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ASYMMETRICAL NONBRIDGEHEAD NITROGEN-17†

COMPLETE SEPARATION INTO ANTIPODES AND ABSOLUTE CONFIGURATION OF CHIRALIC N-ALKOXYISOXAZOLIDINES

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Abstract—*trans*-Stereospecificity of the amidation of 1-alkoxyisoxazolidine-3,3-dicarboxylic ester (**1**) has been elucidated. Alkaline hydrolysis of monester **4** yielded the salt **6** which after its ion exchange in the form of *S*(−) and *R*-(+)-phenylethylammonium salts was completely separated into the enantiomeric salts (+**10** and −**10**). Esterification and amidation of these salts afforded antipodes 2 *S*-(+**12**) and 2 *R*-(−**12**) containing only a nitrogen asymmetric center. Optical purities of the products were established on the basis of their NMR spectra with shift-reagent. Molecular and crystal structure as well as an absolute configuration of +**10** were detected by means of X-ray analysis.

High configuration stability of N-alkoxyisoxazolidines allows their separation into antipodes with a chiralic nitrogen center. Principally the possibility of such separation was first shown by the authors. Using the methods of asymmetric amidation,[1,3] crystallization from chiralic solvent,[1,3] assymmetric inversion reaction in chiralic solvent,[4] the partially enriched N-alkoxyisoxazolidine enantiomers were obtained.[a]

The present paper is concerned with complete separation of N-alkoxyisoxaolidines into the antipodes with a chiralic center only at the N atom.[b] It is the third example of such a separation. Earlier, the enantiomers of 1-methoxyaziridine-2,2-dicarboxylic[7–9] and 1-methyldiaziridine-3,3-dicarboxylic esters[8,10] have been separated.

It is known that a racemate is more easily separated into its antipodes when it has some reactive functional groups enable the introduction of an auxiliary chiralic center into the separating substrate. For this purpose the salt-producing groups are most useful. This consideration determined our choice of 2-methoxyisoxazolidine-3,3-dicarboxylic ester (**1**) as the separation medium.

To prepare N-alkoxyisoxazolidine carboxylic acid the alkaline hydrolysis of compound **1** was studied. Compound **1** was treated with an equimolar amount of KOH ethanolic solution to give a hygroscopic mixture of products (from the NMR spectrum) which we failed to separate and identify. Exhaustive hydrolysis of ester **1** (Scheme 1) yielded a decarboxylation product: potassium salt of isoxazoline-3-carboxylic acid (**2**).

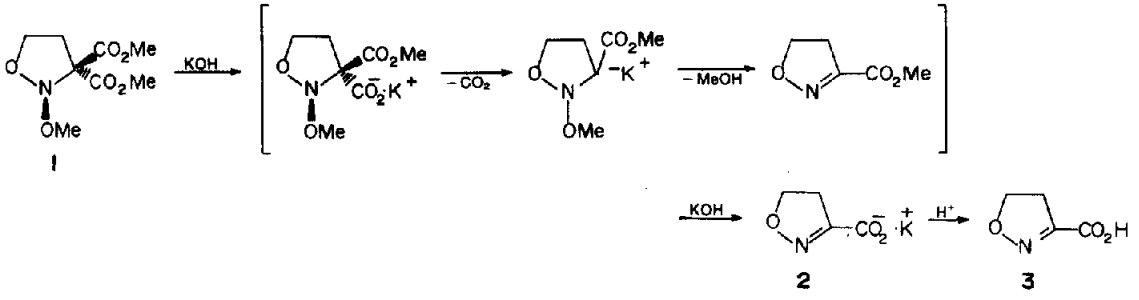
Easy decarboxylation may be explained by stabilization of an intermediate carbanion with delocalizing CO_2Me substituent. After replacement of CO_2Me with CONHMe, reducing the delocalizing ability of the substituent due to its concurrent amide conjugation, the decarboxylation would be more difficult. In this view the amidation of compound **1** was performed. Treatment of ester **1** with an equimolar amount of $MeNH_2$ gave the monoamide **4** (Scheme 2).

The NMR spectra show (Table 1) that compound **4** is formed as one isomer, no other isomer being revealed in the mixture after removal of the solvent and unreacted **1**. X-ray analysis of compound +**10** (see below) manifests *trans*-configuration of **4** (from the amide group orientation with respect to the nitrogen substituent). Thus amidation of **1** is *trans*-stereospecific. Earlier *trans*-stereospecificity of the amidation and alkaline hydrolysis reactions has been observed for 1-alkoxyaziridine-2,2-dicarboxylic[11] and 1-methyldiaziridine-3,3-dicarboxylic esters.[12]

†*Cf.* Ref. 1 for part 16.

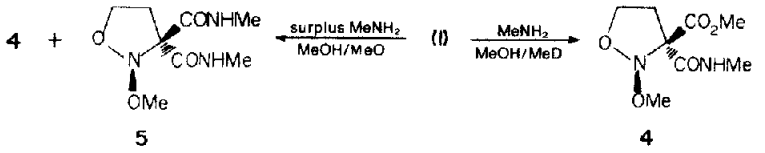
[a]Recently a separation of diastereomeric N-alkoxyisoxazolidines of steroid series containing in addition to N C chiralic center has been described.[5]

[b]Preliminary communication is Ref. 6.



1 2 3

Scheme 1.



5 4

Scheme 2.

It should be noted that further amidation of compound **4** is esstentially difficult. Thus treatment of compound **1** with excess of $MeNH_2$ in MeOH with traces of alcoholate gave only the mixture of **4** and **5** products relating as 4:1 (in 7 days) and 1:9 (in 14 days).

Hydrolysis of compound **4** with an equimolar amount of KOH in MeOH afforded the potassium salt **6** in the form of crystallosolvate with MeOH (molar ratio 1:1) (Scheme 3).

The NMR spectrum of compound **6** (Table 1) contains the signals of one isomer, i.e. the hydrolysis of **4** involves no racemization. The salt **6** is thermally stable and may be decarboxylated only by attempting to isolate the free acid (Scheme 3). On the basis of salt, **6** the separation of enantiomers of N-alkoxyisoxazolidines was carried out (Scheme 4).

By ion exchange on a Dowes-50wx12 column the cation K^+ of salt **6** was replaced by the cation *S*-(−)-α-phenylethylamine (PEA) to give diastereomeric salt **8** (Table 2). Thus a diastereomeric salt was prepared avoidind isolation of the free acid. Repeated crystallization of **8** from MeOH produces the diastereomerically pure salt **+10** (Table 2) whose rotation angle and m.p. did not change after subsequent crystallization. By treatment of the crystallization liquids as shown in Scheme 4 the salt with *R*-(+)-PEA (**9**) was isolated. It was twice recrystallized from MeOH to yield diastereomeric salt **−10** (Table 2). To remove an auxiliary asymmetric center from **+10** and **−10** salts, we developed a simple preparative method of the carboxylic acid esterification by action of diazomethane directly on their ammonium salts. This procedure gave optically active diastereomeric amides **+11** and **−11** (Table 2) avoiding an isolation step of the thermally unstable carboxylic acids (Scheme 4). According to the NMR spectra, the monoamides **+11** and **−11** are identical with a racemic sample **5**. The absence of epimer signals at the N atom shows that all steps of the synthesis through Scheme 4 occur without racemization. Amidation of **+11** and **−11** with $MeNH_2$ under the mild conditions leads to enantiomers **+12** and **−12** (Scheme 4. Table 2, Fig. 1).

