9)	220 (3600)	
IIa	0,59	3060	1740	3400	90,6 (7,8)	220 (5900)	89
IIb	0,40				−89,8 (3,0)	220 (−5500)	
IIIa	0,48	3070	1740	—	7,5 (0,6)	226 (25 900), 198 (−16 300)	74
IIIb	0,52				−12,7 (1,2)	226 (−28 400), 198 (17 600)	68
IVa	0,56	3070	1740	—	−8,0 (1,4)	226 (−42 800), 199 (23 200)	77
IVb	0,66				2,2 (3,3)	226 (36 400), 199 (−27 200)	81

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*A satisfactory elemental analysis was not obtained due to high hygroscopicity.

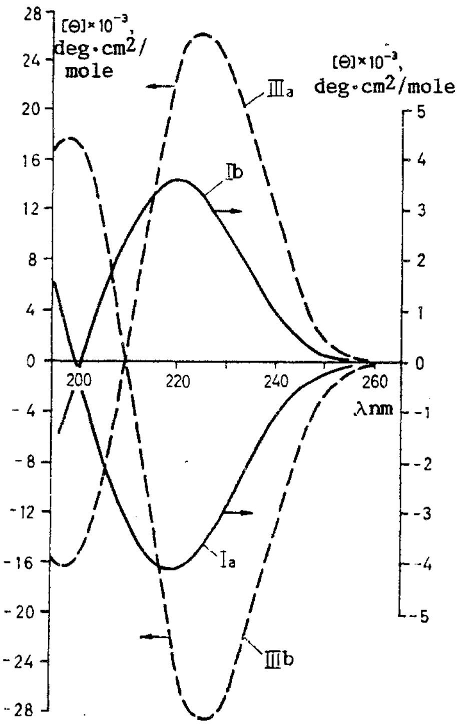


Fig. 1. CD spectra of diastereomers of 1-(β-hydroxyalkyl)aziridine-carboxylate (Ia and Ib) and 2-ethyl-1-aza-4-oxabicyclo[4.1.0]heptan-5-one (IIIa and IIIb).

Pure diastereomers of 1-aza-4-oxabicyclo[4.1.0]heptanones IIIa, IIIb, IVa, and IVb (Table 2) were obtained from pure diastereomers Ia, Ib, IIa, and IIb.

In the presence of dicyclohexyl-18-crown-6, Cs_2CO_3 in acetonitrile is a more efficient catalyst than diazabicycloundecene and permits the lactonization of esters Ia and IIa in 3.5 h.

The CD and PMR spectra of IIIa, IIIb, IVa and IVb were studied in order to elucidate the absolute configuration. The CD spectra show dichroic absorption bands of opposite signs at 226 and ∿220 nm (Fig. 1 and Table 2). The band at 226 nm is due to an n_0, π^*_{CO} transition of the δ-lactone chromophore, for which a sector rule has been reported [3, 4] relating the absolute configuration with the sign of the Cotton effect. In order to use this rule in the case of oxaazabicycloheptanones, we must determine the most populated conformation of the lactone ring since the major perturbing fragment (the $N(_1)$–$C(_2)$ bond) in the two possible conformations of this ring (distorted boat (A) and half-chair (B)) falls in sectors with opposite signs (Fig. 2). Conformation A was established for the lactone ring in an x-ray diffraction structural analysis of 2,2-di(hydroxymethyl)-1-aza-4-oxabicyclo[4.1.0]heptan-5-one. The same

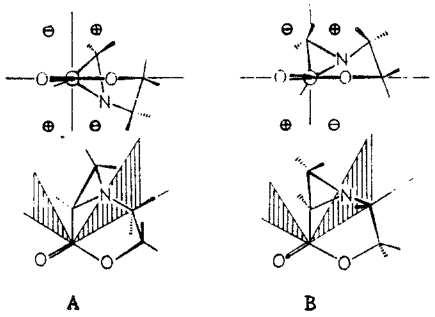


Fig. 2. Application of the sector rule for the lactone chromophore of (1S,6R)-1-aza-4-oxabicyclo[4.1.0]heptan-5-one in the half-boat (A) and half-chair conformations (B).

