Tetrahedron Vol. 49, No. 21, pp. 4671-4676, 1993
Printed in Great Britain

0040-4020/93 $6.00+.00

Synthesis and Structure of Optically Active 3-Amino-2H-azirines

I.P. Piskunova, A.V. Eremeev, A.F. Mishnev, I.A. Vosekalna

Institute of Organic Synthesis, Latvian Academy of Sciences, Aizkraukles Str., 21, 226006 Riga, Latvia

(*Received in UK* 14 *December* 1992)

Abstract. Synthesis of optically active 3-amino-2H-azirines using the modified Neber reaction has been carried out for the first time. The structure and absolute configuration of diastereomeric derivatives of 3-amino-2H-azirines have been determined.

Structural similarity with natural amino acids and high reactivity of amino-2H-azirines [1-4] predetermine the wide possibilities for the synthesis of various classes of organic compounds including peptide and depsipeptide derivatives on the basis of optically active 3-amino-2H-azirines. However, up to now the latter have not been synthesized.

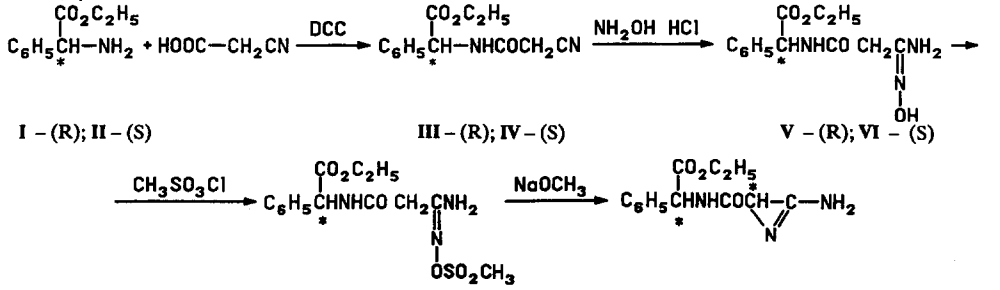
At the same time it is known that optically active 2H-azirines with asymmetric centre in the azirine cycle, namely, azirinomycine and desidazirine possess the pronounced antibiotical and cytostatic activity.[5,6] In this connection finding methods for asymmetric synthesis affording optically active 3-amino-2H-azirines becomes urgent.

Our studies are aimed at developing such syntheses and determination of the structure and absolute configuration of diastereomeric derivatives of 3-amino-2H-azirines with an exocyclic primary amino group. The presenting optically active aminoazirines of an unsubstituted amino group, i.e. an additional reactivity centre in a molecule, substantially widens their synthetic possibilities.

The synthesis of optically active 3-amino-2-[N-(phenylethoxycarbonylmethyl)carbamoyl]-2H-azirines using the modified Neber reaction[7] has been carried out for the first time.

Ethyl esters (S) and (R) of phenylglycine I, II successively converted into amidoximes V, VI according to the scheme have been used as key chiral substances for obtaining initial O-mesyl derivatives of amidoximes VII, VIII.

On acylation of amidoximes V and VI with mesyl chloride, chiral O-mesyl derivatives of amidoximes VII, VIII are obtained with 95% yield. On treatment with sodium methylate, the latter is converted into optically active 3-amino-2H-azirines, IX and X, with two asymmetric centres on carbon atoms - one endocyclic (C_2 of the azirine ring) and the other exocyclic (the carbon of the amino and fragment). The structure of chiral 3-amino-2H-azirines IX, X is confirmed by IR, ^1H, ^{13}C NMR and elemental analysis data (Tables 1,2).



I – (R); II – (S) III – (R); IV – (S) V – (R); VI – (S)

VII – (R); VIII – (S) IXa – (2R, 3'R); IXb –(2S, 3'R); Xa - (2S, 3'S); Xb - (2R, 3'S)