Optical purity of **+12** compound (Fig. 2) which is 100%, was determined from the NMR spectra in the presence of optically active shift reagent, tris-(3-trifluoromethyloxymethylene-D-camphorate) of europium, ($Eu(tfc)_3$). This value seems surprising at first glance since optical purity of *S*-(−)-PEA employed for separation was 96.3%. However, it is shown for compound **−12** (Experimental) that its optical purity

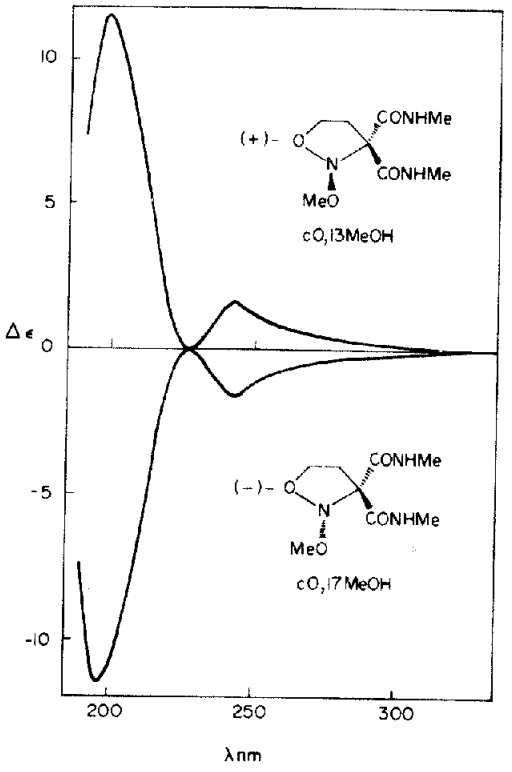


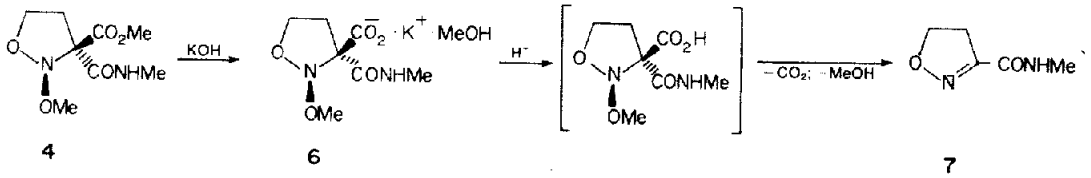
Fig. 1. The spectra of circular dichroism of enanthiomers (+12) and (−12).

increases after crystallization, thus isolation of an optically pure **+12** is obvious. Optical purity of **−12** (93.3% was determined by correlation of the rotation angles of compounds **+12** and **−12**.

Thus for the first time a complete separation of N-alkoxyisoxazolidines enantiomers has been carried out.

For elucidating an absolute configuration of the chiralic N atom in the optically active alkoxyisoxazolidines (**+10**, **+11** and **+12**) and stereospecific character of the amidation of compound **1** we conducted an X-ray investigation of the crystals of 2-methoxyisoxazolidine-3,3-dicarboxylic acid *trans*-monomethylamide *S*-(−)-α-phenylethylammonium salt (**+10**).

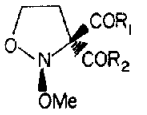
Crystallographic data: $[C_8H_{12}N]^+$ $[C_7H_{11}N_2O_5]^-$, M 325.37, m.p. 155–156°, rhombic, a = 21.410(6), b = 12.958(4), c = 6.032(4) Å, v = 1673 Å^3. $\rho_{calc.}$ = 1.298 g/cm^3, v = 4. Spatual group P $2_12_12_1$ (D_2^4, N19). Intensities of



4 6 7

Scheme 3.

Table 1. Derivatives of 2-methoxyisoxasolidine-3,3-dicarboxilic acid



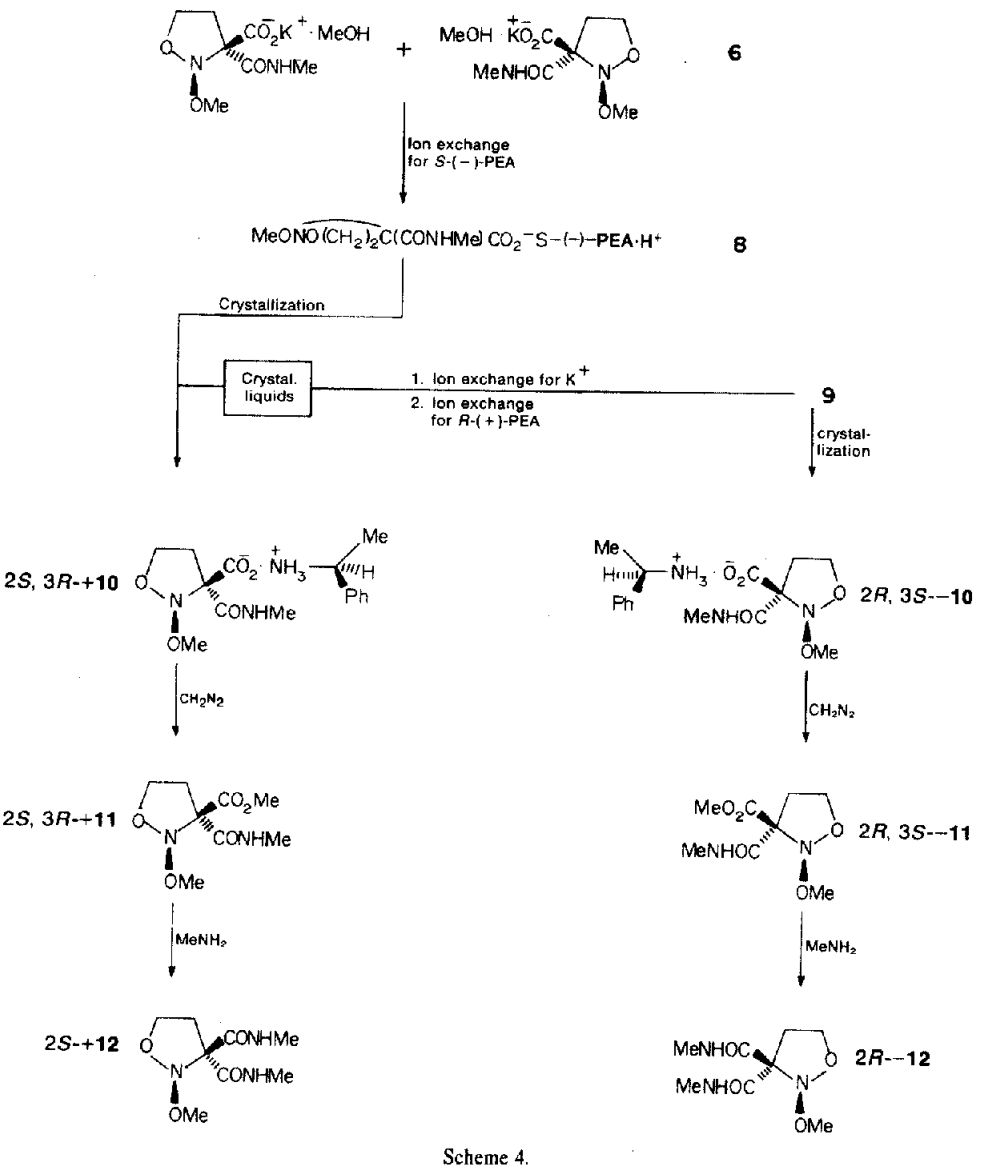
Compound	R_1	R_2	Yield,%	M.p.,°C	NMR, δ ppm from HMDS, 80 MHz				
					Solvent	MeO	R_1	R_2	Cycle protons[d]
(1)	MeO	MeO	31.0	b.p. 96-97(1.5)	C_6H_6[a]	3.39	3.25	3.17	3.90-3.45; 3.11-2.76; 2.56-2.24
(4)	MeO	MeNH	63.5	118	$CDCl_3$	3.61	3.76	2.84 (J_{MeNH}=5Hz)	4.28-3.98; 3.02-2.81
(5)	MeNH	MeNH	73.9	167-168	$CDCl_3$	3.64	2.81 (J_{MeNH}=5Hz)		4.36-3.88; 3.11-2.66
(6)	KO	MeNH	99.7	153(decomp.)	D_2O[b]	3.86	-[c]	3.01	3.30-2.89; 4.44-4.03

