ABSOLUTE CONFIGURATION OF DIASTEREOMERIC DERIVATIVES OF N-SUBSTITUTED AZIRIDINE-2-CARBOXYLIC ACIDS*
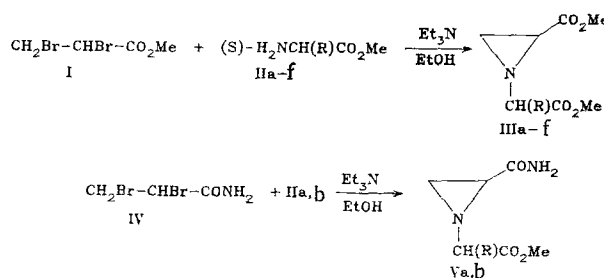
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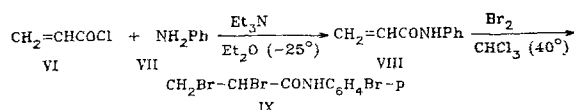Sh. S. Nasibov, and R. G. Kostyanovskii

Individual diastereomers of a number of anilides of N-substituted aziridine-2-carboxylic acids have been obtained. Conclusions regarding the spatial structure of the compounds indicated have been drawn on the basis of the ^{1}H NMR, ^{15}N NMR, and CD spectra.

We previously obtained diastereomeric esters of a number of N-substituted aziridine-2-carboxylic acids [1]. These mixtures of diastereomers were recovered in the form of oily, noncrystallizing liquids, therefore, we synthesized amides Va and b, one of which (Va) could be separated into individual diastereomers by fractional crystallization.

$CH_2Br-CHBr-CO_2Me$ + $(S)-H_2NCH(R)CO_2Me$ $\xrightarrow[EtOH]{Et_3N}$
I   IIa-f

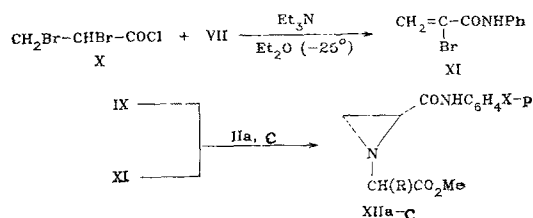$CH_2Br-CHBr-CONH_2$ + IIa,b $\xrightarrow[EtOH]{Et_3N}$
IV

II, III, V a R=Me; b R=CH₂Ph; II, III c R=*iso*-Pr; d R=CH₂CO₂Me; e R=(CH₂)₂CO₂Me;
f R=(CH₂)₂SMe

In the present work the diastereomers of the esters of type III were separated by high-performance liquid chromatography (HPLC). However, the diastereomers of IIIb are unstable (the signals of decomposition products appear in the PMR spectra after 24 h). For the purpose of obtaining stable diastereomers, we synthesized crystalline anilides XIIa-c. It was found that the addition of bromide to acrylanilide is accompanied by the bromination of the benzene ring.

$CH_2=CHCOCl$ + NH_2Ph $\xrightarrow[Et_2O\ (-25°)]{Et_3N}$ $CH_2=CHCONHPh$ $\xrightarrow[CHCl_3\ (40°)]{Br_2}$
VI   VII   VIII

$CH_2Br-CHBr-CONHC_6H_4Br-p$
IX

For this reason, the acylation of aniline by 2,3-dibromopropionyl chloride was employed to obtain the unsubstituted anilides:

$CH_2Br-CHBr-COCl$ + VII $\xrightarrow[Et_2O\ (-25°)]{Et_3N}$ $CH_2=C-CONHPh$
X   Br
XI

IX ──┐
       ├ IIa, c → (aziridine) CONHC₆H₄X-p
XI ──┘   CH(R)CO₂Me
XIIa-c

XII a X=H, R=Me; b X=Br, R=Me; c X=Br, R=*iso*-Pr

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*Report 37 of the series entitled "Asymmetric nonbridging nitrogen." For report 36 see [1].