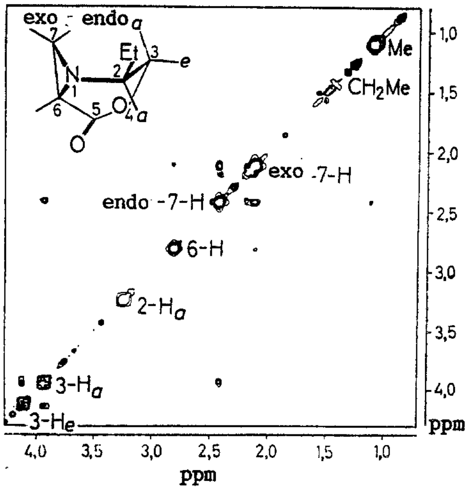
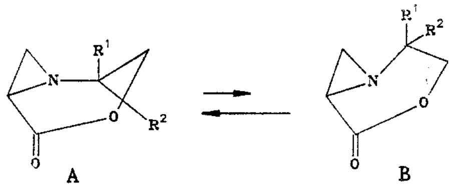


Fig. 3. Two-dimensional NOESY PMR spectra of IIIa.

conformation of this ring in IIIa and IVa in solutions was confirmed in our laboratory using two-dimensional NOESY PMR spectroscopy [5]. The observed off-diagonal cross peaks due to the nuclear Overhauser effect indicate close approximation of the 3a-H and endo-7-H protons (Fig. 3). Indeed, judging from Dreiding molecular models, the distance between these protons in conformation A is about 1.5 Å.



The reason for the shift in the conformational equilibrium toward A is apparently, as in the case of 1-aza- and 1,5-diazabicyclo[3.1.0]hexanes, the tendency to minimize the destabilizing effect of the p orbital of the nitrogen atom with the occupied group σ orbital of the adjacent CR^1R^2 group [6].

Thus, the positive long-wavelength Cotton effect in the CD spectra of IIIa and IVb according to the sector rule (Fig. 2) corresponds to the (1R, 6S) absolute configuration, while the negative sector on the spectra of IIIb and IVa corresponds to the (1S, 6R) absolute configuration. The observed ^3J coupling constants in the PMR spectra are in accord with this assignment (Table 3) and show that the orientation of 2-H in (1R, 2R, 6S)-IIIa and (1S, 2S, 6R)-IVa is axial, while this orientation in (1S, 2R, 6R)-IIIb and (1R, 2S, 6S)-IVb is equatorial.

Hence, we determine the absolute configuration of the starting hydroxyesters (1S, 2S)-Ia and IIb and (1S, 2R)-Ib and IIa. We should note that, as in the case of other

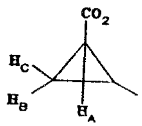


TABLE 2. PMR Spectral Parameters of IIIa, IIIb, IVa, and IVb

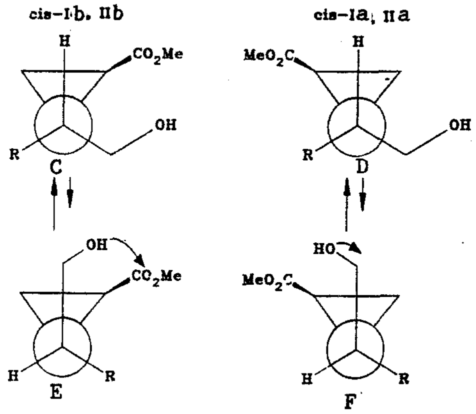
Compound	δ, ppm				J, Hz								Other protons
	2-H	3-H	6-H	7-H	2a,3a	2a,3e	2e,3a	2e,3e	3a,3e	6,exo-7	6,endo-7	exo-7 endo-7	
IIIa	3,23 (a)	3,94 (a); 4,11 (e)	2,80	2,10 (exo) 2,41 (endo)	12,5	4,6	—	—	−12,6	6,4	2,9	0,7	1,09 (Me), $^3J=7,5$ Hz; 1,44 and 1,54 (α-CH$_2$Me), $^2J=13,9$, $^3J=7,6$ Hz
IIIb	2,89 (e)	4,29 (a); 4,12 (e)	2,70	2,26 (exo); 2,45 (endo)	—	—	3,4	2,0	−12,7	6,4	3,2	0,7	1,08 (Me), $^3J=7,5$ Hz; 1,60 and 1,75 (α-CH$_2$Me), $^2J=13,2$, $^3J=7,3$ Hz
IVa	3,04 (a)	4,06 (a); 4,20 (e)	2,78	2,15 (exo); 2,45 (endo)	12,7	4,6	—	—	−12,7	6,4	2,9	0,7	1,00 and 1,14 (Me$_2$C), $^3J=6,8$ Hz; 1,71 (CHMe$_2$), $^3J=7,5$ Hz
IVb	2,50 (e)	4,19 (a); 4,22 (e)	2,62	2,21 (exo); 2,28 (endo)	—	—	3,6	2,4	−12,7	6,6	3,2	0,6	0,97 and 1,07 (Me$_2$C), $^3J=6,8$ Hz; 1,82 (α-CHMe$_2$), $^3J=7,6$ Hz