a) δ from HMDS; b) outer standart TMS; c) δ MeOH 3.59; d) The region of cycle proton signals.

Table 2. Optically active derivatives 2-methoxyisoxasolidine-3,3-dicarboxylic acid

Compound	Yield,%	M.p.,°C	$[\alpha]_D^{20}$ (deg.)	$[\alpha]_{546}^{20}$ (deg.)	$[\theta]_{max}^{20} \cdot 10^{-2}$ (λ nm)	Concentration,vol.%, (solvent)
(8)	89.0	129-145	-	-1.7	-	7.63(H_2O)
(9)	61.0	131-146	-	-36.3	-	5.50(H_2O)
(+10)	31.7[a]	155-156	170.4	205.8	-	0.41(H_2O)
(-10)	22.8[a]	149	-	-210.4	-	0.48(H_2O)
(+11)	97.8	66-67	292.3	345.2	-12.2(231) 181.0(212)	0.55(MeOH)
(-11)	96.3	79-80	-264.6	-312.2	-	0.16(MeOH)
(+12)	51.8	169-170	248.1	291.1	54.1(243) 379.9(196)	0.13(MeOH)
(-12)	66.5	167-168	-231.6	-276.3	50.9(243) 357.1(196)	0.27(MeOH)

a) per diastereomericalli pure form starting from (8).



Scheme 4.

1505 independent nonzero ($1 > 2\delta(1)$) hk0-hk6 reflections were measured on an automatic diffractometer DAR-UM on Cu under K_α irradiation with graphite monochromator in the region of 2θ from 4 to 142°. Absorption was ignored ($\mu(Cu, K_\alpha) = 8.2\,cm^{-1}$). The structural amplitude phases were computed by statistical method with "Rentgen-75" program.[13] The structure was refined by least squares procedure using block-diagonal anisotropic (O, N, C atoms) and isotropic (H atoms) approximations down to R = 0.038. Cruickshank's weights scheme[14] was used for refinement process. The H atoms were localized on difference syntheses. Atomic coordinates and temperature corrections are listed in Tables 3 and 4.

Salt +10 *carboxylate anion.* The anion conformation is shown in Fig. 3. The bond lengths and bond angles are given Table 5. The anion heterocycle is envelope-like as in the earlier studied N-alkoxyisoxazolidines (Table 6). The N-methoxy group is axially located. Such location of the nitrogen substituent is in agreement with anomeric effect.[15] It is seen from Table 6 that the most flattened pyramid is realized in the anion at N(1). The difference between *exo*- and *endo*-bond length in NO (N(1)–O(2) 1,434(3) Å and N(1)–O(1) 1.418(3) Å) is negligible while exocyclic bonds C(3)–C(4) (1.535(3) Å) and C(3)–C(5) (1.555(3) Å) are essentially longer than endocyclic C(2)–C(3) bonds (1.522(3) Å). Deviation of the endocyclic angles at C atoms (106.8°, 102.8°, 105.2°) from the tetraherdal values serves as evidence of a strained cycle. The methylamide group, C(O)N(H)C is practically plane. Maximum deviation from the mean of this plane fragment was detected for the H atom (0.04 Å). The carboxylate-anion configuration is trigonally planar, the C–O bond lengths being practically equivalent: C(5)–O(4) 1.234(3) Å and C(5)–O(5) 1.239(3) Å. It should specially be noted that N(1)...H(5) length is considerably shorter than the sum of van der Vaals atomic radii of N and H (2.66 Å)[18] and the analogous distance (2.44 Å) given in Ref. 1. Thus one may assume the presence of an intramolecular H bond which besides the electronegative substituents effects (O(1) and O(2) atoms) may also stabilize the N(1) pyramid. An intramolecular H-bond was also detected in the optically diaziridine derivatives. Thus in (−)-1*R*, 2*S*-1-(*S*)-α-phenylethylcarbamoyl-2-methyl-3,3-pentamethylenediaziridine,[19] the $H_3CN(2)...NH$ dis-

