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Synthesis of Cyclopropane Derivatives of Aspartic Acid by Thermal Decomposition of Substituted Pyrazolines

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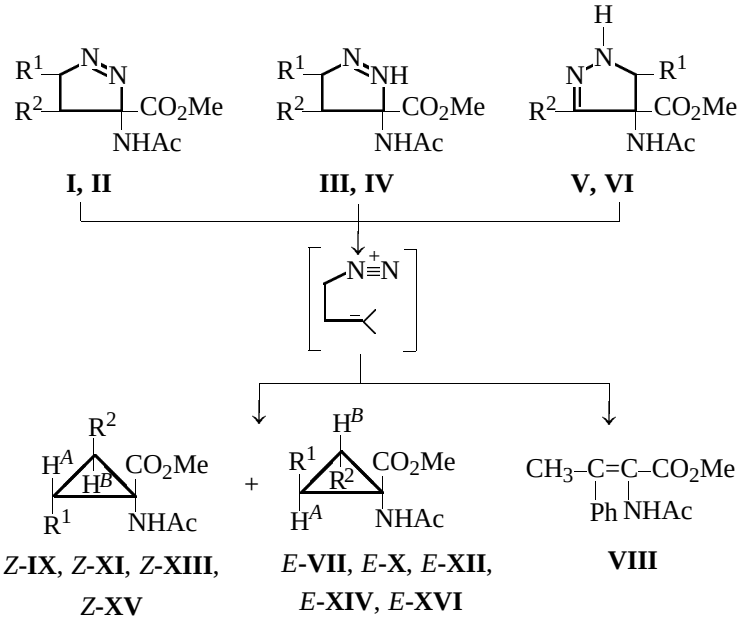
Abstract — Thermal decomposition of substituted Δ^1- and Δ^2-pyrazolines was used to obtain cyclopropane derivatives of aspartic and adipic acids.

The interest in α-amino acids of the cyclopropane series, including cyclopropane analogs of glutamic and aspartic acids, is associated with the possibility of designing on their basis new antispasmodic and psychotropic drugs [1]. In this connection search for synthetic approaches to such amino acids takes on special significance.

One of the methods for preparing precursors of cyclopropane α-amino acids involves decomposition of pyrazoline derivatives. *N*-Unsubstituted pyrazolines decompose under rigid conditions; the reaction involves nitrogen evolution and generally takes two pathways to give either cyclopropane or unsaturated compounds. The ratio of these two products is variable and depends on the structure of the parent pyrazolines [2], as well as on the reaction conditions [3, 4]. According to [5, 6], thermolysis of Δ^1-pyrazolines yields mostly cyclopropane derivatives, while Δ^2-pyrazolines, by contrast, are a source of unsaturated compounds.

In the present work we decomposed Δ^1- (**I, II**) and Δ^2-pyrazolines **III**–**VI** obtained in the previous works [7–10].

Earlier Bregovec and Jakovcic [1] decomposed pyrazoline **I** in toluene under reflux (2.5 h, argon atmosphere). The reaction gave rise to 1-(acetylamino)-cyclopropane-1-carboxylic acid (**VII**) in an yield of 70%. By changing toluene by the higher boiling di-



R^1 = H (**I, VII, VII**–**X**), CO_2Me (**III, V, XI, XII, XV**), CO_2Et (**IV, VI, XIII, XIV, XVI**); R^2 = H (**I, III, IV, VII, XI**–**XIV**), Ph (**II, V, VI, IX, X, XV, XVI).**

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Table 1. Yields, melting points, and elemental analyses of compounds **VII** and **IX**–**XVI**

Comp. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
VII	95	82–84	53.52	7.00	8.93	$C_7H_{11}NO_3$	53.50	7.01	8.92
IX	42	78–79	66.92	6.42	6.02	$C_{13}H_{15}NO_3$	66.95	6.44	6.01
X	20	58–60	66.92	6.40	6.05	$C_{13}H_{15}NO_3$	66.90	6.43	6.02
XI	35	121–122	50.20	6.01	6.65	$C_9H_{13}NO_5$	50.23	6.05	6.51
XII	15	69–70	50.20	6.03	6.55	$C_9H_{13}NO_5$	50.29	6.00	6.50
XIII	35	84–85	52.42	6.53	6.11	$C_{10}H_{15}NO_5$	52.40	6.55	6.10
XIV	15	49–50	52.41	6.56	6.11	$C_{10}H_{15}NO_5$	52.40	6.55	6.10
XV	40	Oil	61.88	5.82	4.90	$C_{15}H_{17}NO_5$	61.86	5.84	4.81
XVI	40	″	62.95	6.23	4.58	$C_{16}H_{19}NO_5$	62.95	6.23	4.59

methylformamide, we could not only reduce the reaction time to 20 min, but also improve the yield of cyclopropane **VII** to 95%.