TABLE 3. PMR Spectral Parameters of Carboxylates Ia, Ib, IIa, and IIb

Compound	δ, ppm; J, Hz			δ, ppm			J, Hz		
	Me	CH$_2$	CH	H$_A$	H$_B$	H$_C$	$^3J_{AB}$	$^3J_{AC}$	$^2J_{BC}$
Ia	0,95 (MeC), $^3J=7,5$; 3,75 (MeO)	1,56 (Et); $^2J=13,4$; $^3J=5,4$; 1,67 (Et); $^3J=8,3$; 3,65 (CH$_2$O); $^2J=11,7$, $^3J=4,9$; 3,70 (CH$_2$O), $^3J==3,4$	1,43	2,30	1,72	2,21	6,6	3,2	0,6
Ib	0,94 (MeC); $^3J=7,5$; 3,75 (MeO)	1,57 (Et); $^2J=11,7$; $^3J=5,4$; 1,69 (Et); $^3J=8,3$; 3,65 (CH$_2$O); $^2J=11,7$; $^3J=3,7$; 3,70 (CH$_2$O); $^3J==5,6$	1,45	2,17	1,84	2,22	6,6	3,2	0,6
IIa	0,98; 1,03 (Me$_2$C); $^3J==6,8$; 3,75 (MeO)	3,72 (CH$_2$O); $^2J=12,0$; $^3J=5,0$; 3,74 (CH$_2$O); $^3J==3,5$	1,29 (CHN), 2,01 (CHMe$_2$)	2,30	1,75	2,27	6,6	3,4	1,0
IIb	0,98; 0,99 (Me$_2$C); $^3J==6,8$; 3,75 (MeO)	3,71 (CH$_2$O); $^2J=11,7$; $^3J=3,7$; 3,76 (CH$_2$O); $^3J==6,1$	1,35 (CHN), 1,98 (CHMe$_2$)	2,17	1,87	2,21	6,6	3,4	1,0

diastereomeric derivatives of aziridine-2-carboxylic acids [7], (1S, 2S, αR)-Ia and (1R, 2R, αS)-IIa have a greater difference in the chemical shifts of aziridine ring protons H_A and H_B ($\Delta\nu_{AB}$) than for their isomers, (1R, 2R, αR)-Ib and (1S, 2S, αS)-IIb (Table 3).

Knowledge of the absolute configuration of aziridinecarboxylates Ia, Ib, IIa, and IIb permits us to explain the higher rate of lactonization of diastereomers Ib and IIb in comparison with Ia and IIa. The conformation, in which the aziridine ring is eclipsed by the least bulky substituent (hydrogen atom), is most favorable at the $N-C_\alpha$ bond for three-membered heterocycles containing an asymmetric $CHRR^1$ N-substituent [8]. The reacting OH and CO_2Me in the conformations (C and D) in cis-esters Ib and IIb are closely approximated, while these groups in cis esters Ia and IIa are far from each other. If conformations E and F with the most closely approximated reacting groups are occupied, then, in the first case, the steric interaction of the α-alkyl group R with the aziridine ring facilitates an even closer approximation of the OH and CO_2Me groups, while in the second case, this interaction leads to the removal of these groups from each other.



Conformers C–F of only the cis-esters* were examined in the scheme, since lactonization of the trans-invertomers is sterically impossible. However the trans form is occupied predominantly for most 1,2-disubstituted aziridines [9]. Thus, the transformation of (hydroxyalkyl)aziridinecarboxylates to azaoxabicycloheptanones involves inversion of the nitrogen atom. Previously, this step in the isomerization of 1,2-divinylaziridines and azepines was shown not to be rate-limiting due to the low inversion barrier of the nitrogen atom [10]. The data on the inversion barriers in N-alkylaziridines (about 18 kcal/mole [11]) indicate that inversion cannot be the rate-limiting step in the case of the cyclization of I and II.