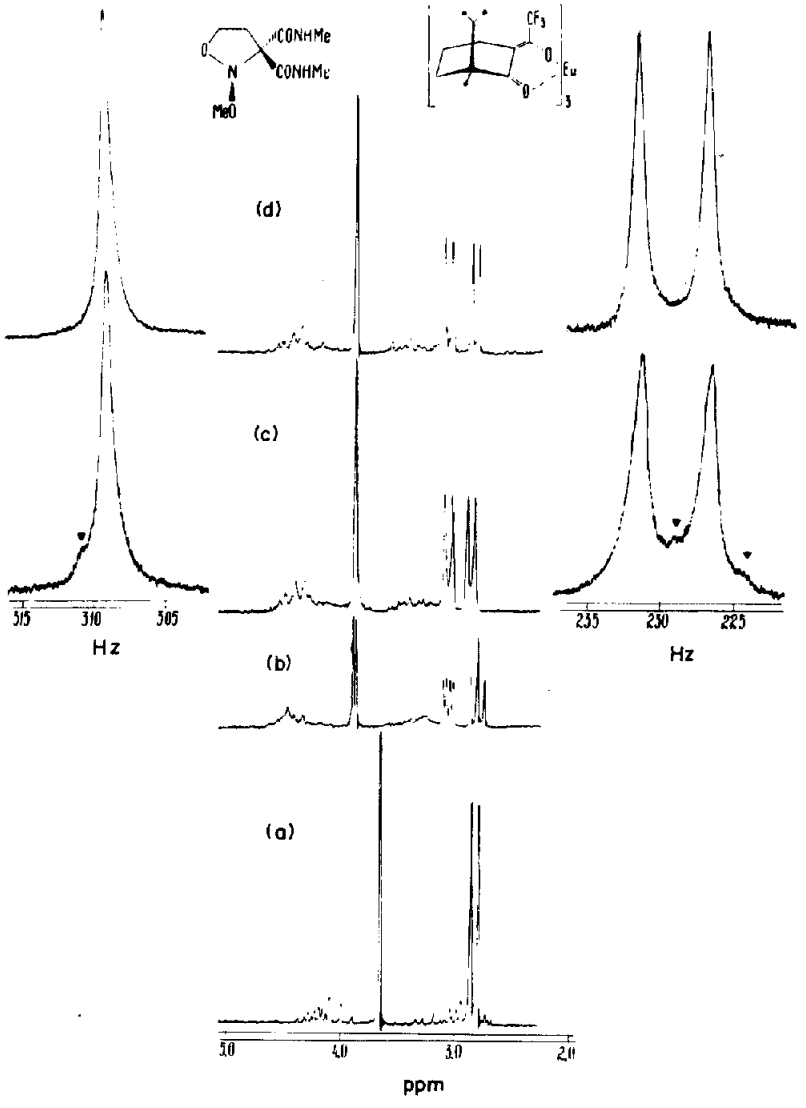


Fig. 2. NMR spectra (80 MHz, $CDCl_3$, δ from HMDS): (a) (+12), normal spectrum; (b) (5) with $Eu(tfc)_3$ additive, molar ratio (5)/$Eu(tfc)_3$ = 14.2, $\Delta\delta$ of MeON group signals of the antipodes 2.4 Hz, MeN groups 5 and 3 Hz, (d) (+12) with shift-reagent additive, molar ratio (+12)/$Eu(tfc)_3$ = 14.2; (c) same as in (d) but the racemate additive, signals of added antipode are marked with triangle; in (c) and (d) the right part—scanning of the MeNHCO group upfield signals, the left part—the NOMe group signals. In (d) signals of added antipode are absent, which confirms optical purity of (+12).

tance is 2.26(7) Å, while in 1*S*,2*S*-(*S*)-α-phenylethylamide of 1-methyldiaziridine-3,3-dicarboxylic acid methyl ester[12] the $H_3CN \ldots HN$ distance is 2.38(3) Å.

H-bond N(1) ... H(5) stabilizes *trans*-orientation of the amide group with respect to a nitrogen substituent. Thus at an equilibrium of thermal *cis-trans*-isomerization of compound 4 (15 hr, 100° in benzene) the *cis-trans* ratio is 19/1. This could be one of the reasons for *trans*-stereospecificity of amidation of 1. As it has been mentioned earlier,[1] another factor is consistent with sterical shielding of the CO group in *cis*-position to MeO as one may observe by comparing the C(5)–O(2) (2.681(3) Å) and C(4)–O(2) (3.655(4) Å) distances.

Salt +10, *S-α-phenylethylammonium cation.* The general form of the cation is shown in Fig. 4. Its bond lengths and angles are given in Table 5.

Structure description. Crystal structure projection of compound +10 on XOZ plane is shown in Fig. 5. It is seen from the Fig. that all NH_3 group hydrogens of each cation produce N–H ... O type H-bonds with the carboxyl oxygens of three anions. Moreover the translationally equivalent anions are combined to each other via N–H ... O H-bonds as well. The parameters of H-bonds are given in Table 7. Anions $[C_7H_{11}N_2O_5]^-$ and cations $[C_8H_{12}N]^+$ attached to each other via H-bonds produce layers parallel to the YOZ plane. Interaction between the layers is defined by van der Walls contacts.

Determination of an absolute configuration. An absolute *S*-configuration of the chiral N atom N(1) and *R* configuration of C(3) carbon are found in the asymmetric C(8) center coordinates of the known *S*-configuration and confirmed independently by refining adsorption correction Δf.[20] Such a method reflects how an absolute configuration of atomic coordinates corresponds to a refined structure and indicates an experimental value of the correction itself. In the present work account was

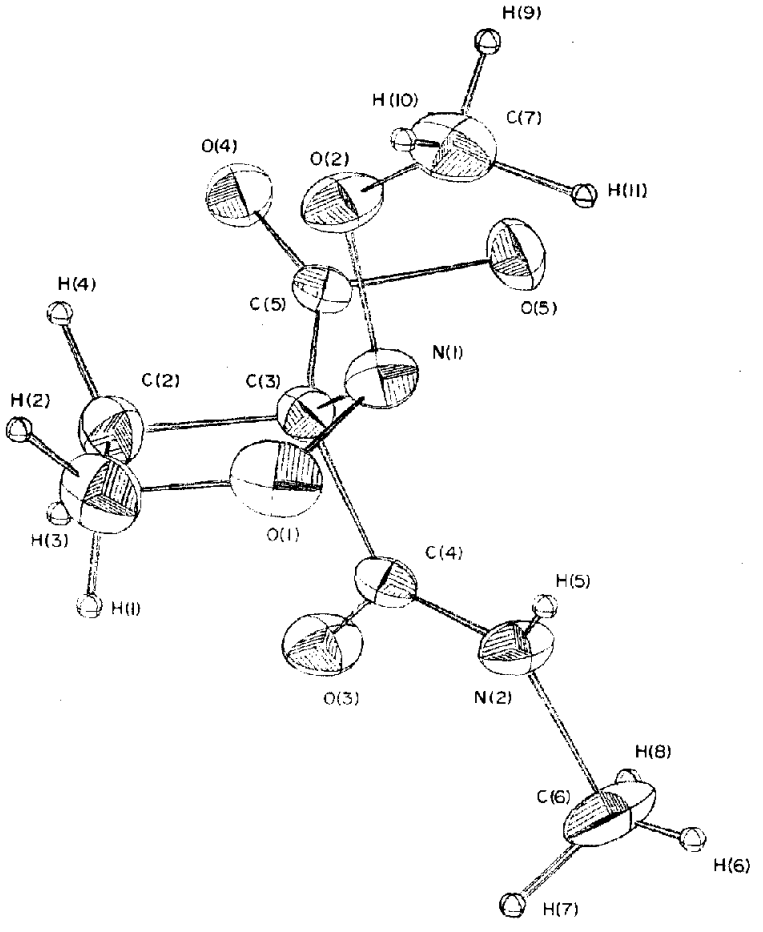


Fig. 3. Molecular structure of carboxylate-anion (+**10**) with 30% probabilities nonhydrogen atomic thermal vibration ellipsoids.

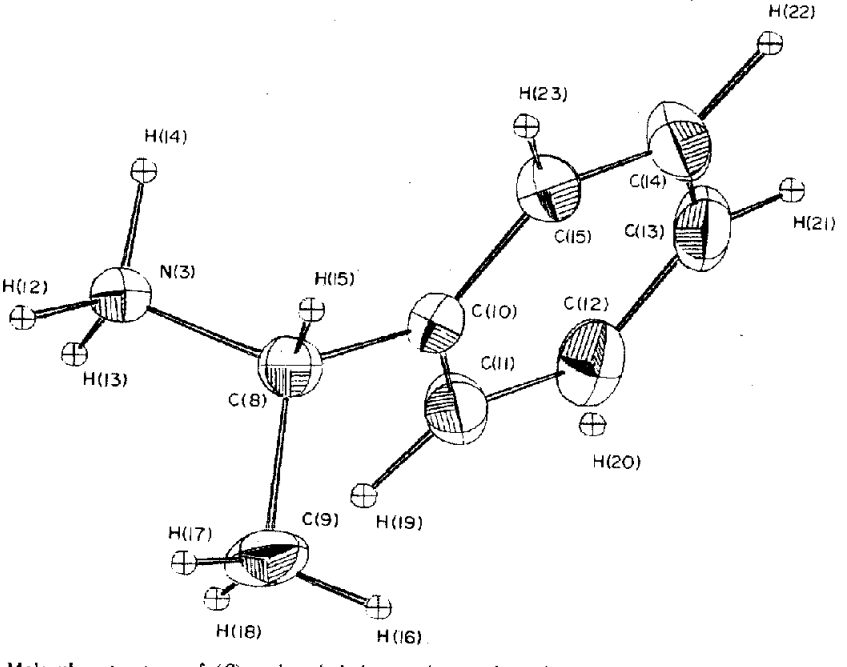


Fig. 4. Molecular structure of (*S*)-α-phenylethylammonium cation of salt (+**10**) with 30% probabilities nonhydrogen thermal vibration ellipsoids.