TABLE 1. Parameters of the PMR Spectra of Derivatives of Aziridine-2-carboxylic Acid

Structure labels: COX, H_C, H_A, H_B, N, R, COOMe, H — (S,S) and (R,S) diastereomers.

Compound	X	R	Solvent	δ [a], ppm							J, Hz			
				R	CH–R	MeO	X	H_A	H_B	H_C	H_AH_B	H_AH_C	H_BH_C	CH–R
IIIa (S, S)	MeO	Me	CDCl₃	1,36	2,27	3,66; 3,67	—	2,08	1,83	2,29	6,0	3,3	0,4	6,5
IIIa (R, S)	MeO	Me	CDCl₃	1,38	2,28	3,67; 3,69	—	2,29	1,62	2,22	6,5	3,0	0,4	6,5
XIIa (S, S)	NHPh	Me	CDCl₃	1,45	2,47	3,78	7,31 (Ph); 8,31 (NH)	2,25	1,97	2,21	7,0	3,3	0,4	7,0
XIIa (S, S)	NHPh	Me	CDCl₃	1,45	2,45	3,75	7,31 (Ph); 8,71 (NH)	2,34	1,77	2,12	7,3	3,3	0,4	7,0
XIIa (S, S)	NHC₆H₄Br-p	Me	CDCl₃	1,47	2,51	3,81	7,45 (Ph); 8,34 (NH)	2,27	2,0	2,23	6,6	3,1	0,4	6,6
XIIb (R, S)	NHC₆H₄Br-p	Me	CDCl₃	1,45	2,46	3,52	7,44 (Ph); 8,79 (NH)	2,30	1,78	2,11	7,0	3,0	0,4	6,6
XIIkc (S, S)b	NHC₆H₄Br-p	iso-Pr	CDCl₃	1,07; 1,08; 2,20; J=7,0 Hz	2,33	3,73	7,44 (Ph); 8,81 (NH)	2,21	1,87	2,19	6,6	3,2	0,4	5,0
			C₆D₆	0,82; 0,89; 1,90; J=7,0 Hz	1,73	3,22	7,31 (Ph)	1,91	1,05	1,59	7,1	3,3	0,6	5,0
XIIc (R, S)c	NHC₆H₄Br-p	iso-Pr	CDCl₃	1,04; 1,06; 2,24; J=6,9 Hz	2,34	3,78	7,43 (Ph); 8,39 (NH)	2,31	1,84	2,17	7,1	3,2	0,4	5,3
			C₆D₆	0,82; 0,88; 1,94; J=7,0 Hz	1,78	3,28	7,16 (Ph)	1,95	1,21	1,65	7,1	3,1	0,4	5,5
XIII (S, S, S)	NHCH(CH₂Ph)CO₂Me	PhCH₂	CDCl₃	3,03; 3,17 (CH₂), J_{gem}=13,7 Hz (Ph), 7,22	2,54	3,73; 3,78	2,55 (CHNH); J_{CHCH_2}=5,6 and 2,94 and 3,14 (CH₂); J=7,7 Hz (CHNH); J_{gem}=13,9 Hz; 7,20 (Ph); 7,07 (NH)	1,73	1,66	1,68	7,1	3,3	0,4	5,7; 7,8

[a] The spectrum of IIIa was measured on a Bruker WM-360 spectrometer, and the spectra of XIIa–c and XIII were measured on a Nicolet NT-360 WB spectrometer. [b] ¹⁵N NMR in the aziridine ring: $^2J_{^{15}N^1H_C} = 0$ in CDCl₃ and 5.9 Hz in C₆D₆; $^2J_{^{15}N_\alpha^1H} = 0$. [c] ¹⁵N NMR in the aziridine ring: $^2J_{^{15}N^1H_C} = 5.9$ Hz in CDCl₃ and CD₃OD and 5.8 Hz in C₆D₆; $^2J_{^{15}N_\alpha^1H} = 0$.

