SYNTHESIS AND ABSOLUTE CONFIGURATIONS OF DIASTEREOMERIC AZIRIDINE-2-CARBOXYLIC ACID DERIVATIVES CONTAINING VALINE AND HEXAFLUOROVALINE FRAGMENTS*

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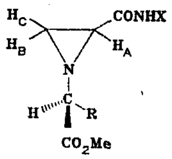
Individual diastereomers of aziridine-2-carboxylic acid esters that contain R- and S-valine and R- and S-hexafluorovaline fragments were isolated by high-performance liquid chromatogrpahy (HPLC). The absolute configurations of both asymmetric centers of the diastereomeric esters were determined on the basis of the parameters of the PMR spectra ($\Delta\nu_{AB}$) and circular dichroism (the sign of the cotton effect at 200-220 nm).

The structure and chiroptical properties of diastereomeric aziridine-2-carboxylic acid amides of the I type with an asymmetric substituent attached to the nitrogen atom of the aziridine ring were previously investigated [2].



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It was shown that in the case of the S configuration of this substituent the absolute configuration of the asymmetric carbon atom of the aziridine ring can be correlated with the criteria of the PMR spectra ($\Delta\nu_{AB}$) and the circular dichroism (CD) spectra [the sign of the Cotton effect (CE) at 200-220 nm (the band of the n → π* transition of the amide chromophore)]: the larger $\Delta\nu AB$ value and a positive ("+") sign of the CE correspond to the RS† diastereomer, and the smaller $\Delta\nu_{AB}$ value and a negative ("–") sign of the CE corresponds to the SS diastereomer. According to the proposed conformational model, in the case of an R configuration of the substituent the larger $\Delta\nu_{AB}$ value should correspond to the SR diastereomer, and the smaller $\Delta\nu_{AB}$ value should correspond to the RR diastereomer. The correspondence of the absolute configuration of the aziridine asymmetric carbon atom to the sign of the CE should remain unchanged.

In the present paper we present an investigation of the structures and chiroptical properties of diastereomeric derivatives of aziridine-2-carboxylic acid that contain valine and 4,4,4,4',4',4'-hexafluorovaline fragments.

Diastereomeric aziridine-2-carboxylic acid derivatives V-VIII (Table 1) were obtained on the basis of methyl 2,3-dibromopropionate (II) and S- and R-valine methyl esters in the presence of triethylamine, and diastereomers XII-XV (Table 1) were obtained by the reaction of methyl β,β-bis(trifluoromethyl)acrylate with methyl esters of S- and R-aziridine-2-carboxylic acids.

Individual diastereomerically pure compounds were isolated by high-performance liquid chromatography (HPLC). The configuration of the amino acid fragment is known for diastere-

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*Communication 44 from the series "Asymmetric unbridged nitrogen." See [1] for communication 43.

†The absolute configuration of the asymmetric carbon atom of aziridine is indicated first.

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TABLE 1. Characteristics of V-VIII and XII-XV

Compound*	bp, °C (mm)	$[\alpha]_D$ (c, EtOH)	Found, %			Empirical formula	Yield, %
			C	H	N		
V	80 (0,01)	+64,6 (0,54)	55,5	7,7	6,6	$C_{10}H_{17}NO_4$†	
VI		−84,5 (1,12)	55,9	7,8	6,4		85
VII		−66,3 (0,93)	55,4	7,9	6,7		
VIII		+85,7 (0,63)	55,6	7,7	6,3		81
XII	50 (0,5)	−16,9 (0,95)	37,4	3,5	4,4	$C_{10}H_{11}F_6NO_4$‡	
XIII		−99,0 (0,62)	37,1	3,4	4,2		55
XIV		+16,0 (0,64)	36,9	3,4	4,5		
XV		+87,2 (0,61)	37,5	3,3	4,4		52

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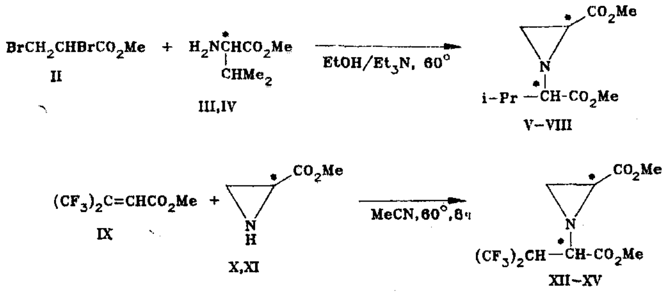
*The IR spectra of all of the compounds contain a ν_{CO} band at 1750 cm^{-1}.

†Calculated: C 55.8; H 7.9; N 6.5%.