Table 3. Coordinates and thermal parameters of O, N, C atoms. Temperature factor $T = \exp[-(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + B_{12}hk + B_{13}hl + B_{33}kl)]$.

Atom	X	Y	Z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
O(1)	0.6698(1)	0.9178(2)	0.3504(4)	0.0022	0.0076	0.0405	0.0007	-0.0070	0.0039
O(2)	0.6048(1)	0.7953(1)	0.2007(3)	0.0031	0.0035	0.0339	0.0012	-0.0016	-0.0018
O(3)	0.5719(1)	1.1471(1)	0.0796(3)	0.0033	0.0036	0.0305	0.0002	-0.0011	0.0030
O(4)	0.5436(1)	0.9153(2)	-0.2239(3)	0.0021	0.0072	0.0255	-0.0012	-0.0012	-0.0041
O(5)	0.4852(1)	0.9270(2)	0.0769(3)	0.0016	0.0070	0.0312	-0.0012	0.0008	0.0015
N(1)	0.6066(1)	0.8964(1)	0.2975(4)	0.0021	0.0036	0.0293	0.0011	-0.0031	-0.0001
N(2)	0.5670(1)	1.0797(1)	0.4227(3)	0.0029	0.0031	0.0253	0.0003	-0.0016	-0.0001
N(3)	0.4512(1)	0.8583(1)	-0.5090(3)	0.0017	0.0039	0.0277	-0.0002	-0.0008	-0.0002
C(1)	0.7029(1)	0.9505(3)	0.1507(7)	0.0019	0.0090	0.0504	0.0006	-0.0021	0.0010
C(2)	0.6542(1)	0.9724(2)	-0.0220(5)	0.0015	0.0063	0.0360	0.0004	0.0012	-0.0001
C(3)	0.5936(1)	0.9677(2)	0.1097(4)	0.0014	0.0038	0.0260	-0.0001	-0.0003	0.0002
C(4)	0.5766(1)	1.0734(2)	0.2073(4)	0.0016	0.0030	0.0274	-0.0005	-0.0014	0.0019
C(5)	0.5354(1)	0.9321(2)	-0.0245(4)	0.0013	0.0033	0.0254	-0.0002	-0.0001	0.0009
C(6)	0.5508(2)	1.1769(2)	0.5306(6)	0.0046	0.0043	0.0338	0.0013	-0.0022	-0.0065
C(7)	0.5985(1)	0.7227(2)	0.3763(6)	0.0032	0.0041	0.0454	0.0011	-0.0024	0.0049
C(8)	0.3905(1)	0.9006(2)	-0.4264(5)	0.0019	0.0045	0.0289	0.0006	0.0018	0.0016
C(9)	0.3981(1)	1.0150(2)	-0.3790(6)	0.0029	0.0048	0.0431	0.0012	-0.0041	-0.0071
C(10)	0.3388(1)	0.8737(2)	-0.5852(5)	0.0015	0.0043	0.0349	0.0004	0.0020	-0.0012
C(11)	0.3310(1)	0.9250(2)	-0.7842(5)	0.0018	0.0065	0.0377	-0.0008	-0.0010	0.0014
C(12)	0.2831(1)	0.8967(3)	-0.9275(6)	0.0022	0.0099	0.0379	0.0018	-0.0025	-0.0022
C(13)	0.2437(1)	0.8160(3)	-0.8766(7)	0.0014	0.0091	0.0592	0.0005	-0.0030	-0.0119
C(14)	0.2516(1)	0.7646(3)	-0.5796(7)	0.0020	0.0077	0.0599	-0.0017	0.0022	-0.0051
C(15)	0.2983(1)	0.7929(2)	-0.5364(6)	0.0020	0.0055	0.0457	-0.0003	0.0027	0.0009

Table 4. Coordinates and isotopic parameters of hydrogen atoms

Atom	X	Y	Z	B_j, Å^2
H(1)	0.725(2)	1.015(3)	0.188(7)	4.8
H(2)	0.734(2)	0.902(3)	0,111(7)	5.3
H(3)	0.662(1)	1.040(2)	-0.090(5)	2.1
H(4)	0.655(2)	0.929(3)	-0.149(6)	3.9
H(5)	0.575(1)	1.027(2)	0.507(4)	1.9
H(6)	0.547(2)	1.174(3)	0.677(7)	5.6
H(7)	0.588(2)	1.219(4)	0.539(9)	8.1
H(8)	0.514(2)	1.206(4)	0.479(9)	9.4
H(9)	0.568(2)	0.670(4)	0.342(8)	5.2
H(10)	0.640(2)	0.693(3)	0.421(8)	6.2
H(11)	0.588(2)	0.753(5)	0.521(9)	7.5
H(12)	0.481(1)	0.869(2)	-0.393(5)	1.6
H(13)	0.462(1)	0.883(2)	-0.636(5)	2.7
H(14)	0.444(1)	0.791(2)	-0.551(5)	2.0
H(15)	0.382(1)	0.874(2)	-0.267(5)	2.0
H(16)	0.355(2)	1.045(3)	-0.320(7)	6.2
H(17)	0.425(1)	1.029(2)	-0.253(5)	2.2
H(18)	0.415(2)	1.040(3)	-0.504(6)	3.6
H(19)	0.359(1)	0.977(3)	-0.824(6)	3.0
H(20)	0.279(1)	0.931(3)	-1.057(5)	2.8
H(21)	0.213(1)	0.789(3)	-0.969(6)	3.4
H(22)	0.219(2)	0.712(4)	-0.650(8)	5.5
H(23)	0.303(2)	0.755(3)	-0.404(6)	3.2

taken of an abnormal scattering by O atoms. After refinement of $(\Delta f)_{exp}$ from its initial zero value, it become positive and equal to 0.03(1). Thus it may be concluded that absolute configuration of diastereomeric monoamides 2*S*,3*R* is **+11** and that of 2*R*,3*S* is **−11** while enantiomeric diamides *S* and *R* have configurations **+12** and **−12** respectively. Earlier absolute configuration of chiralic nitrogen was determined only for enantiomeric diaziridines.[12] Preliminary data are also available on absolute configuration of enantiomeric oxyaziridines.[21] At first an absolute configuration of a chiralic nitrogen center was established in diastereomeric diaziridines,[19] then in a diastereomeric oxaziridines.[22,23]

EXPERIMENTAL

The NMR spectra were measured on BS-487 C (Tesla) and JNM-c-60 HL (Jeol) spectrometers. Optical rotation was registered on "Polamat A" and "Perkin-Elmer-141" polarimeters. The spectra of CD were taken on "Jobin-Yvon-Dichrographe-III" instrument.