Table 1. Spectral Characteristics of Compounds III-X

Compound	PMR spectra, δ, ppm									IR spectra, ν, cm^{-1}		
	Ar–H (m)	CH_3 (t)	CH_2 (q)	CH_2	CH (d)	NH_2	NH (d)	CH azirine	Solvent	C=O	C(=O)O	NH, (C=N)
III	7.36	1.13	3.73	4.10 (J = 7.2 Hz)	5.36	–	9.1 (J = 7.2 Hz)	–	DMSO-d_6	1630, 1655	1730	3080,3390 (2260)
IV	7.36	1.13	3.72	4.11 (J = 7.2 Hz)	5.36	–	9.1 (J = 7.2 Hz)	–	DMSO-d_6	1630, 1655	1730	3080, 3390 (2260)
V*	7.27	1.17	4.13	3.10 (J = 7.2 Hz)	5.54	5.22	7.98 (J = 7.2 Hz)	–	$CDCl_3$	1650, 1680	1730	3300–3530
VI*	7.26	1.15	4.13	3.10 (J = 7.2 Hz)	5.55	5.18	8.01 (J = 7.2 Hz)	–	$CDCl_3$	1649	1730	3300–3530
VII**	7.33	1.11	4.00	3.09 (J = 7.2 Hz)	5.36	6.69	8.82 (J = 7.2 Hz)	–	DMSO-d_6	1640	1735	3075–3400
VIII***	7.30	1.18	4.18	3.14 (J = 7.2 Hz)	5.46	5.59	7.08 (J = 7.2 Hz)	–	$CDCl_3$	1640, 1680	1735	3080–3400 1835, 1815
IXa	7.29	1.21	4.17	–	5.48 (J = 7.3 Hz)	5.70	6.83 (J = 7.3 Hz)	2.71	$CDCl_3$	1642	1734	3040–3460 1835, 1815
IXb	7.29	1.21	4.17	–	5.48 (J = 7.3 Hz)	5.70	6.83 (J = 7.3 Hz)	2.61	$CDCl_3$			
Xa	7.31	1.11 (J = 7.3 Hz)	4.04	–	5.38	7.22	8.53 (J = 7.3 Hz)	2.71	DMSO-d_6	1630	1735	3060–3460 1815, 1835
Xb	7.32	1.11	4.04	–	5.38	7.22	8.53	2.60	DMSO-d_6			

* Signals of OH group protons, 8.94 ppm

** Signals of OSO_2CH_3 group protons, 3.06 ppm

*** Signals of OSO_2CH_3 group protons, 3.09 ppm

Table 2. Characteristics of Compounds III-X

Compound	Found, %			Empirical formula	Calculated, %			Yield, %
	C	H	N		C	H	N	
III	63.30	5.70	11.35	$C_{13}H_{14}N_2O_3$	63.41	5.69	11.38	92
IV	63.39	5.70	11.40	$C_{13}H_{14}N_2O_3$	63.41	5.69	11.38	90
V	55.90	6.08	15.03	$C_{13}H_{17}N_3O_4$	55.91	6.09	15.05	95
VI	55.89	6.09	15.04	$C_{13}H_{17}N_3O_4$	55.91	6.09	15.05	87
VII	47.06	5.31	11.75	$C_{14}H_{19}N_3O_6S$	47.06	5.32	11.76	91
VIII	47.04	5.32	11.76	$C_{14}H_{19}N_3O_6S$	47.06	5.32	11.76	97
IXa	59.75	5.74	16.10	$C_{13}H_{15}N_3O_3$	59.77	5.75	16.09	82
Xa	59.76	5.75	16.08	$C_{13}H_{15}N_3O_3$	59.77	5.75	16.09	74

The PMR spectrum of optically active 3-amino-3H-azirine IX obtained at 360 MHz reveals the presence of a mixture of diastereomers having the same or similar values of chemical shifts (CS) of protons of the amino acid fragment and amino group, but significantly different CS of methine protons of the azirine

cycle. The integral intensity of CH group signals of the cycle corresponds to 96:4 ratio of diastereomers, i.e., diastereomers are formed with predominance of one of them. It is worth noting that in the predominant isomer IXa, there is considerable deshielding of the ring proton (2.71 ppm) in comparison to isomer IXb (2.61 ppm). Apparently, this can be explained by anisotropic effect of properly oriented phenyl and carbonyl groups relative to the CH cycle. The predominant diastereomers IXa and Xa are obtained optically pure from ethyl acetate by crystallization.

Analysis of circular dichroism (CD) spectra of diastereomeric 3-amino-2H-azirines IXa and Xa within a short wavelength (210-240 nm) (Fig.1) shows that these compounds are characterized by mirror-symmetric CD spectra as well as enantiomers with Cotton effect (CE) of opposite sign and similar value of ellipticity.