Thermolysis of Δ^1-pyrazoline *Z*-**II** under the same conditions allowed preparation (by contrast to data in [2]) of cyclopropane derivatives **IX** and **X** in an yield of 62%, along with alkene **VIII**.

Cyclopropane derivatives from pyrazolines are commonly prepared by catalytic thermolysis [11] or by photolysis [12]. However, under the conditions reported therein we failed to synthesize cyclopropane precursors of aspartic acid from pyrazolines **III** and **IV**. The latter could only be thermolyzed in DMF under reflux to obtain cyclopropanes **XI**–**XIV** in an yield of 50%. We were the first to obtain compounds **XI**–**XIV** by this method. Earlier compounds **XI** and **XII** were synthesized in another way [8].

The use of DMF for decomposing compounds **V** and **VI** allowed us to prepare previously unknown phenylaspartic acid derivatives **XV** and **XVI**.

It should be noted that, unlike Δ^1-pyrazolines, the more stable Δ^2-pyrazolines require longer reaction times to decompose: 40 (**III, IV**) and 60 min (**V, VI**), instead of 20 min. This fact appears to be explained by the additional conjugation of the C=N bond in them with R^1 and R^2 (N=CHCO$_2$R, N=CHPh) and the change from the Δ^2- to Δ^1-pyrazoline structure. The complication of the molecular structure in the series **I**–**VI** not only increases the reaction time, but also reduces the yield of cyclopropanes from 95 and 40% (Table 1).

The formation of cyclopropanes from Δ^1- (**II**) and Δ^2-pyrazolines (**III**–**VI**) can be explained in terms of the effect of solvent polarity on the stability of the intermediate zwitter ion, which is nicely consistent with the mechanism of pyrazoline ring cleavage, proposed by Tabushi *et al.* [13]. The same views have been advanced by Thomas *et al.* [14], who related the stability of the intermediate with the presence of electron-acceptor substituents in the 3 or 5 positions of the pyrazoline ring.

According to [2, 13, 15], thermolysis of Δ^1-pyrazolines should be considered as a stereospecific process, where the configuration of substituents in the decomposition products is the same as in the parent pyrazolines. However, we found that thermolysis of substituted Δ^1- (**II**) and Δ^2- pyrazolines (**III**–**VI**) in DMF occurs nonstereospecifically. Thus, isomer *Z*-**II** in our conditions gives cyclopropanes *Z*-**IX** and *E*-**X**, individual compounds **III** and **IV** give mixtures *Z*-**XI** + *E*-**XII** and *Z*-**XIII** + *E*-**XIV**, respectively, while individual destereomers **V** and **VI** give a mixture of four different stereoisomers of compounds **XV** and **XVI**. By column chromatography we could separate *Z*- and *E* isomers **IX**–**XIV** and isolate the most stable stereoisomers *E*-**XV** and *E*-**XVI** from the stereiosmeric mixture.

The nonstereospecificity of the decomposition of Δ^1- and Δ^2-pyrazolines can be explained by the formation of a stable intermediate and the possibility of rotation in it of substituents about the C^4–C^5 bond.

The structure of amino acids **XI**–**XVI** was established by ^{1}H NMR and IR spectroscopy and by comparison with model compounds **VII**, **IX**, and **X** (Table 2). The ^{1}H NMR spectra of **XI**–**XVI** show signals of all structural fragments and reveal nonequivalence of ring protons which appear as a multiplet (1.1–2.2 ppm) overlapping with the NAc signal. Stereochemical assignment of *Z*-**XI**, *E*-**XII**, *Z*-**XIII**, and *E*-**XIV** was performed on the basis of the chemical shifts of NHAc protons: The signals of *Z*

Table 2. IR and ^{1}H NMR spectra of cyclopropane derivatives **VII** and **IX**–**XVI**