2-Methoxyisoxazolidine-3,3-dicarboxylic acid dimethyl ester (1) was prepared as described[24] (Table 1).

Isoxazoline-3-carboxylic acid potassium salt (2). A soln of 1 (2.19 g; 0.01 mole) and KOH (1.12 g; 0.02 mole) in 30 ml abs MeOH was allowed to stand for 4 days at 20°. The solvent was removed *in vacuo*, the residue dissolved in water (to convert MeOK into KOH) then the solvent was again removed. The residue was crystallized from MeOH, yielding 2 (1.2 g; 78.3%). NMR spectrum (60 MHz, D_2O, δppm from HMDS as outer standard): 3.96 and 2.99, the multiplet centers of cyclic proton signals. Compound 2 was identified via its conversion into 3.

Isoxazoline-3-carboxylic acid (3). Compound 2 (0.61 g; 0.00398 mole) and 1.5 g Dowex 50WX 12 ionexchanger (capacity of 4.5 mequ/g) and 30 mol MeOH were stirred for 2 hr at 20°. The ion exchanger was separated by filtration, washed with MeOH. The solvent was removed from the filtrate, the residue crystallized from CCl_4–C_6H_6 mixture yielding 3 (0.36 g, 78.6%), m.p. 101°. Literature data: m.p. 105–105.5°, (C_6H_6–CCl_4).[24] Found: C, 41.75; H, 4.52; N, 12.16. Calc. for $C_4H_5NO_3$: C, 41.75; H, 4.38; N, 12.17%.

2-Methoxyisoxazolidine-3,3-dicarboxylic acid trans-*methylamide methyl ester* (4). A soln of 1 (4.38 g; 0.02 mol) and $MeNH_2$ (0.62 g; 0.02 mole) in 30 ml abs MeOH with traces of MeONa was allowed to stand for 4 days at 20°. The solvent was removed, the residue washed with ether and recrystallized from CCl_4. Yielding 4 (2.77 g) (Table 1). Found: C, 44.13; H, 6.60; N 12.78. Calc. for $C_8H_{14}N_2O_5$: C, 44.04; H, 6.47; N, 12.84%. Compound 1 (1.53 g; 35%) was isolated from the ethreal extract.

2-Methoxyisoxazolidine-3,3-dicarboxylic acid bis-methylamide (5). A soln of 1 (0.45 g; 0.002 mole) in 30 ml abs MeOH saturated with $MeNH_2$ and containing the traces of MeONa was kept in a sealed ampoule for 2 weeks at 20°. After removal of the solvent the residue was crystallized from C_6H_6 yielding 5 (0.33 g) (Table 1). Found: C, 44.43; H, 7.02; N, 19.24. Calc. for $C_8H_{15}N_3O_4$: C, 44.39; H, 6.94; N, 19.29%.

2-Methoxyisoxazolidine-3,3-dicarboxylic acid trans-*methylamide potassium salt* (6). A soln of 4 (3.14 g; 0.0144 mole) and KOH (0.896 g; 0.016 mole) in 30 ml abs MeOH was allowed to stand for 2 days at 20°. The solvent was removed, the residue crystallized from MeOH yielding 6 (3.94 g) in the form of crystallosolvate with MeOH (Table 1). Found: C, 35.01; H, 5.41; N, 10.29. Calc. for $C_8H_{15}N_2O_6K$: C, 35.03; H, 5.51; N, 10.21%.

Isoxazoline-3-carboxylic acid methylamide (7). Compound 6 (0.36 g; 0.0013 mole) and Dowex 50WX12 ion exchanger in 10 ml MeOH were stirred for 1 hr at 20°. The ion exchanger was filtered off, washed with MeOH, the solvent was removed from the filtrate, the residue was crystallized from CCl_4 yielding 7 (0.1 g, 59.6%), m.p. 96–97°. Found: C, 46.50; H, 6.45; N, 21.86. Calc. for $C_5H_8N_2O_2$: C, 46.87; H, 6.29; N, 21.86%. The NMR spectrum (80 MHz, C_6H_6, δ ppm from HMDS, J Hz): 2.28 (MeN, J = 5), 3.56, 2.48, multiplet centers of cyclic proton signals.

Separation of diastereomeric 2-methoxyisoxazolidine-3,3-dicarboxylic acid trans-*methylamide α-phenylethylammonium salts.* Separation of α-phenylethylamine into antipodes was per-

Table 5. Bond lengths (Å) and bond angles (deg.)

Carboxylate anion $[C_7H_{11}N_2O_5]^-$ of salt (+10)

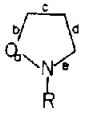
O(1) - N(1)	1.418(3)	C(1) - H(2)	0.95(4)
O(1) - C(1)	1.460(4)	C(2) - C(3)	1.522(3)
O(2) - N(1)	1.434(3)	C(2) - H(3)	0.99(3)
O(2) - C(7)	1.423(4)	C(2) - H(4)	0.95(4)
O(3) - C(4)	1.231(3)	C(3) - C(4)	1.535(3)
O(4) - C(5)	1.234(3)	C(3) - C(5)	1.555(3)
O(5) - C(5)	1.239(3)	C(6) - H(6)	0.89(5)
N(1) - C(3)	1.488(3)	C(6) - H(7)	0.96(5)
N(2) - C(4)	1.318(3)	C(6) - H(8)	0.93(5)
N(2) - C(6)	1.459(4)	C(7) - H(9)	0.96(5)
N(2) - H(5)	0.86(3)	C(7) - H(10)	1.01(4)
C(1) - C(2)	1.501(4)	C(7) - H(11)	0.98(5)
C(1) - H(1)	0.98(4)		

N(1)-O(1)-C(1)	109.5(2)	C(1)-C(2)-H(4)	115(2)
N(1)-O(2)-C(7)	107.6(2)	C(3)-C(2)-H(3)	114(2)
O(1)-N(1)-O(2)	107.2(2)	C(3)-C(2)-H(4)	115(2)
O(1)-N(1)-C(3)	103.1(2)	H(3)-C(2)-H(4)	101(3)
O(2)-N(1)-C(3)	104.5(2)	N(1)-C(3)-C(2)	105.2(2)
C(4)-N(2)-C(6)	122.0(2)	N(1)-C(3)-C(4)	107.8(2)
C(4)-N(2)-H(5)	120(2)	N(1)-C(3)-C(5)	111.2(2)
C(6)-N(2)-H(5)	117(2)	C(2)-C(3)-C(4)	111.4(2)
O(1)-C(1)-C(2)	106.8(2)	C(2)-C(3)-C(5)	115.0(2)
O(1)-C(1)-H(1)	107(2)	C(4)-C(3)-C(5)	105.9(2)
O(1)-C(1)-H(2)	111(3)	O(3)-C(4)-N(2)	123.7(2)
C(2)-C(1)-H(1)	109(2)	O(3)-C(4)-C(3)	118.1(2)
C(2)-C(1)-H(2)	116(2)	N(2)-C(4)-C(3)	118.1(2)
H(1)-C(1)-H(2)	107(3)	O(4)-C(5)-O(5)	126.5(2)
C(1)-C(2)-C(3)	102.8(2)	O(4)-C(5)-C(3)	116.4(2)
C(1)-C(2)-H(3)	110(2)	O(5)-C(5)-C(3)	116.9(2)
N(2)-C(6)-H(6)	115(3)	O(2)-C(7)-H(9)	112(3)
N(2)-C(6)-H(7)	108(3)	O(2)-C(7)-H(10)	111(2)
N(2)-C(6)-H(8)	113(3)	O(2)-C(7)-H(11)	114(3)
H(6)-C(6)-H(7)	93(4)	H(9)-C(7)-H(10)	113(4)
H(6)-C(6)-H(8)	106(4)	H(9)-C(7)-H(11)	110(4)
H(7)-C(6)-H(8)	120(4)		

