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DERIVATIVES OF HETEROCYCLIC α-IMINOCARBOXYLIC ACIDS.

3.* SYNTHESIS OF N-ALKOXYCARBONYL AND N-ALKOXYCARBONYLALKENYL DERIVATIVES OF α-IMINOCARBOXYLIC ACIDS

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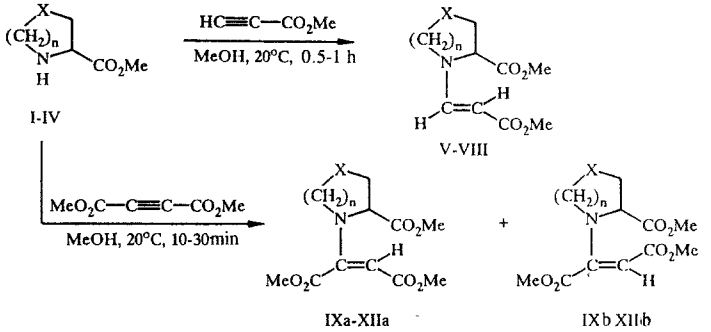
By the interaction of L-proline, L-thioproline, pipecolic acid, tetrahydro-1,4-thiazine-3-carboxylic acid, and diastereomeric esters of tetrahydro-1,4-thiazine-3,5-dicarboxylic acid with methyl chloroformate, methyl propiolate, and acetylenecarboxylic acid, we have obtained N-alkoxycarbonyl and N-alkoxycarbonylalkenyl derivatives of α-iminocarboxylic acids. By the reaction of N-methoxycarbonyltetrahydro-1,4-thiazine-3-carboxylic acid with hydrazine hydrate, we have obtained 8-amino-7,9-dioxo-4-thia-1,8-diazabicyclo[4.3.0]nonane.

The synthesis of dicarbonyl and tricarbonyl derivatives in the heterocyclic iminocarboxylic acid series is of definite interest in connection with the possible use of such compounds in constructing new polycyclic heterosystems. It is known that N-alkoxy derivatives of aziridine-2-carboxylic acid can be obtained readily by the interaction of such compounds with chloroformic esters [2]. N-Alkoxycarbonylalkenyl derivatives of this series are formed in the reaction of aziridine-2-carboxylic acids with acetylenecarboxylic acids [3]. Here we are reporting on a study of the feasibility of functionalizing esters of L-proline (I), L-thioproline (II), pipecolic acid (IV), and tetrahydro-1,4-thiazine-3-carboxylic acid (V), and also diastereomers of esters of tetrahydro-1,4-thiazine-3,5-dicarboxylic acid (XIIIa,b), by their interaction with esters of chloroformic and acetylenecarboxylic acids.



In all cases, the reactions of the acetylenecarboxylic acids with the α-iminocarboxylic acids proceeded smoothly; high yields of the desired products were obtained within 0.5-1.0 h at room temperature. Only in the reaction of the ester II with methyl propiolate was it necessary to reflux the reaction mixture for 6 h. As a result of these reactions, we obtained the N-substituted acrylic V-VIII, maleic IXa-XIIa, and fumaric IXb-XIIb derivatives of the esters of cyclic α-iminocarboxylic acids.

*For Communication 2, see [1].

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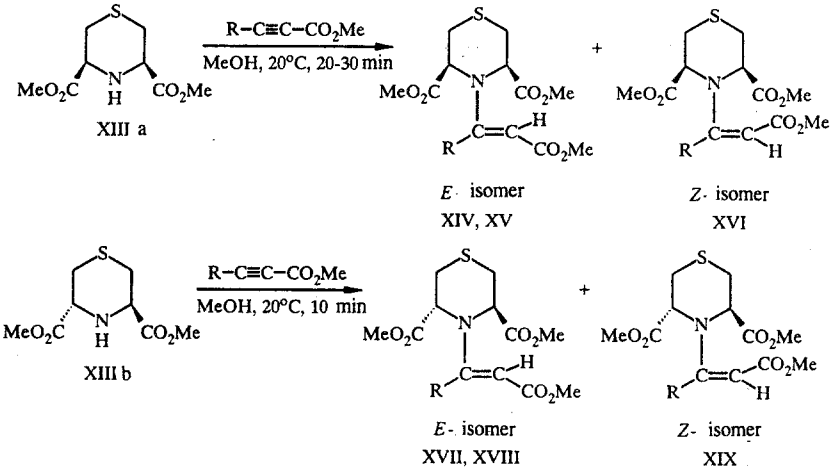
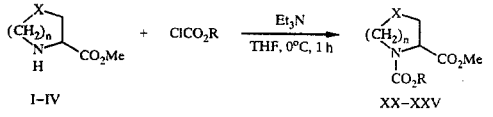
The cis and trans diesters of tetrahydro-1,4-thiazinedicarboxylic acid XIIIa,b exhibit substantial differences in their reactivities with esters of acetylenecarboxylic acids. For the trans isomer of the diester XIIIb, the addition products XVII-XIX are formed within 10 min at room temperature; for the cis isomer of the diester XIIIa, probably as a consequence of steric hindrance, the adducts XIV-XVIII are formed only after the reaction is continued for 20-30 h.