TABLE 2. Values of $\Delta\nu_{AB}$ and Absolute Configuration of Di-
astereomeric Derivatives of N-Substituted Aziridine-2-carbox-
ylic Acids

Com-pound	X	R	Solvent	$\Delta\nu_{AB}$, ppm	Configuration
III a	MeO	Me	CDCl₃	0,25 0,67	S,S R,S
IIIb [1]	MeO	PhCH₂	CH₂Cl₂	0,46 0,74	S,S R,S
			CD₃OD	0,32 0,52	S,S R,S
Va [1]	NH₂	Me	CDCl₃	0,22 0,52	S,Sᵃ R,Sᵃ
V b	NH₂	PhCH₂	CDCl₃	0,45	R,S b
XIIa	NHPh	Me	CDCl₃	0,28 0,57	S,S R,S
XIIb	NHC₆H₄Br-p	Me	CDCl₃	0,27 0,52	S,S R,S
XII c	NHC₆H₄Br-p	iso-Pr	CDCl₃	0,34 0,47	S,S R,S
XIII	NHCHCH₂PhCO₂Me	PhCH₂	CDCl₃	0,07	S,S,Sᶜ

ᵃAccording to data from x-ray diffraction analysis [1]. ᵇBy
comparing it to compounds V and XIII. ᶜAccording to data
from x-ray diffraction analysis [6, 7].

TABLE 3. Chemical Shifts ($\Delta\delta$) Induced by d-Eu(tfc)₃
for Protons in Va, XIIb, and XIIc for $c_p/c_s = 0.2$
(CDCl₃)

Compound	$\Delta\delta$, ppm					Configuration
	MeO	H_C	Me	H_A	H_B	
Va	0,32 0,07	— —	0,56 0,20	— —	0,98 0,33	R, Sᵃ S, Sᵃ
XII b	0,26 0,14	1,08 0,27	— —	— —	0,60 0,19	R, S S, S
XIIᶜ	0,24 0,11	— —	— —	0,31 0,11	0,63 0,27	R, S S, S

ᵃAccording to data from x-ray diffraction analysis [1].

The individual diastereomers of anilides XII were isolated by HPLC.

The PMR spectra of the protons in the aziridine rings in compounds III, V, and XII
correspond to an ABC system (Table 1). The diastereomers have similar values for the spin-
spin coupling constants, but they differ strongly with respect to the chemical shifts of the
ring protons. From a comparison of the diastereomers of Va (their absolute configuration is
known [1]) it follows that the H_B and H_C protons are considerably deshielded in the S,S
isomer.* This may be attributed to the anisotropic effect of the carbonyl group in the
CO_2Me substituent. In the R,S isomer this substituent is at a greater distance from the ring
CH_2 group. The small shielding of the H_A proton in the S,S diastereomer in comparison to the
R,S isomer may be attributed to the anisotropic effect of the C—C bond in the N-substituent.

According to the x-ray structural data in [1], the ring H—CN fragments in both isomers of
Va are characterized by a trans orientation of the α proton and the lone pair of the N atom;
the esteric group of the N-substituent in the S,S isomer is directed toward the ring CH_2
group, while in the R,S isomer it is directed toward the substituted carbon atom in the ring.

*Similar values for $\Delta\nu_{AB}$ are observed in the series of S,S diastereomers of esters of α-[2-
(α-hydroxybenzyl)aziridino]-α-methylcarboxylic acids [2].

In order to ascertain whether this situation is maintained in solution, we synthesized aziridine XIIc labeled by ^{15}N in the aziridine ring. The PMR spectra of both diastereomers of XIIc isolated displayed spin–spin coupling of the ^{15}N nucleus only with the H_C proton (Table 1). This is completely consistent with the calculated angular dependence of the constant $^2J_{^{15}NH}$ [3], which was experimentally confirmed in [4] and, in particular, for three-membered rings in [5]. The absence of the constant $^2J_{^{15}N-^1H}$ is apparently evidence that the trans orientation of the α-H nucleus relative to the lone pair of the N atom is also maintained in solution.

The greatest difference between the chemical shifts of the diastereomers is observed for the H_B proton; therefore, the difference $\Delta\nu_{AB} = \nu H_B$ was adopted as a spectral criterion of a stereochemical difference. In the case of Va, this parameter is comparatively larger for the R,S isomer; therefore, in the remaining pairs of diastereomers we shall assume that the diastereomer having the larger value of $\Delta\nu_{AB}$ has an R,S configuration (Table 2).