(S)-α-phenylethylammonium cation $[C_8H_{12}N]^+$ of salt (+10)

N(3) - C(8)	1.495(3)	C(10) - C(15)	1.390(4)
N(3) - H(12)	0.95(3)	C(11) - C(12)	1.391(4)
N(3) - H(13)	0.86(3)	C(11) - H(19)	0.93(3)
N(3) - H(14)	0.92(3)	C(12) - C(13)	1.378(5)
C(8) - C(9)	1.518(4)	C(12) - H(20)	0.90(3)
C(8) - C(10)	1.506(4)	C(13) - C(14)	1.373(6)
C(8) - H(15)	1.04(3)	C(13) - H(21)	0.93(3)
C(9) - H(16)	1.07(4)	C(14) - C(15)	1.371(5)
C(9) - H(17)	0.97(3)	C(14) - H(22)	0.99(5)
C(9) - H(18)	0.90(4)	C(15) - H(23)	0.95(4)
C(10)- C(11)	1.382(4)		

C(8)-N(3)-H(12)	106(2)	C(8)-C(9)-H(18)	104(2)
C(8)-N(3)-H(13)	112(2)	H(16)-C(9)-H(17)	100(3)
C(8)-N(3)-H(14)	107(2)	H(16)-C(9)-H(18)	119(3)
H(12)-N(3)-H(13)	115(2)	H(17)-C(9)-H(18)	111(3)
H(12)-N(3)-H(14)	117(2)	C(8)-C(10)-C(11)	121.9(2)
H(13)-N(3)-H(14)	99(3)	C(8)-C(10)-C(15)	119.9(2)
N(3)-C(8)-C(9)	109.1(2)	C(11)-C(10)-C(15)	118.1(2)
N(3)-C(8)-C(10)	110.0(2)	C(10)-C(11)-C(12)	120.1(3)
N(3)-C(8)-H(15)	110(2)	C(10)-C(11)-H(19)	120(2)
C(9)-C(8)-C(10)	115.1(2)	C(12)-C(11)-H(19)	120(2)
C(9)-C(8)-H(15)	99(2)	C(11)-C(12)-C(13)	120.8(3)
C(10)-C(8)-H(15)	112(2)	C(11)-C(12)-H(20)	119(3)
C(8)-C(9)-H(16)	109(2)	C(13)-C(12)-H(20)	120(2)
C(8)-C(9)-H(17)	113(2)	C(12)-C(13)-C(14)	119.0(3)
C(12)-C(13)-H(21)	126(2)	C(15)-C(14)-H(22)	125(3)
C(14)-C(13)-H(21)	115(2)	C(10)-C(15)-C(14)	121.5(3)
C(13)-C(14)-C(15)	120.3(3)	C(10)-C(15)-H(23)	120(2)
C(13)-C(14)-H(22)	114(3)	C(14)-C(15)-H(23)	118(2)

Table 6. Structural parameters of isoxasolidine cycle 

Parameters	Compounds			
	Trans-2-methoxy-3,3-dimethoxycarbonyl-5-cyanoisoxazolidine.[16]	3-Cyano-5-parabromophenyl-2-methoxyisoxazolidine.[17]	2-Methoxyisoxasolidine-3,3,5,5-tetracarboxylic acid tetraamide.[1]	S-α-Phenylethilammonium salt of 2-methoxyisoxasolidine-3,3-dicarboxylic acid trans-methylamide
a		1.412(8)	1.430(2)	1.418(3)
b		1.455(8)	1.450(2)	1.460(4)
c		1.533(10)	1.524(2)	1.501(4)
d		1.512(10)	1.523(2)	1.522(3)
e		1.498(9)	1.477(2)	1.488(3)
ab		109.1(5)	109.2(1)	109.5(2)
bc		105.0(5)	106.2(1)	106.8(2)
cd		103.5(6)	100.9(1)	102.8(2)
de		105.9(6)	104.2(1)	105.2(2)
ea	102	102.1(5)	101.4(1)	103.1(2)
Δ[a)]			0.57	0.49
h[b)]			0.60	0.58
Σ[c)]	311	310.6	311.9	314.8

a) Δ, Å - the exit of N atom from everage plane, withdrawn throught the rest atoms of the cycle

b) h, Å - the exit of N atom from everage plane, withdrawn throught the connecting with one