In contrast to unsubstituted aziridine, derivatives of aziridine-2-carboxylic acid react stereospecifically with esters of acetylenecarboxylic acid, forming trans-aminoacrylates [3]. The interaction of methyl propiolate with secondary amines gives trans-aminoacrylates exclusively [6]. The geometry of such adducts can be determined easily on the basis that the SSCC of the trans-vinyl protons is substantially greater than that of the cis-vinyl protons, amounting to at least 13.0 Hz. The chemical shift of the 3-H proton of the acrylic fragment for the trans isomers is also greater than for the corresponding cis isomers. From these data we have established that when the heterocyclic α-iminocarboxylic acids I-IV interact with esters of propiolic acid, the trans isomers are formed exclusively, whereas addition of acetylenedicarboxylic acids gives a mixture of Z and E isomers, with the latter predominating. In this case it is rather difficult to arrive at a correct assignment of the products to the maleic or fumaric series, since the chemical shift of the vinyl proton in the PMR spectra will depend on the solvent and also on the nature of the amine substituent [7]. Therefore, we have chosen as a model for a more detailed structural study the products obtained by addition of the ester IV to the dimethyl ester of acetylenecarboxylic acid, with the initial premise that the N-substituted aminofumarates are the more thermodynamically stable compounds [6, 8-10]. Upon heating the original mixture of adducts (90:10) in a mixture of methanol with tert-butanol, it was established that the ratio of isomers changed to 60:40 over the course of 3 h.

Thus, we can conclude tentatively that the isomer making up 90% of the original mixture should be classed among the derivatives of aminomaleic acids (Table 1).

The acylation of the esters I-IV with chloroformic ester also proceeds readily, giving nearly quantitative yields of the dicarboxylic acid esters XX-XXV:



The structure of the diesters XX-XXV was confirmed by spectrometric methods and elemental analysis, and also by subsequent conversions; the results of these studies will be published later. It was established that among the compounds XX-XXV, only the diester XXV reacts with hydrazine hydrate in methanol. The product from this interaction is 8-amino-7,9-dioxo-4-thia-1,8-diazabicyclo[4.3.0]nonane (XXVI). In order to confirm the formation of the N-aminoimidazolidine fragment, the bicyclic compound XXVI was converted to the corresponding azomethine derivative XXVII:

