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Catalytic Cyclopropanation of Alkyl 2-Allyl-2-acetylaminomalonate and Methyl *N*-(Acetyl)(phenyl)dehydroalanine with Alkyl Diazoacetates

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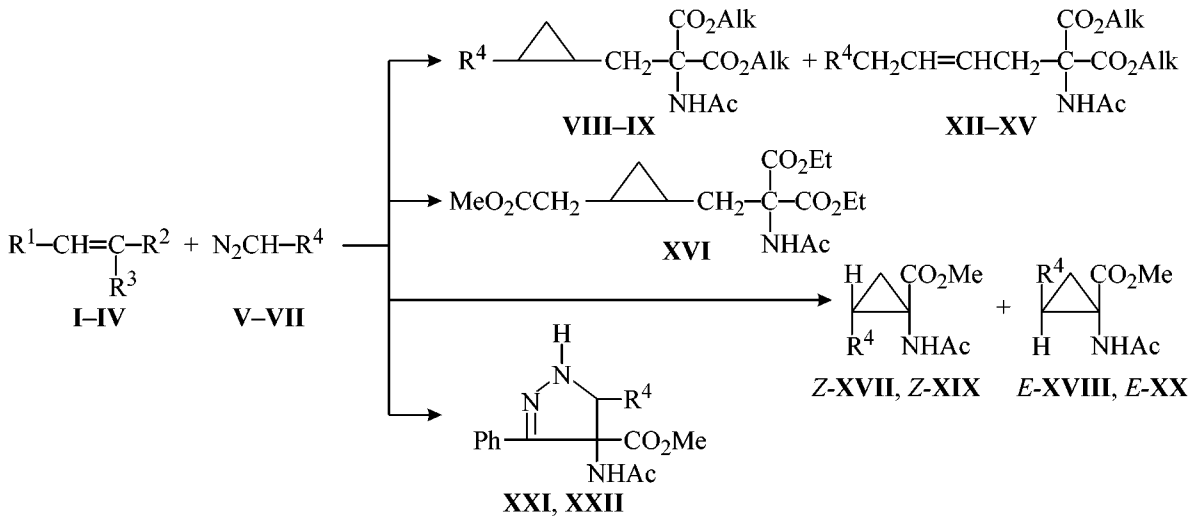
Abstract—Cyclopropane analogs of aspartic and adipic acids were prepared by catalytic cyclopropanation of dehydro amino acid derivatives with alkyl diazoacetates in the presence of catalyst (dirhodium tetraacetate).

Amino acids of the cyclopropane series widely occur in the nature; they exhibit diverse physiological activity and accomplish important functions in plants and animals [1, 2]. Therefore, studies in the field of synthesis of cyclopropanes with the aim of searching for practically useful compounds, primarily drugs, show much promise.

At present, cyclopropanation of unsaturated amino acids with aliphatic diazo compounds in the presence of catalysts is an efficient synthetic route to amino acids of the cyclopropane series and their synthetic analogs [3, 4]. There are virtually no data in the literature on catalytic cyclopropanation of dehydro amino acids of various structures with alkyl diazoacetates.

With the aim of searching for new amino dicarboxylic acids of the cyclopropane series, we have performed for the first time cyclopropanation of dehydro amino acids **I**–**IV** containing isolated (**I, II**), activated (**III**), and conjugated (**IV**) C=C bonds with diazo compounds **V**–**VII**.



R^1 = H (**I**–**III**), Ph (**IV**); R^2 = $CH_2C(NHAc)(CO_2Me)CO_2Me$ (**I**), $CH_2C(NHAc)(CO_2Et)CO_2Et$ (**II**), CO_2Me (**III, IV**); Alk = Me (**VIII, IX, XII, XIII**), Et (**X, XI, XIV, XV**); R^3 = H (**I, II**), NHAc (**III, IV**); R^4 = CO_2Me (**V, VIII, XI, XII, XV, XVII, XVIII, XXI**), CO_2Et (**VI, IX, X, XIII, XIV, XIX, XX, XXII**), H (**VII**).