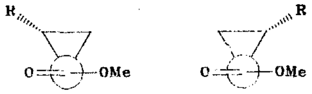
‡Calculated: C 37.1; H 3.4; N 4.3%.

omers V-VIII, and the configuration of the aziridine fragment is known for diastereomers XII-XV. Different $\Delta\nu_{AB}$ values for pairs that differ with respect to the configuration of the aziridine fragment are observed in the PMR spectra of diastereomers V-VIII and XII-XV (Table 2). This makes it possible to determine the absolute configurations of diastereomers V-VIII and XII-XV using the dependence of $\Delta\nu_{AB}$ on the configuration proposed in [2]. The correctness of the configuration was also confirmed on the basis of the signs of the CE at 210-220 nm.



III, X **S-isomer**; IV, XI *R*-isomer; VII, XII *SR*; VI, XIII *SS*; V, XIV *RS*; VIII, XV *RR*

One Cotton effect (CE), which can be ascribed to the N→π* transition of ester groups, is observed in the CD spectra of diastereomers V-VIII and XII-XV at 210-230 nm (Table 3). As we have shown above, the sign of the CE correlates with the configuration of the aziridine fragment, and this makes it possible to examine the conformation of the ester groups of the aziridine fragment with the use of the sector rule [3]. In order to obtain agreement with this rule one must assume that in diastereomers that differ with respect to the configuration of the aziridine fragment the ester group takes on different orientations relative to the three-membered ring; in the SS diastereomer the carbonyl oxygen atom is found near the nitrogen atom, whereas in the RS diastereomer the MeO group is found near the nitrogen atom.



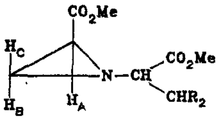
SS diastereomer *RS* diastereomer

An analysis of the CD spectra of hexafluorovaline derivatives XII-XV shows that the SR and SS diastereomers, on the one hand, and the RR and RS diastereomers, on the other, are characterized by CE with the same sign and approximately the same ellipticity values. This constitutes evidence for the extremely small contribution of the asymmetric fluorine-containing amino acid fragment of XII-XV to the circular dichroism of the molecules as compared with the hydrocarbon analogs.

EXPERIMENTAL

The PMR spectra of the compounds were obtained with Bruker WH-90 (90 MHz) and WM-400 (400 MHz) spectrometers. The IR spectra were obtained with a Perkin-Elmer 580-B spectrometer.

TABLE 2. Parameters of the PMR Spectra of V-VIII and XII-XV



Compound*	R	δ, ppm				J, Hz					
		H_A	H_B	H_C	other protons	AB	AC	BC	CHCH	CHMe	$CHCF_3$
V	Me	2,23	1,72	2,37	3,73; 3,74 (CO_2Me); 2,15 (NCH); 0,98; 1,08 (Me_2C); 2,22 ($CHMe_2$)	6,35	3,42	0,73	6,84	6,84	—
VI	Me	2,18	1,72	2,30	3,74; 3,75 (CO_2Me); 2,14 (NCH); 1,00; 1,05 (Me_2C); 2,22 ($HCMe_2$)	6,59	3,42	0,49	6,84	6,84	—
VII	Me	2,23	1,72	2,37	3,73; 3,74 (CO_2Me); 2,15 (NCH); 0,98; 1,08 (Me_2C); 2,22 ($HCMe_2$)	6,35	3,42	0,73	6,84	6,84	—
VIII	Me	2,18	1,72	2,30	3,74; 3,75 (CO_2Me); 2,15 (NCH); 1,0; 1,05 (Me_2C); 2,22 ($HCMe_2$)	6,59	3,42	0,49	6,84	6,84	—
XII	CF_3	2,44	1,84	2,44	3,77; 3,83 (CO_2Me); 3,30 [$CH(CF_3)_2$]; 2,95 (NCH)	—	—	—	3,66		8,3
XIII	CF_3	2,39	1,97	2,56	3,74; 3,85 (CO_2Me); 3,96 [$CH(CF_3)_2$]; 2,95 (NCH)	—	—	—	3,17		8,3
XIV	CF_3	2,44	1,84	2,44	3,77; 3,83 (CO_2Me); 3,90 [$CH(CF_3)_2$]; 2,95 (NCH)	—	—	—	3,42		8,06
XV	CF_3	2,39	1,97	2,56	3,74; 3,85 (CO_2Me); 3,96 [$CH(CF_3)_2$]; 2,95 (NCH)	—	—	—	3,17		8,3

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*For XII-XV the assignment of the signals of the ring protons was made in analogy with [2]; the constants of the ABO system were not determined because of marked broadening of the signals.