Accordingly, a small value of $\Delta\nu_{AB}$ is observed for XIII, which was obtained in the form of a single diastereomer having an S,S,S configuration according to the data from x-ray diffraction analysis [6, 7].

CONHCH(CH₂Ph)CO₂Me — (structure)

$$\text{CONHCH(CH_2Ph)CO_2Me}$$

N
|
CH(CH₂Ph)CO₂Me

XIII
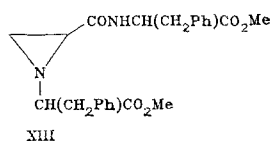
In the case of the diastereomers of Va, it was found that the dependence of the chemical shifts $\Delta\delta$ induced by d-Eu(tfc)$_3$ on the concentration of the shift reagent is expressed considerably more strongly for the R,S diastereomer in comparison to the S,S diastereomer (Table 3). The observed difference between the induced shifts was used to determine the absolute configuration of diastereomers XIIb and c (Table 3). A consistent assignment of the absolute configuration was obtained from the circular dichroism (CD) spectra of diastereomers XIIa by comparing them with the spectra of the diastereomers of Va (Fig. 1) on the basis of the coincidence of the signs of the Cotton effects in the 200–220-nm region. It is surprising that the S,S diastereomers of Va, as well as of XIIa, have CD spectra with practically mirror symmetry as enantiomers. This can be explained on the basis of the following arguments. If we assume that in solution (in contrast to the solid phase [1, 7]) the amide group is turned 180° (the carbonyl is directed toward the three-membered ring), we can obtain agreement with the quadrant rule for an amide chromophore [8] in the correlation of the absolute configuration and the sign of the Cotton effect in the 200–220-nm region. In addition, in accordance with the aforementioned deshielding of the H_B and H_C protons it may be postulated that in solution (as opposed to the solid phase [1, 7]) the esteric group of the S,S diastereomer is turned 180° (the carbonyl is directed toward the ring CH₂ group). Then, using the lactone rule [8], we can obtain agreement between the observed signs of the Cotton effect in the 200–220-nm region and the absolute configuartion.

The CD spectra of the diastereomers of Va and XIIa in the 200–250-nm region have mirror symmetry and contain one (the diastereomers of Va) and two (diastereomers of XIIa) Cotton effects (Fig. 1). The Cotton effects at 216 ($\Delta\varepsilon = -2.58$) and 214 nm ($\Delta\varepsilon = 2.39$) for diastereomers of Va and at 206 ($\Delta\varepsilon = 3.45$) and 206 nm ($\Delta\varepsilon = -3.61$) for the diastereomers of XIIa are assigned to an n→π* transition of the amide group, whereas the effects at 240 ($\Delta\varepsilon = 4.8$) and 238 nm ($\Delta\varepsilon = -4.12$) for the diastereomers of XIIa are attributed to contributions of transitions of various chromophores, including the aromatic ring [9].

Therefore, on the basis of the available data it may be concluded that in the case of the diastereomeric pairs of III, V, and XII, the diastereomer with an asymmetric carbon atom in the ring with an R configuration has a larger value of $\Delta\nu_{AB}$, a stronger concentration dependence of the proton chemical shifts induced by d-Eu(tfc)$_3$ in the PMR spectra, and a positive sign for the Cotton effect in the 200–220-nm region in the CD spectra. The

diastereomer with an asymmetric atom with an S configuration in the aziridine ring has a smaller value of $\Delta\nu_{AB}$, a weaker concentration dependence of the induced shifts, and a negative sign for the Cotton effect in the 200–220-nm region.