Comp. no.	IR spectrum ($CHCl_3$), ν, cm^{-1}				^{1}H NMR spectrum ($CDCl_3$), δ, ppm; *J*, Hz								
	C=O	N–H	C–H	CH_2	R^1	R^2	CH–CH (ring)	CO_2Me	NHAc	NH	J_{AB}	J_{A,R^2}	J_{B,R^2}
VII	1720, 1680	3420			1.04 m (1H)	1.44 m (1H)	1.44 m (2H)	3.62 s (3H)	1.93 s (3H)	7.49 s (1H)	7.2	8.5	4.5
***Z*-IX**	1720, 1678	3420	3000	1250	1.15–2.00 m (1H)	7.18–7.23 m (5H, Ph)	2.28 m (2H)	3.75 s (3H)	1.75 s (3H)	7.18 s (1H)	9.0	–	4.5
ð-X	1720, 1700	3420	3000	1260	1.12–1.98 m (1H)	7.18–8.23 m (5H, Ph)	1.70 m (2H)	3.70 s (3H)	1.82 s (3H)	7.18 s (1H)	7.0	–	4.3
***Z*-XI**	1725, 1720, 1690	3420, 3400–3200	3040	1270, 1225, 1180	3.40 s (3H, CO_2Me)	1.23 d.d (1H)	1.87 d.d (2H)	3.40 s (3H)	1.68 s (3H)	7.36 s (1H)	9.0	8.0	2.5
***E*-XII**	1720, 1710, 1690	3420, 3410–3220	3030	1280, 1210 1180	3.65 s (3H, CO_2Me)	1.78 d.d (1H)	1.64 d.d (2H)	3.67 s (3H)	1.91 s (3H)	6.62 s (1H)	7.5	9.5	4.5
***Z*-XIII**	1720, 1715, 1690		3445, 3440–3200	1265, 1230, 1190	1.20 t (3H), 4.11 q (2H) (CO_2Et)	1.74 m (1H)	1.63 d.d (2H)	3.70 s (3H)	1.93 s (3H)	6.38 s (1H)	8.5	7.5	5.0
***E*-XIV**	1730, 1720, 1695		3443, 3400–3200	1270, 1240, 1170	1.16 t (3H), 4.09 q (2H) (CO_2Et)	1.46 m (1H)	1.98 d.d (2H)	3.62 s (3H)	1.90 s (3H)	7.33 s (1H)	7.5	9.0	4.5
***Z*-XV**	1720, 1700, 1680		3420	1150, 1210, 1230	3.70 s (3H, CO_2Me)	7.20–7.37 m (5H, Ph)	2.06 m (2H)	3.69 s (3H)	1.76 s (3H)	6.97 s (1H)	9.5	–	–
***Z*-XVI**	1730, 1710, 1690		3420	1155, 1200, 1230	1.16 t (3H), 4.15 q (2H) (CO_2Et)	7.17–7.31 m (5H, Ph)	1.89 m (2H)	3.70 s (3H)	1.76 s (3H)	6.94 s (1H)	7.5	–	–

isomers are downfield from those of *E* isomers. This fact can be explained by the through-space electron-acceptor effect of the CO_2R group which in the former isomers is on the same side with NHAc with respect to the ring plane. The IR spectra display absorption bands of the cyclopropane system at 1290–1160 (deformation vibrations) and 3040–2980 cm^{-1} (stretching vibrations) [16].

EXPERIMENTAL

The IR spectra were obtained on a UR-20 spectrometer in $CHCl_3$. The ^{1}H NMR spectra were measured on a Tesla BS-487C spectrometer at 80 MHz in $CDCl_3$. Column chromatography was performed on Silica gel L 100/250 (Chemapol). The separation of *Z* and *E* isomers was controlled by GLC. Thin-layer chromatography was performed on Silufol-254 plates in a 3:2 hexane–acetone mixture.

Pyrazolines **I**–**VI** were prepared by cycloaddition of aliphatic diazo compounds to corresponding dehydrogenated amino acids by the procedure [7, 8]. Cyclopropanes **VII**, **IX**, and **X** were obtained by modified procedures [1, 2].

Methyl 1-(acetylamino)cyclopropane-1-carboxylate (VII). A solution of 5 g of pyrazoline **III** in 50 ml of DMF was refluxed for 20 min. The solvent was removed on a rotary evaporator, and the residue (tarry substance) was subjected to chromatography (eluent chloroform). Yield 4 g (95%).

Methyl 1-(acetylamino)-2-phenylcyclopropane-1-carboxylates (*Z*-IX) and (*E*-X) were prepared by the above procedure from 5 g of compound **II**. Column chromatography gave 2.77 g (62%) of a 2:1 mixture of isomers *Z*-**IX** and *E*-**X** (eluent chloroform). Methyl 2-(acetylamino)-3-phenyl-2-butenoate (**VIII**): eluent benzene, yield 0.89 g (20%), mp 140°C (from $CHCl_3$) {physicochemical characteristics of compound **VIII** coincide with those reported in [2]}.

Dimethyl 1-(acetylamino)cyclopropane-1,2-dicarboxylates (*Z*-XI) and (*E*-XII) and 1-(acetyl-

amino)-2-(ethoxycarbonyl)-1-(methoxycarbonyl)-cyclopropanes (*Z*-XIII) and (*E*-XIV) were synthesized by refluxing 5 g of pyrazolines **III** and **IV** in DMF for 40 min and isolated like compounds **IX** and **X**. Yield 2.21 g (50%) (esters **XI** and **XII**) and 2.23 g (50%) (esters **XIII** and **XIV**). The products all are colorless crystals.

Dimethyl 1-(acetylamino)-3-phenyl-2-cyclopropane-1,2-dicarboxylate (XV) and 1-(acetylamino)-2-(ethoxycarbonyl)-1-(methoxycarbonyl)-3-phenylcyclopropane (XVI) were obtained by refluxing pyrazolines **V** and **VI** for 60 min and isolated by chromatography (eluent toluene). Compound **XV**: yield 1.83 g, colorless oil, R_f 0.65. Compound **XVI**: 1.84 g, R_f 0.69.

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