TABLE 3. Circular Dichroism (CD) Spectra, $\Delta\nu_{AB}$ Values, and Absolute Configurations of Diastereomers V-VIII and XII-XV

Compound	λ, nm ([θ]·10^{-3}, deg-cm^2-dmole^{-1})	$\Delta\nu_{AB}$,* ppm	Absolute configuration†
V	218 (+9,4)	0,51	*RS*
VI	228 (−3,8)	0,46	*SS*
VII	217 (−8,8)	0,51	*SR*
VIII	225 (+4,2)	0,46	*RR*
XII	220 (−7,3)	0,60	*SR*
XIII	221 (−5,9)	0,42	*SS*
XIV	218 (+4,6)	0,60	*RS*
XV	220 (+4,0)	0,42	*RR*

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*The chemical shifts were determined with an accuracy of up to 0.001 ppm and were rounded off to the nearest 0.01 ppm.

†The first symbol pertains to the asymmetric carbon atom of the aziridine ring.

Analytical and preparative HPLC was carried out with a Dupont 830 Prep LC chromatograph with a UV spectrophotometer as the detector and Zorbax SIL 4.6 by 250 mm and Zorbax SIL 22.7 by 250 mm columns. The CD spectra were obtained with a Jobin-Ivon Mark III dichrograph.

Methyl 2-(2-Methoxycarbonylaziridino)isovalerates V-VIII. These compounds were obtained by means of the Gabriel—Cromwell reaction by the method in [1] from R- or S-valine methyl ester. The individual diastereomers were isolated by preparative liquid chromatography.

Methyl 2-(2-Methoxycarbonylaziridino)-3-trifluoromethyl-4,4,4-trifluorobutanoates XII-XV. A 0.101-g (10 mmole) sample of R- or S-aziridine-2-carboxylic acid methyl ester, obtained by a method similar to that used to prepare benzyl S-aziridine-2-carboxylate [4], was added to a solution of 0.222 g (10 mmole) of acrylate IX, and the mixture was heated at 60°C for 8 h. The solution was then evaporated, and the residue was separated by preparative liquid chromatography.

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ADDUCTS OF METHYL β,β-BIS(TRIFLUOROMETHYL)ACRYLATE WITH NUCLEOPHILES AND ALLYLIC REARRANGEMENT DURING THEIR DEHYDROFLUORINATION

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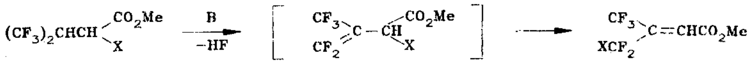
A number of adducts of methyl β,β-bis(trifluoromethyl)acrylate with various nucleophiles were synthesized. The boundaries of the allylic rearrangement of 2-substituted 3-trifluoromethyl-4,4-difluoro-3-butenoates, obtained by dehydrofluorination of the cited adducts, were investigated.

We have previously observed allylic rearrangement with migration of an aziridinyl subsitutent [1]:

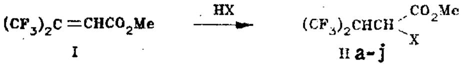


$$(CF_3)_2CHCH\begin{smallmatrix}CO_2Me\\X\end{smallmatrix} \xrightarrow[-HF]{B} \left[\begin{smallmatrix}CF_3\\CF_2\end{smallmatrix}{=}C-CH\begin{smallmatrix}CO_2Me\\X\end{smallmatrix}\right] \longrightarrow \begin{smallmatrix}CF_3\\XCF_2\end{smallmatrix}C{=}CHCO_2Me$$

X= aziridino and 2-methylaziridino

In the present research we investigated the boundaries of this rearrangement as a function of the types of substituents in the 2 position of the aziridinyl residue, as well as other heteroatomic α-substituents X (X = R^1R^2N, MeO). For this, we synthesized adducts of β,β-bis(trifluoromethyl)acrylate I with a number of nucleophiles (Tables 1 and 2).

In addition to IIa, allylic rearrangement product III (12%) was isolated from the reaction mixture by high-performance liquid chromatography (HPLC) in the preparation of adducts IIa by heating an equimolar mixture of the starting reagents (50°C, MeCN), i.e., under the reaction conditions the dehydrofluorination of adduct IIa proceeds under the influence of nucleophile HX. Adducts IIb-i were obtained in 55-85% yields by the addition of the corresponding amines with cooling (−30°C, Et_2O). We were able to realize the addition of methanol only by heating (150°C) ester I in a sealed ampul with excess reagent in the presence of KF applied to Al_2O_3: adduct IId was obtained in 55% yield.



$$(CF_3)_2C{=}CHCO_2Me \xrightarrow{HX} (CF_3)_2CHCH\begin{smallmatrix}CO_2Me\\X\end{smallmatrix}$$

II a X=2-methoxycarboxylaziridino; b X= 2,2-dimethylaziridino; X = Me_2N; dX = MeO; e X= azetidino; e X=pyrrolidino; g X= piperidino; h X=HOHN; i X=H_2N; j X=Me_2NHN

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