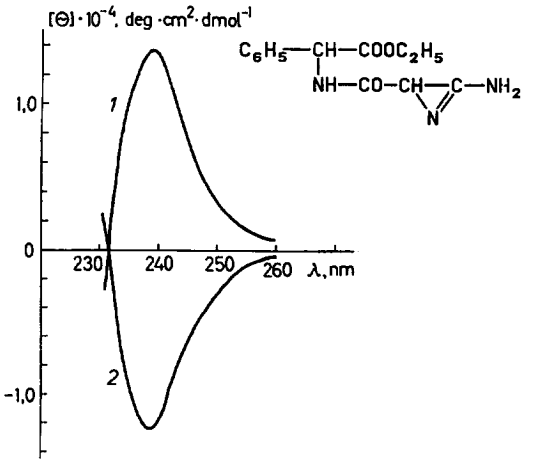


Fig. 1. CD spectra of IXa (*1*) and Xa (*2*) within a short wave-length range.

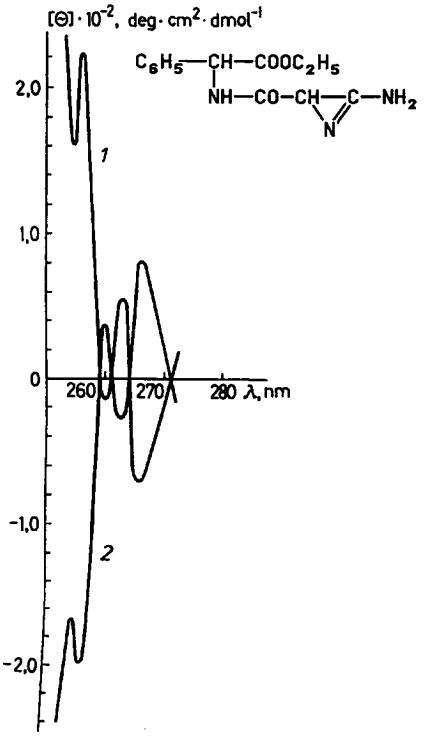


Fig. 2. CD spectra of IXa (*1*) and Xa (*2*) in the near UV-region.

Obviously, $n - \pi^*$ transition of amide chromophore corresponds to CE at 240 nm. Shift of this transition towards the long-wave region in comparison to the standard wavelength for the given transition in amides (229 nm) indicates the weakening of amide conjugation. Data of CD spectra in near UV region (Fig.2) also evidences for an opposite surrounding of asymmetric carbon atom for both stereoisomers. Some small CE within 250-270 nm range are explained by the contributions of transitions of various chromophores including mainly ^1L_b transition of aromatic chromophore.

To determine the absolute configuration of IX monocrystals of diastereoisomer IXa have been obtained; its molecular and crystal structure has been defined by X-ray analysis. The model of IXa molecule with the indication of bond length, valent and torsion angles is presented in Fig.3.

Table 3. Coordinates of Non-hydrogen Atom 1 in Crystal Structure IXa (x 10^4)

Atom	X	Y	Z
03	4977 (4)	3432 (0)	3094 (3)
01	3544 (5)	-3420 (15)	3609 (3)
N3	3717 (4)	792 (17)	3264 (3)
02	5041 (3)	-197 (18)	2446 (3)
N1	2635 (5)	-380 (18)	4327 (4)
C1	3615 (5)	-932 (19)	3722 (4)
C5	4675 (5)	1268 (19)	2755 (4)
C4	3787 (5)	-83 (20)	2607 (4)
C2	3550 (5)	330 (19)	4361 (4)
N2	3911 (4)	-2929 (18)	5568 (3)
C8	2893 (5)	465 (19)	1741 (4)
C3	3450 (5)	-1386 (19)	4898 (4)
C9	2237 (6)	2515 (22)	1571 (5)
C13	2721 (6)	-1010 (22)	1080 (5)
C6	5932 (6)	784 (27)	2577 (5)
C11	1265 (6)	1465 (28)	112 (5)
C10	1437 (7)	3005 (28)	760 (6)
C12	1900 (7)	-514 (26)	282 (6)
C7	5663 (7)	2650 (33)	1885 (6)

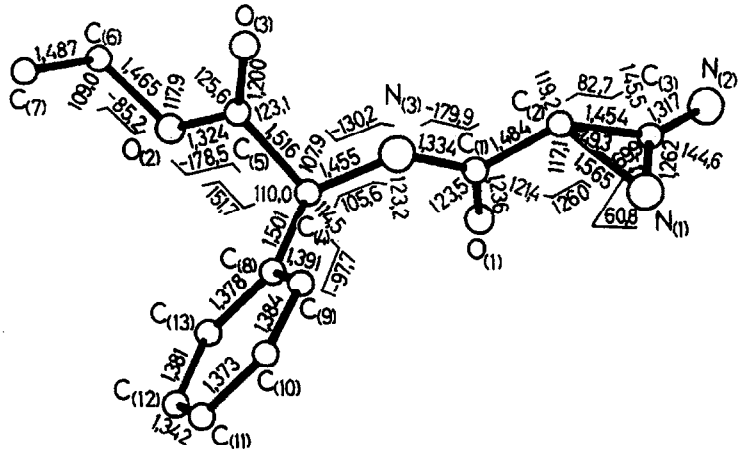


Fig. 3. Spacial structure of IXa.