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^{1}H NMR and analytical data for cyclopropane derivatives **VIII**–**XI** and **XVI**[a]

Comp. no.	^{1}H NMR spectrum ($CDCl_3$), δ, ppm						
	NHAc	CO_2Me	CO_2Et	CH_2	CH_2 ring	CH–CH	NH
VIII	1.99 s (3H)	3.71 s (3H), 3.67 s (3H)		2.47 m (2H)	1.14 m (2H)	1.60 m, 2.29 m (2H)	7.19 s (1H)
IX	1.98 s (3H)	3.62 s (6H)	1.13 t (3H), 4.20 q (2H)	2.41 m (2H)	1.21 m (2H)	1.60 m, 2.63 m (2H)	6.70 s (1H)
X	2.00 s (3H)		1.18 t (9H), 4.20 q (6H)	2.30 m (2H)	1.18 m (2H)	1.58 m, 2.53 m (2H)	6.89 s (1H)
XI	1.98 s (3H)	3.73 s (3H)	1.18 t (6H), 4.20 q (4H)	2.31 m (2H)	1.18 m (2H)	1.58 m, 2.73 m (2H)	6.47 s (1H)
XVI	2.01 s (3H)	3.72 s (6H),	1.19 t (6H), 4.09 q (4H)	2.29 m (2H, CH_2) 2.54 m (2H, CH_2)	1.30 m (2H, CH_2)	1.30 m, 2.01 m (2H)	6.89 s (1H)

Comp. no.	Found, %			Formula	Calculated, %		
	C	H	N		C	H	N
VIII	51.80, 51.85	6.30, 6.33	4.68, 4.70	$C_{13}H_{19}NO_7$	51.83	6.31	4.65
IX	53.32, 53.36	6.68, 6.70	4.45, 4.50	$C_{14}H_{21}NO_7$	53.33	6.67	4.44
X	55.95, 55.98	7.26, 7.30	4.08, 4.10	$C_{16}H_{25}NO_7$	55.98	7.29	4.08
XI	54.70, 54.74	6.97, 7.00	4.25, 4.30	$C_{15}H_{23}NO_7$	54.71	6.99	4.26
XVI	55.97, 55.99	7.28, 7.31	4.07, 4.10	$C_{16}H_{25}NO_7$	55.98	7.29	4.08

[a] The coupling constants were not determined, because the multiplets overlapped.

Esters **I** and **II** reacted with alkyl diazoacetates **V** and **VI** (CH_2Cl_2, 0°C, palladium acetate) by two pathways: formation of new cyclopropane derivatives of adipic acid **VIII**–**XI** in 7% yield and of unsaturated compounds **XII**–**XV** in 10% yield. By varying the reaction conditions, we were able to increase the yield of one of the products. For example, replacement of palladium(II) acetate by dirhodium tetraacetate, other conditions being similar, increased the yield of cyclopropanes **VIII**–**XI** to 40%, and at the reaction temperature increased to 22°C unsaturated compounds **XII**–**XV** were obtained in a quantitative yield.

Insertion product **XV** does not react with alkyl diazoacetate **V**, whereas with diazomethane **VII** it reacts even in the absence of catalyst to give the previously unknown cyclopropane derivative of pimelic acid **XVI** in 90% yield. Different reactivity of **V** and **VII** toward **XV** may be due to the smaller volume and stronger nucleophilicity of diazomethane as compared to alkyl diazoacetate, which is consistent with published data [5].

Methyl *N*-(acetyl)dehydroalaninate **III** reacts with alkyl diazoacetates **V** and **VI** to give cyclopropane derivatives *Z*-**VII**, *Z*-**XIX**, *E*-**XVIII**, and *E*-**XX** of aspartic acid in a low yield (10%). The reaction is accompanied by formation of a polymer. The low yield of cyclopropane derivatives is due to weak nucleophilicity of the double bond in **III** and to the fact that the electron-withdrawing substituent in this case prevents addition of carbene [5]. Compounds **XVII** and **XIX** were prepared previously by other procedures [6, 7].