c) Σ(°)- the sum of valent angles of N atom

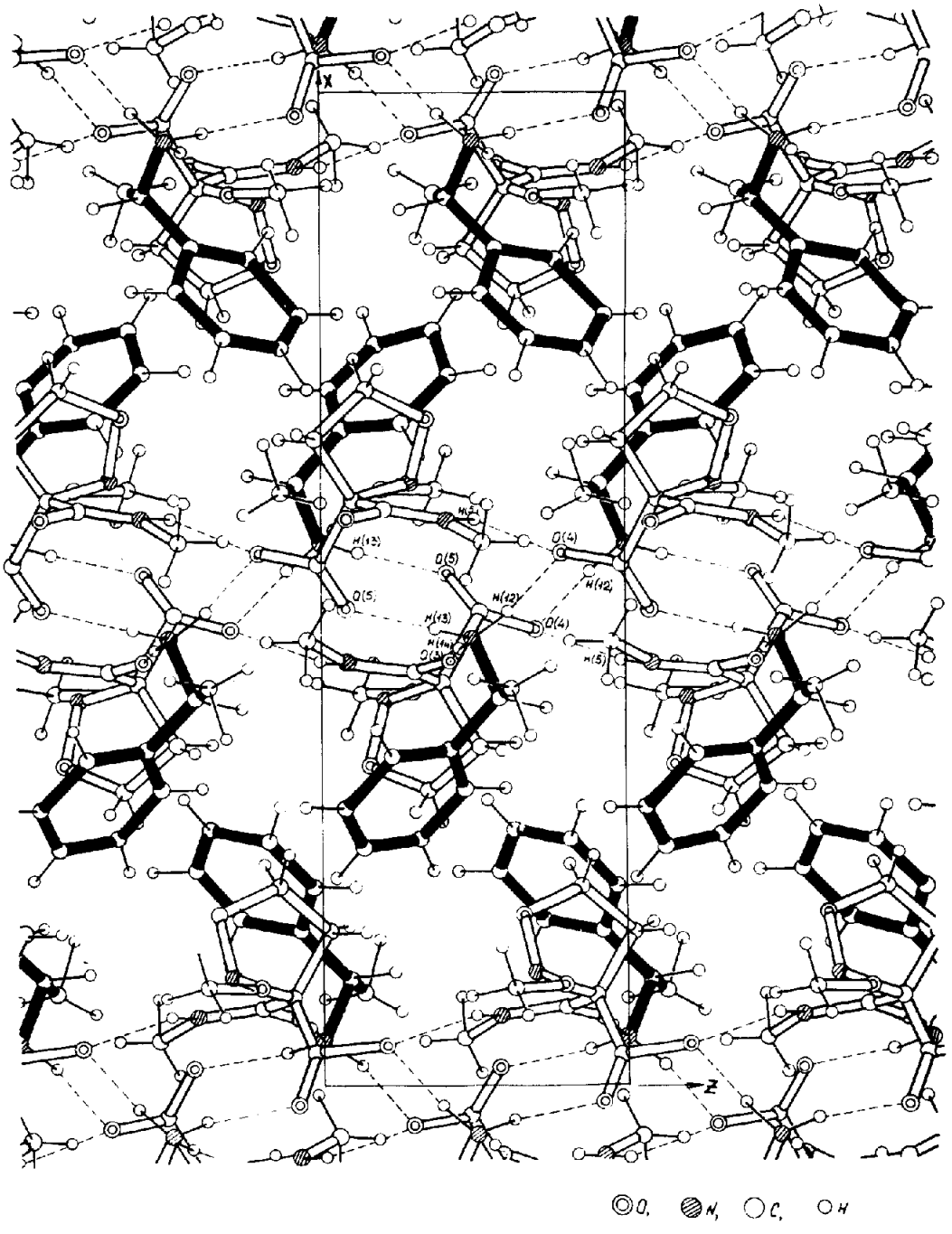


Fig. 5. Crystal structure of (+ **10**), projection on XOZ plane.

formed as described.[25] *S*-(−)-PEA with $[\alpha]_{546}^{20}$ −46.4° (pure liquid), optical purity 96.3%, and *R*-(+)-PEA with $[\alpha]_{546}^{20}$ +47.58° (pure liquid), optical density 98.8% were used for separation.

(A) *S-(−)-α-Phenylethylammonium salt of 2-methoxyisoxazolidine-3,3-dicarboxylic acid* trans-*methylamide* (**8**). A soln of **6** (3.59 g; 0.013 mole) in 30 ml distilled water was passed through an ion exchange column (Dowex 50WX12, 10-fold molar excess, in the form of $PhCH(Me)NH_3^+$). Fractions output was controlled by UV spectrum. The eluate (120 ml) was evaporated *in vacuo* on rotor evaporator with further liophile drying yield **8** (3.79 g (Table 2). Found: C, 55.23; H, 7.24; N, 12.80. Calc. for $C_{15}H_{23}N_3O_5$: C, 55.37; H, 7.13; N, 12.92%. The NMR spectrum (80 MHz, CD_3OD, δ ppm from HMDS, J Hz): 7.34 (Ph), 3.51 (MeO), 2.66 (MeN), 1.54 (Me, J=7), 4.46–3.51 (the region of –CH and cyclic proton signals), 2.89–2.66 (cyclic proton signals).

(B) *Diastereomerically pure S-(−)-α-phenylethylammonium salt of 2-methoxyisoxazolidine-3,3-dicarboxylic acid* trans-*methylamide* (+ **10**). Compound **8** (3.79 g; 0.0116 mole) was successively crystallized from 50 and 30 ml MeOH and + **10** (0.6 g) was obtained (Table 2). The NMR spectrum is similar to that of **8**.

(C) *R-(+)-α-Phenylethylammonium salt of 2-methoxyisoxazolidine-3,3-dicarboxylic acid* trans-*methylamide* (**9**). Crystallization liquids from a previous run were evaporated *in vacuo*, the residue was dissolved in 30 ml distilled water and the soln was passed through the ion exchange column (Dowex 50WX12, 10-fold molar excess, in K^+ form). The eluate (100 ml) was partly evaporated *in vacuo* on rotor evaporator to *ca* 20 ml and passed through the ion exchange column (Dowex 50WX12, 10-fold molar excess, in R-(+)-$PhCH(Me)NH_3^+$ form). The fraction output

Table 7. Hydrogen bonds, interatomic distances (Å) and angles (deg.)

H(5)...O(4')	2.28(3)	O(4')...H(5)-N(2)	150(2)
N(2)...O(4')	3.051(3)		
H(12')...O(4')	1.79(3)	O(4')...H(12')-N(3')	165(2)
N(3')...O(4')	2.724(3)		
H(13')...O(5)	1.89(3)	O(5)...H(13')-N(3')	175(3)
N(3')...O(5)	2.750(3)		
H(14')...O(3")	1.91(3)	O(3")...H(14')-N(3')	169(3)
N(3')...O(3")	2.813(3)		
H(5)...N(1)	2.22(3)		

(') x,y,z+1

(") $\bar{x}$,1/2+y,1/2-z

was controlled by UV spectrum. The eluate (100 ml) was evaporated *in vacuo* on rotor evaporator. After liophile drying 1.95 g of **9** was obtained (Table 2). Found: C, 55.31; H, 7.02; N, 12.78. Cal. for $C_{15}H_{23}N_3O_5$: C, 55.37; H, 7.13; N, 12.92%. The NMR spectrum was similar to that of **8**.

D. *Diastereomerically pure* R-(+)-*α-phenylethylammonium salt of* 2-*methoxyisoxazolidine*-3,3-*dicarboxylic acid* trans-*methylamide* (−**10**). Compound **9** (1.95 g) was successively crystallized from 20 and 17 ml of MeOH and −**10** (0.41 g) was obtained (Table 2). The NMR spectrum is similar to that of **8**.

(+)-2-*Methoxyisoxazolidine*-3,3-*dicarboxylic acid methyl ester* trans-*methylamide* (+**11**). A suspension of +**10** (0.58 g; 0.00178 mole) in 20 ml MeOH was treated at 20° with an ethereal diazomethane soln. After complete solutions of +**10** (12 hr) the soln was partly evaporated *in vacuo*, 1 g of Dowex 50WX12 ionexchanger (H^+-form, capacity of 4.5 mequ/g) was added and the mixture stirred for 1.5 hr at 20°. The ion exchanger was filtered off, washed with MeOH. The solvent was evaporated from the filtrate, the residue was crystallized from the mixture of CCl_4-heptane yielding −**11** (0.38 g) (Table 2).

(−)-2-*Methoxyisoxazolidine*-3,3-*dicarboxylic acid methyl ester* trans-*methylamide* (−**11**). Analogously to the previous synthesis, reaction of −**10** (0.594 g) with an ethereal soln of diazomethane gave 0.385 g of −**11** (Table 2).

(+)-2-*Methoxyisoxazolidine*-3,3-*dicarboxylic acid bis-methylamide* (+**12**). A soln of +**11** (0.08 g; 0.000366 mole) in 110 ml abs MeOH saturated with $MeNH_2$ (20 ml) and containing traces of MeONa was kept in a sealed ampoule for 2 weeks at 20°. After removal of the solvent the residue was crystallized form C_6H_6 yielding +**12** (0.0413 g) (Table 2).

(−)-2-*Methoxyisoxazolidine*-3,3-*dicarboxylic acid bis-methylamide* (−**12**). A soln of −**11** (0.296 g; 0.00135 mole) and 19 ml $MeNH_2$ in 30 ml MeOH containing traces of MeONa was kept in a sealed ampoule for 2 weeks at 20°. After removal of the solvent the residue was extracted with $CHCl_3$ yielding −**12** (0.284 g; 96.5%) with $[\alpha]_D^{20}$ − 199.8°. Crystallization from C_6H_6 gave 0.197 g of −**12** (Table 2) with $[\alpha]_D^{20}$ − 231.6°.

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