As the asymmetric carbon atom of amino acid fragment is not involved (CD spectra clearly evidences for this fact) in the synthesis of optically active 3-amino-2H-azirines IX, X, its configuration, consequently, does not change. After the known R-configuration of α-carbon atom C (4) the absolute configuration of asymmetric carbon atom C(2) of 3-amino-2-[N-(phenylethoxycarbonylmethyl)carbamoyl]-2H-azirine IXa which appearing to be R has been determined.

In azirine cycle C=N double bond (1.262 Å) practically corresponds to its length in imines (1.24 Å) and is close to the value obtained for 3-phenoxy-3-dimethylcarbamoylamino-2-azirine (XI, 1.279 Å).[8] However, the length of $N_{(1)}$-$C_{(2)}$ bond is dramatically increased (1.565 Å) in comparison to XI (1.490 Å). Endocyclic valent angle at $C_{(3)}$ atom is also increased and the values of exocyclic angles at this atom are equal, while in XI the values of these angles differ by 10°. The other bonds are close to their standard values. A system of intramolecular hydrogen bonds of N-H...O($N_{(2)}$...$O_{(3)}$ = 2.789, H...$O_{(3)}$ = 1.95 Å, $N_{(2)}$-H-$O_{(3)}$ = 174.8° and $N_{(3)}$ ... $O_{(1)}$ = 2.992, H ... $O_{(1)}$ = 2.21 Å, $N_{(3)}$-H-$O_{(1)}$ = 161.8° type has been revealed in the crystal structure IXa.

It should be noted that $N_{(1)}$ atom is also involved in the intramolecular interactions due to the hydrogen bond ($N_{(2)}$-H...$N_{(1)}$ ($N_{(2)}$ ... $N_{(1)}$ = 3.013, H ... $N_{(1)}$ = 2.20 Å, $N_{(2)}$-H-$N_{(1)}$ = 136.6°).

Thus, optically active 3-amino-2H-azirines with high optical yield have been obtained for the first time under the modified Neber reaction using amino acid derivatives as chiral subtraces. Simplicity of the reaction and high yields of the final products allow to apply this method for the preparation of optically active 3-amino-2H-azirines.

EXPERIMENTAL

IR spectra were obtained on a Perkin Elmer 580 B spectrometer in nujol; PMR spectra were registered on Bruker WH-90 and Bruker WH-360 spectrometers. Internal standard - TMS. CD spectra were registered on Yobin-Ivon Mark III dichrograph (France). Dichrograph was calibrated according to 10^{-3} -10^{-4} camphorsulfonic acid and epiandrosterone standards. Cuvettes from melted kvartz of Hellma Company with the length of optical route 1 cm in 350-250 nm spectral range and 0.1 - 0.01 cm in the region of 250-200 nm have been used. Concentration of solutions in methanol is 10^{-3}-10^{-4} M. Slot programme corresponded to 20 Å. Molecular ellipticity Θ was measured in deg cm²/dmol. Monocrystals of IX, $C_{13}H_{15}N_3O_3$, were monoclynic: a = 17.101 (6), b = 4.915 (2), c = 20.013 (6) Å, β = 126.61 (2) °, v = 1350.5 (4) Å³, M = 261.28, $d_{calc.}$ = 1.29 g/cm³, F_{000} = 552, z = 4, space gr. C2. Parameters of the unit cell and intensities of 1330 independent reflections up to 2Θ max = 50° were measured on automatic difractometer Syntex P21, (MoKα-radiation, graphite monochromator, Θ/2Θ-scanning). 756 reflections with I>2s(1) were used for calculations. The structure was solved with the help of SHELXS86 programme and refined in full matrix anisotropic approximation according to SHELX76 programme to the final R = 0.071. Coordinates of nonhydrogen atoms are given in Table 3. Standard deviations of bond lengths and valent angles do not exceed 0.01 Å and 1°, respectively.