Introduction of the phenyl substituents into the β-position of the double bond in dehydroalanine, as expected, deactivates the double bond. Attempts to perform cyclopropanation of methyl *N*-acetyldehydrophenylalaninate **IV** with diazo compounds **V** and **VI** under similar and more rigorous conditions (CH_2Cl_2, refluxing, 20 h) failed. This result is consistent with the published data that trisubstituted olefins [5], in particular, dehydrophenylalanine [8], do not react with diazoacetates even in the presence of a catalyst. However, replacement of the solvent CH_2Cl_2 by more polar $CHCl_3$ and refluxing of the reaction mixture for 6 h in the presence of the catalyst allowed us to perform for the first time cycloaddition of alkyl diazoacetates **V** and **VI** to alkene **IV**. In contrast to the initial dehydro amino acids containing isolated (**I, II**) or activated (**III**) double bonds, reaction of diazo com-

pounds with **IV** in the presence of a catalyst yields 1,3-dipolar cycloaddition products, Δ^2-pyrazolines **XXI** and **XXII**. Despite the rigorous reaction conditions and the use of the catalyst, no cyclopropane products were detected in the reaction mixture. The structure of Δ^2-pyrazolines **XXI** and **XXII** shows that the cycloaddition occurs against the Auwers rule [8].

Formation of pyrazolines in this reaction can be due to the fact that incorporation of alkene **IV** into the coordination sphere of rhodium is hindered sterically and electronically; competing incorporation into the rhodium coordination sphere of smaller alkyl diazoacetate molecules seems more probable. The resulting diazo compound–catalyst complex attacks the C=C bond to give Δ^2-pyrazolines. The capability of rhodium to form stable complexes with diazo compounds was proved in [5].

The structure of new cyclopropanes **VIII**–**XI** and **XVI** was proved by ^{1}H NMR and IR spectroscopy (see table).

Compounds **VIII**–**XI** and **XVI** contain two geminal and two vicinal protons giving a characteristic upfield multiplet in the ^{1}H NMR spectra. The geminal protons give signals at δ 1.14–1.30 ppm, and the vicinal protons, which are in the geminal position in the ring relative to the acetamidomalonate moiety, give a multiplet (δ 1.30–1.60 ppm). The signal of the H^X proton at the C^3 atom of the cyclopropane ring is shifted downfield (a multiplet at δ 2.01–2.73 ppm). In the IR spectra, the geminal protons give a strong bending vibration band at 1310–1180 cm^{-1}, and the vicinal protons give a strong band at 3030–2960 cm^{-1}. Such a pattern is probably due to the high degree of polarization of the CH bond in the strained ring.

The ester groups in these compounds give the expected signals in the ^{1}H NMR spectra. The ethoxycarbonyl group gives a triplet (δ 1.13–1.19 ppm) and a quartet (δ 4.09–4.21 ppm) with the coupling constant *J* 7.0 Hz. The methoxycarbonyl group protons give a singlet at δ 3.62–3.73 ppm. In the IR spectra of **VIII**–**XI** and **XVI** the high-frequency carbonyl band is split; graphical resolution reveals the presence of three ester groups (ν, cm^{-1}: 1750, 1745–1725, 1725–1720). The low-frequency band (1725–1720 cm^{-1}) should be assigned to vibrations of the carbonyl group at the ring, and the band at 1750 cm^{-1}, to vibrations of the ester group that is most hindered sterically.

The acetamide protons in the ^{1}H NMR spectra give a characteristic singlet in the range δ 1.98–2.01 ppm. In the IR spectra, this group gives a carbonyl band at 1690–1670 cm^{-1}.