EXPERIMENTAL

The PMR spectra were taken on a Bruker WM-400 spectrometer in $CDCl_3$ with TMS as the internal standard. Optical rotation was determined on a Perkin–Elmer 141 polarimeter and the CD spectra were taken on a JASCO 500A spectropolarimeter with a DP 500N processor. The IR spectra were taken on a Perkin–Elmer 580B spectrophotometer. The synthesis and lactonization of the esters of 1-(hydroxyalkyl)aziridine-2-carboxylic acids was monitored by gas-liquid chromatography on a Chrom 5 chromatograph using a 3.5 × 1200-mm column packed with SE-30 on Chromosorb W/AW (100-120 mesh) at 110°C. The mixtures of the diastereomers of I and II were analyzed on a Du Pont 830 Prep chromatograph on a 4.6× 250-mm Zorbax Sil column using 15:85 dioxane-hexane as the eluent. The preparative separation of the mixtures was carried out on a 21.2 × 250-mm Zorbax Sil column. The R_f values were found on Merck UV-254 plates using ethyl acetate as the eluent with development by iodine vapor.

Esters of 1-(β-hydroxyalkyl)aziridine-2-carboxylic acids (Ia, Ib, IIa, and IIb). A mixture of 5.7 mmoles aminoalcohol and 1.54 ml (11 mmoles) triethylamine was added dropwise with stirring to a solution of 0.63 ml (5 mmoles) methyl 1,2-dibromopropionate in 30 ml dry acetonitrile at from −5 to 0°C. The mixture was stirred for 1 h at 60°C. After removal of the solvent in vacuum, the residue was extracted with absolute ether. The extract was passed through a 3 × 5-cm column packed with silica gel (40-100 µm). Ether was evaporated in vacuum and the mixture of the epimeric hydroxyesters was separated by HELC.

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*The scheme is given for IIb and IIa. The elements of the scheme for Ib and Ia should be represented as mirror antipodes.

1-Aza-4-oxabicyclo[4.1.0]heptanones (IIIa, IIIb, IVa, and IVb). A sample of 1.4 g cesium carbonate and 0.15 g dicyclohexyl-18-crown-6 were added to a solution of 1 mmole hydroxyester in 5 ml dry acetonitrile and then the mixture was stirred for 3.5 h at room temperature. The solution was evaporated in vacuum and the residue was purified as described in the above procedure.

Comparison of the lactonization rates of the epimers was carried out relative to their conversion to lactones over a given time using an equimolar amount of diazabicycloundecene. For this purpose, 0.152 g (1 mmole) diazabicycloundecene was added to 5 ml of a solution of the hydroxyester (0.2 mole/liter) in acetonitrile and the mixture was stirred at room temperature. The conversion of the hydroxyester to the lactone was evaluated by gas-liquid chromatography.

LITERATURE CITED

1. A. V. Eremeev, O. N. Krutius, A. F. Mishnev, Ya. Ya. Bleidelis, É. É. Liepin'sh, A. G. Odynets, D. A. Berzinya, and A. A. Kimenis, Khim. Geterotsikl. Soedin., No. 10, 1349 (1984).
2. O. N. Krutius, F. D. Polyak, and A. V. Eremeev, Khim. Geterotsikl. Soedin., No. 10, 1340 (1988).
3. J. P. Jennings, W. Klyne, and P. M. Scopes, J. Chem. Soc., No. 12, 7229 (1965).
4. M. Legrand and M. J. Rougier, in: H. B. Kagan (editor), Stereochemistry. Fundamentals and Methods, Vol. 2, Georg Thieme, Stuttgart (1977), p. 33.
5. A. Bax and R. Freeman, J. Magn. Reson., 44, 542 (1981).
6. G. V. Shustov, S. N. Denisenko, I. I. Chervin, N. L. Asfandiarov, and R. G. Kostyanovskii (Kostyanovsky), Tetrahedron, 41, 5719 (1985).
7. A. V. Eremeev, F. D. Polyak, I. A. Vosekalna, I. I. Chervin, Sh. S. Nasibov, and R. G. Kostyanovskii, Khim. Geterotsikl. Soedin., No. 10, 1343 (1984).
8. G. V. Shustov, F. D. Polyak, V. S. Nosova, I. T. Liepinya, G. V. Nikiforivich, and R. G. Kostyanovskii, Khim. Geterotsikl. Soedin., No. 11, 1461 (1988).
9. I. I. Chervin, A. A. Fomichev, A. S. Moskalenko, N. L. Zaichenko, A. É. Aliev, A. V. Prosyanik, V. N. Voznesenskii, and R. G. Kostyanovskii, Izv. Akad. Nauk SSSR, Ser. Khim., No. 5, 1110 (1988).
10. E. L. Stogryn and S. Brois, J. Am. Chem. Soc., 89, 605 (1967).
11. J. M. Lehn, Topics Curr. Chem., 15, 311 (1970).