EXPERIMENTAL

The NMR spectra were measured on Bruker WH-90, Bruker WM-360, and Nicolet NT-360 WB spectrometers, and the IR spectra were measured on a UR-20 spectrometer in liquid petrolatum or in thin layers. The HPLC separation was carried out on an EAK instrument from the Special Design Office of the Academy of Sciences of the Estonian SSR with a UV detector. The analytical column (250 × 6 mm) was filled with Silasorb silica gel, and the preparative column (250 × 22.7 mm) was filled with Chrompack. The angles of optical rotation were measured on a Perkin–Elmer model 141 polarimeter in ethanol, and the CD spectra were recorded on Jobin-Ivon Mark III dichrograph (which was calibrated with the use of epiandrosterone and 10-camphorsulfonic acid standards) in Hellma quartz cuvettes (1 cm for the 250–320-nm region, 0.1 cm for the 210–260-nm region, and 0.01 cm for the 185–250-nm region). The concentration of the solutions in methanol was $5 \cdot 10^{-3}$ to $1 \cdot 10^{-3}$ M. The spectra were treated on a wang 2200 VP computer with a device for the input of graphical information with the aid of a specially developed program package [10].

Acrylic Anilide (VIII). A solution of 9.3 g (100 mmole) of aniline and 10.1 g (100 mmole) of triethylamine in 100 ml of absolute ether at −30°C was given an addition of 9.1 g (100 mmole) of acrylyl chloride in 20 ml of absolute ether. The mixture was held for 1 h at −30°C and 3 h at 20°C. The precipitate was filtered out, and filtrate was washed with a solution of citric acid, a 1 N sodium carbonate solution, and water. Then the ethereal layer was dried by magnesium sulfate, and the ether was driven off in a vacuum. The residue, which weighed 13.6 g (93%), was used without further purification.

2,3-Dibromopropionic p-Bromanilide (IX). A solution of 12 g (82 mmole) of anilide VIII in 150 ml of chloroform at 50°C was given an addition of bromine (6.3 ml) until the original substance vanished (monitoring by TLC). The mixture was held for 1 h at 50°C, cooled, washed with water, and dried with magnesium sulfate, and the solvent was removed in a vacuum. This gave 24.2 g (76%) of anilide IX, mp 179–181°C (from aqueous ethanol). IR spectrum: 1660 (CO), 3300 cm^{-1} (NH). PMR spectrum: 3.87, 3.99 (two q, 2H, CH_2, J_{gem} = 10 Hz), 4.59 (d. d, 1H, CH, CH, J_1 = 7.5, J_2 = 5 Hz), 7.44 (s, 4H, C_6H_4), 7.73 ppm (broad signal, 1H, NH). Found: C, 27.7; H, 2.3; N, 3.4%, M 386 (mass-spectrometrically). Calculated for $C_6H_9Br_3NO$: C, 28.0; H, 2.1; N, 3.6%.

α-Bromoacrylic Anilide (XI). A solution of 1.85 g (17 mmole) of aniline and 3.4 g (34 mmole) of triethylamine in 100 ml of absolute ether at −30°C was given an addition of 4.25 g (17 mmole) of 2,3-dibromopropionyl chloride in 30 ml of absolute ether. The mixture was held for 1 h at −30°C and for 3 h at ∿20°C. The precipitate was filtered out, and the filtrate was evaporated. The amide remaining XI [2.82 g (73%)] was used without further purification.

Methyl 2-[2-(Phenylcarbamoyl)aziridino]propionate (XIIa). A solution of 2.8 g (12 mole) of anilide XI in 200 ml of ethanol at 5°C was given an addition of 1.2 g (12 mmole) of triethylamine. The mixture was held for 30 min and treated with 1.7 g (12 mmole) of the hydrochloride of the methyl ester of α-alanine and 18 mmole of triethylamine in 150 ml of ethanol and then held for 5 h more at 20°C and 5 h at 70°C. The solvent was removed, and the residue was diluted with a small quantity of water and extracted three times with ethyl acetate. The extracts were combined and dried by magnesium sulfate, and the solvent was evaporated. This gave 2.5 g (81%) of a residue in the form of a viscous mass which was purified chromatographically in a column with silica gel 40 × 100 μ (the eluent was 1:1 hexane–ethyl acetate mixture). R$_f$ 0.26 (Silufol UV-254, 1:1 hexane–ethyl acetate). IR spectrum: 1687 (amide CO), 1738 (esteric CO), 3072 cm^{-1} (ring CH). Found: C, 62.6; H, 6.3; N, 11.1%. Calculated for $C_{13}H_{16}N_2O_3$: C, 62.9; H, 6.5; N, 11.3%. According to the data from analytical high-performance liquid chromatography (the eluent was a 1:4 2-propanol–hexane mixture), the reaction product is a mixture of two substances, which were separated by preparative high-performance liquid chromatography. The following were recovered: S,S-XIIa with $[\alpha]_D^{20}$ −71.9° (c 1.13) and R,S-XIIa with $[\alpha]_D^{20}$ + 112.5° (c 1.07).