The amino group in the ^{1}H NMR spectra gives a singlet at δ 6.47–6.89 ppm. In the IR spectra, this group is manifested as a narrow band in the range 3420–3410 cm^{-1}, and only the vibrations of the free amino group are observed. Thus, no absorption related to the presence of hydrogen bonds is observed; this is due to the presence of the methylene group between the ring and acetamidomalonate fragment, which makes formation of intramolecular hydrogen bonds less probable.

In cyclopropane derivatives of adipic acid **VIII**–**XI**, the substituents presumably have the *E* arrangement relative to the ring.

Our study showed that preparation of aminodicarboxylic acids of the cyclopropane series by catalytic cyclopropanation is feasible only if the initial substituted dehydro amino acids contain the isolated double bond. Unsaturated amino acid derivatives with the activated C=C bond polymerize under conditions of this reaction, and the yield of the corresponding cyclopropanes is low; dehydro amino acids with the conjugated C=C bond yield 1,3-dipolar cycloaddition products, pyrazolines.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer (solutions in $CHCl_3$), and the ^{1}H NMR spectra, on a Tesla BS-487C spectrometer (80 MHz, $CDCl_3$, internal reference HMDS).

The compounds were isolated and purified by column chromatography on Chemapol L 100/250 silica gel using the Trappe solvent series; separation of the *Z* and *E* isomers was monitored by GLC. The retention factors R_f were determined on Silufol-254 plates in a 3 : 2 hexane–acetone mixture.

Cyclopropanes VIII–XI and heptenedioate derivatives XII–XV. To a solution of 2 g of alkene **I** or **II** in 10 ml of CH_2Cl_2 was added 0.2 g of dirhodium tetraacetate. The mixture was cooled to 0°C, and a twofold excess of diazo compounds **V** and **VI** was added dropwise with stirring. The mixture was stirred at 0°C for an additional 5 h and then allowed to stand at 0°C for 12 h. The catalyst was filtered off, the solvent was evaporated, and the oily residue was chromatographed. From the fraction eluted with chloroform, yellow oily cyclopropane derivatives **VIII**–**XI** were isolated in 38–40% yield. Methyl 2-acetylamino-2-methoxycarbonyl-3-(2-methoxycarbonylcyclopropyl)propanoate **VIII**: yield 1.4 g (40%); methyl 2-acetylamino-2-methoxycarbonyl-3-(2-ethoxycarbonylcyclopropyl)propanoate **IX**: yield 1.3 g (39%);

ethyl 2-acetylamino-2-ethoxycarbonyl-3-(2-ethoxycarbonylcyclopropyl)propanoate **X**: yield 1.37 g (38%); ethyl 2-acetylamino-2-ethoxycarbonyl-3-(2-methoxycarbonylcyclopropyl)propanoate **XI**: yield 1.38 g (38%).

From the fraction eluted with benzene, yellow oily insertion products **XII**–**XV** were isolated in 22–24% yield. Dimethyl 2-acetylamino-2-methoxycarbonyl-4-heptenedioate **XII**: yield 0.66 g (22%); ^{1}H NMR spectrum, δ, ppm: 1.97 s (3H, NHAc), 3.70 s (3H, CO_2Me), 3.72 s (3H, NHAc), 2.69 m (2H, CH_2), 3.0 m (2H, CH_2), 5.19 d (1H, =CH), 5.50 m (1H, =CH), 7.02 s (1H, NH)]. 1-*O*-Methyl 7-*O*-ethyl 2-acetylamino-2-methoxycarbonyl-4-heptenedioate **XIII**: yield 0.73 g (24%); ^{1}H NMR spectrum, δ, ppm: 1.98 s (3H, NHAc), 3.73 s (3H, CO_2Me), 1.22 t (3H) and 4.20 q (2H, CO_2Et), 2.67 m (2H, CH_2), 3.02 m (2H, CH_2), 5.17 d (1H, =CH), 5.51 m (1H, =CH), 6.97 s (1H, NH)]. Diethyl 2-acetylamino-2-ethoxycarbonyl-4-heptenedioate **XIV**: yield 0.90 g (24%); ^{1}H NMR spectrum, δ, ppm: 1.97 s (3H, NHAc), 1.18 t (2H) and 4.20 m (3H, CO_2Et), 2.70 m (2H, CH_2), 3.02 m (2H, CH_2); 5.20 d (1H, =CH), 5.52 m (1H, =CH), 6.95 s (1H, NH)]. 1-*O*-Ethyl 7-*O*-methyl 2-acetylamino-2-ethoxycarbonyl-4-heptenedioate **XV**: yield 0.76 g (22%). The physicochemical parameters of **XV** are given in [9].