(R)-[N-(phenylethoxycarbonylmethyl)carbamoyl]acetonitrile (III). Solution of ethyl ester (5.01 g, 0.028 mol) of R-phenylglycine and cyanoacetic acid (2.38 g, 0.028 mol) in 20 ml dimethylformamide (DMF) was added to hydroxybenzotriazole (3.77 g, 0.028 mol) in 10 ml DMF and to the solution of dicyclohexylcarbodiimide (6.37 g, 0.031 mol) in 20 ml DMF at 0–10°C. The reaction mixture was kept for 2 h at 0°C and for 2 h at room temperature, then the residue of dicyclohexylurea was filtered off. The filter was poured out into cold water, the precipitate was again filtered off and washed with water. The aqueous layer was extracted 2 times with ethyl acetate (200 ml). Ethyl acetate extract was washed with 0.1 N solution of sodium bicarbonate, 0.1 M citric acid and water, dried over anhydrous Na_2SO_4, then the solvent was removed and product III was additionally obtained. Residues were mixed and compound III (6.33 g, 92%) was obtained. $[\alpha]_D^{20}$ = -157 (c = 0.1 EtOH); mp = 108°C.

Compound IV was obtained in a similar way. $[\alpha]_D^{20}$ = +156 (c = 0.1 EtOH); mp = 107°C.

(R)-[N-(Phenylethoxycarbonylmethyl)carbamoyl]acetamidoxime (V). Solution of the nitrile III (2.46 g, 0.01 mol) in 100 ml of ethanol was added to the aqueous solution of hydroxylamine hydrochlor (1.4 g, 0.02 mol) at mixing and to soda (2.2 g, 0.01 mol) in 30 ml of 50% ethanol. Reaction mixture was heated for 1 h at 35°C and was kept at room temperature for 5 days. The solvent was evaporated, the residue was dissolved in ethyl acetate and dried over Na_2SO_4. The residue obtained after evaporation of ethyl acetate was recrystallized from ethyl acetate-hexane to give acetamidoxime V (2.65 g, 95%) was obtained. $[\alpha]_D^{20}$ = -81 (c = 0.1 EtOH); mp = 105°C. Compound VI was obtained in a similar way.

(R)-[N-(Phenylethoxycarbonylmethyl)carbamoyl]-O-mesylacetamidoxime (VII). Amidoxime V (2.79 g, 0.01 mol) in 20 ml absolute pyridine at -30° - -25°C was added gradually to methane sulfonyl chloride (1.48 g, 0.013 ml) and kept for 0.5 h at -25°-O° C. The mixture was poured out into 300 ml of cold distilled water. The residue was filtered off, washed with cold water and recrystallized from ethyl acetate. Amidoxime VII (3.21 g, 91%) was obtained. $[\alpha]_D^{20}$ = -88 (c = 0.1 EtOH); mp = 121°C.

Compound VIII was obtained analogously; mp = 122°C; $[\alpha]_D^{20}$ = +92 (c = 0.1 EtOH).

2R,3'R-Amino-2-[N-(phenylethoxycarbonylmethyl)]-2H-azirine (IX). A solution of mesylate VII (3.57 g, 0.01 mol) in 250 ml absolute ethanol was added very slowly to sodium methylate (1.2 g, 0.01 mol) at 22°. and kept for 2 h. The solvent was evaporated and the residue was washed with water and ether (15 ml). Analysis was made according to PMR spectrum. Recrystallization from ethyl acetate was carried out; as result IXa (2.14 g) was obtained. $[\alpha]_D^{20}$ = -140 (c = 0.1EtOH).

2S,3'S-3-amino-2-[N-(phenylethoxycarbonylmethyl)carbamoyl]-2H-azirine Xa was obtained analogously. $[\alpha]_D^{20}$ = +142 (c = 0.1 EtOH); mp = 142°C.

REFERENCES

1. Eremeev, A.; Piskunova, I. *Khim. Geterotsi.cl Soed.*, **1990**, *7*, 867.
2. Heimgartner, H. *Isr. J. Chem.*, **1986**, *27*, 3.
3. Wipf, P.; Heimgartner, H. *Helv. Chim. Acta*, **1990**, *73*, 13.
4. Nair, V. *Chemistry of Heterocyclic Compounds*, 1986, 215.
5. Molinski, T.; Ireland, C. *J. Org. Chem.*, **1988**, *53*, 2103.
6. Miller, T.; Tristram, E.; Wolf, F. *J. Antibiot.*, **1971**, *24*, 48.
7. Eremeev, A.; Piskunova, I.; Elkinson, R. *Khim. Geterotsicl. Soed.*, **1985**, *9*, 1202 (In Russian).
8. Galloy, J.; Putzeys, J.; Germain, G.; Declercq, J.-P.; van Meenssche, M. *Acta Cryst.*, **1970**, *B30*, 2462.