Methyl 2-[2-(4-Bromophenyl carbamoyl)aziridono]propionate (XIIb). This compound was obtained in analogy to XIIa from 2,3-dibromopropionic p-bromoanilide. The yield of unpurified XIIb was 80%, and it was isolated in the form of a dark viscous mass, which was
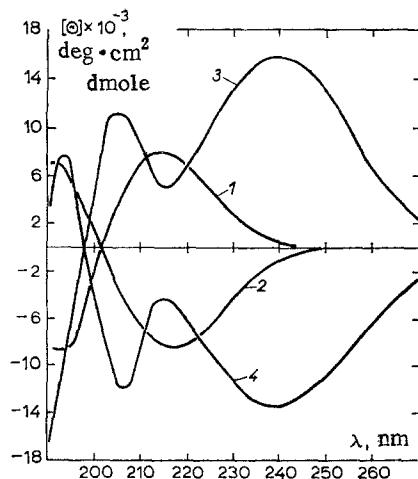
Fig. 1. Circular dichroism spectra
of diastereomers: 1) R,S-Va; 2) S,S-
Va; 3) R,S-XIIa; 4) S,S-XIIa.

chromatographed in a column with silica gel 40×100 μ (the eluent was a 1:1 hexane—ethyl
acetate mixture). The residue remaining after the evaporation of the solvent was a viscous
mass, R_f 0.30 (Silufol UV-254, 1:1 hexane—ethyl acetate). IR spectrum: 1684 (amide CO),
1735 (esteric CO), 3070 cm^{-1} (ring CH). Found: C, 47.2; H, 4.4; N, 8.7%. Calculated for
$C_{13}H_{15}BrN_2O_3$: C, 47.7; H, 4.6; N, 8.6%. According to the data from analytical high-perform-
ance liquid chromatography (the eluent was a 1:4 2-propanol—hexane mixture), the reaction
product is a mixture of two substances, which were separated by preparative high-performance
liquid chromatography (the eluent was a 3:7 2-propanol—hexane mixture). The following were
isolated: S,S-XIIb with $[\alpha]_D^{20}$ −75.4° (c 1.20) and R,S-XIIb with $[\alpha]_D^{20}$ +111.0° (c 1.47).

Methyl 2-[2-(4-Bromophenylcarbamoyl)aziridino]-2-methylpropionate (XIIc). This compound
was obtained in analogy to XIIb. The product isolated consisted of 2.8 g (79%) of a dark
viscous mass, R_f 0.58 (Silufol UV-254, 1:1 hexane—ethyl acetate). IR spectrum: 1682 (amide
CO), 1737 (esteric CO), 3070 cm^{-1} (ring CH). Found: C, 50.3; H, 5.3; N, 7.0%. Calculated
for $C_{15}H_{19}BrN_2O_3$: C, 50.7; H, 5.4; N, 7.9%. According to the data from analytical high-
performance liquid chromatography (the eluent was 1:12.3 2-propanol—hexane mixture), the
reaction product is a mixture of two substances, which were separated by preparative high-
performance liquid chromatography (the eluent was a 1:12.3 2-propanol—hexane mixture). The
following were isolated: R,S-XIIc with $[\alpha]_D^{20}$ +136.0° (c 1.73°) and S,S-XIIc $[\alpha]_D^{20}$ −87.0°
(c 0.89).

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