The reaction of **I** with **V** with palladium acetate as catalyst was performed similarly. Compounds **VIII** (yield 7%) and **XII** (yield 10%) were isolated.

Ethyl 1-(acetylamino)-2-ethoxycarbonyl-3-(2-methoxycarbonylmethylcyclopropyl)propanoate XVI was prepared as described above by reaction of insertion product **XV** with diazomethane **VII** in the absence of catalyst (0°C) and isolated by column chromatography (elution with chloroform). Yellow oily substance; yield 1.87 g (90%), R_f 0.69.

Dimethyl 1-(acetylamino)-1,2-cyclopropanedicarboxylate *Z*-XVII, *E*-XVIII and 1-*O*-methyl 2-*O*-ethyl 1-acetylamino-1,2-cyclopropanedicarboxylate *Z*-XIX, *E*-XX were prepared as described above by reactions of **III** with **V** and **VI**. Isomers *Z*-**XVII**, *Z*-**XIX** and *E*-**XVIII**, *E*-**XX** were isolated by column chromatography (eluent chloroform) in a 2 : 1 ratio; yield 10%. The physicochemical characteristics of **XVII**–**XX** coincide with those given in [6, 7]. Increase of the reaction temperature to 22°C results in complete polymerization of the reaction mixture.

4-Acetylamino-4,5-dimethoxycarbonyl-3-phenyl-Δ^2-pyrazoline XXI and 4-acetylamino-5-ethoxycarbonyl-4-methoxycarbonyl-3-phenyl-Δ^2-pyrazoline XXII. The preparation procedures and physicochemical parameters of **XXI** and **XXII** are given in [10, 11].

REFERENCES

1. Wagner, J. and Musso, H., *Angew. Chem.*, 1983, vol. 95, no. 11, p. 827.
2. Stammer, C., *Tetrahedron*, 1990, vol. 46, no. 7, p. 2231.
3. Shimamoto, K. and Ohfune, Y., *Tetrahedron Lett.*, 1989, vol. 30, no. 29, p. 3803.
4. Yamanoi, K. and Ohfune, Y., *Tetrahedron Lett.*, 1988, vol. 29, no. 10, p. 1181.
5. Dzhemilev, U.M., Dokichev, V.A., Sultanov, S.Z., Khusnutdiev, R.I., Tomilov, Yu.V., Nefedov, O.M., and Tolstikov, V.A., *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, no. 8, p. 1861.
6. Anisimova, N.A., Berkova, G.A., and Deiko, L.I., *Zh. Org. Khim.*, 1992, vol. 28, no. 1, p. 205.
7. Anisimova, N.A., Berkova, G.A., and Deiko, L.I., *Zh. Obshch. Khim.*, 1998, vol. 68, no. 7, p. 1165.
8. D'yakonov, I.A., *Alifaticheskie diazosoedineniya* (Aliphatic Diazo Compounds), Leningrad: Leningr. Gos. Univ., 1958.
9. Anisimova, N.A., Berkova, G.A., and Deiko, L.I., *Zh. Org. Khim.*, 1999, vol. 35, no. 4, p. 544.
10. Anisimova, N.A., Berkova, G.A., and Deiko, L.I., *Zh. Obshch. Khim.*, 1999, vol. 69, no. 9, p. 1529.
11. Anisimova, N.A., Berkova, G.A., and Deiko, L.I., *Zh. Org. Khim.*, 1998, vol. 34, no. 8, p. 1263.