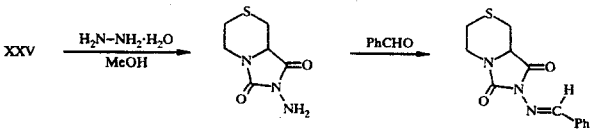


TABLE 1. PMR Spectra of Compounds V-XIX in $CDCl_3$

Compound	Isomer	Chemical shift δ, ppm				Isomer, %
		H	CO_2Me	H_R	ring protons	
V*	*E*	4,53	3,62 3,71	7,56	2,0...2,2 (4H, m, $C_{(3)}H_2$, $C_{(4)}H_2$), 3,3...3,5 (2H, m, $C_{(5)}H$), 4,00 (1H,q, $C_{(2)}H$)	100
VI*	*E*	4,68	3,67 3,78	7,56	3,27(2H, dd , S-CH_2), 4,33 (2H, d S-CH_2-N), 4,49 (1H, t $C_{(2)}H$)	100
VII*	*E*	4,61	3,62 3,80	7,30	2,0...4,3 (9H, m, protons of piperidine ring)	100
VIII*[2]	*E*	4,70	3,71 3,81	7,30	2,6...4,4 (7H, m, protons of tetrahydrothiazine ring)	100
IX	*E*	4,57	3,62 3,70	3,80	1,8...2,3 (4H, m, $C_{(3)}H_2$, $C_{(4)}H_2$), 3,5 (2H, m, $C_{(5)}H_2$), 4,15 (1H, t, $C_{(2)}H_2$)	96
	Z	5,20				4
X	*E*	4,78	3,64	3,91	3,2...3,4 (2H, dd S—CH_2), 3,78 (3H, s., OCH_3), 4,38 (2H, dd S—CH_2—N), 4,56 (1H,t, $C_{(4)}H$)	97
	Z	5,20				3
XI	*E*	4,67	3,64	3,71	2,2...4,45 (9H, m, protons of piperidine ring) , 3,80 (3H, s, CO_2CH_3)	96
	Z	5,40				4
XII	*E*	5,10	3,60	3,90	2,9...4,4 (7H, m, protons of tetrahydrothiazine ring)	90
	Z	5,40				10
XIV*[3]	*E*	5,06	3,67	3,91	2,8...3,0 (4H, m, S-CH_2), 3,79 (6H, s., CO_2Me), 4,26 (2H, t, $C_{(3)}H$)	100
XV	*E*	5,06	3,67	3,91	2,9...3,1 (4H, m, S-CH_2), 3,80 (6H, s , CO_2Me), 4,26 (2H, t , $C_{(3)}H$)	77
XVI	*Z*	5,77	3,69	3,85	3,0...3,7 (4H, m, S-CH_2), 3,79 (6H, s, CO_2Me), 4,30 (2H, t , $C_{(3)}H$)	23
XVII*[3]	*E*	4,73	3,67	7,67	3,10...3,49 (4H, m, S-CH_2), 3,82 (6H, s, CO_2Me), 4,50 (2H, t, $C_{(3)}H$)	100
XVIII	*E*	4,63	3,61	3,85	3,05...3,50 (4H, m, S-CH_2), 3,80 (6H, s , CO_2Me), 4,49 (2H, t, $C_{(3)}H$)	90
XIX	*Z*	4,83	3,70	3,86	3,21...3,37 (4H, m, S-CH_2), 3,80 (6H, s , CO_2Me), 5,73 (2H, t., C(3)H)	10

*^3JH—H_R = 12 Hz
*^2JH—H_R = 13,2 Hz
*^3JH—H_R = 12,6 Hz

EXPERIMENTAL

^1H and ^{13}C NMR spectra were obtained in Bruker WH-90/OS (90 MHz) and Bruker WH-360 (360 MHz) instruments; internal standards TMS and HMDS (PMR), cyclohexane and $CDCl_3$ (^{13}C NMR). The mass spectra were taken in an MS-50 AEI spectrometer (ionizing voltage 70 eV). The chromatogram/mass spectra were obtained in a Kratos MS-25 instrument (ionizing voltage 70 eV). The angles of optical rotation were measured in a Perkin—Elmer 141 polarimeter. IR spectra were taken in UR-20 and Perkin—Elmer 580-B spectrometers in white mineral oil, or on the pure substance. Analytical chromatography was performed in a Chrom 5 instrument, in columns with SE-30 stationary phase.

Analytical and preparative high-performance liquid chromatography was carried out in a Du Pont 830 Prep instrument, UV detector (λ = 229, 254, and 334 nm), analytical column with Zorbax-Sil (250 × 4.6 mm), preparative column with Zorbax-Sil (250 × 22.4 mm). The course of the reaction and the product purities were monitored by means of TLC on Silufol UV-254 plates with detection in UV light at 254 nm), and also with development of the spots in iodine vapor.

General Procedure for Synthesis of Products from Addition of Esters of Acetylenecarboxylic Acids to Esters of Cyclic α-Iminocarboxylic Acids (V-XII, XIV-XXIX). To a solution of 0.1 mole of an ester of a cyclic α-iminocarboxylic acid I-IV or XIIIa,b in 50 ml of methanol, at 20°C, 0.1 mole of an ester of acetylenecarboxylic acid was added slowly, dropwise with stirring. After completion of the reaction, the solvent was driven off, and the residue was distilled under a vacuum of 1×10^{-3} mm Hg/120-150°C (see Table 1 for PMR spectra).

3-(2-Methoxycarbonylvinyl)-4-methoxycarbonyl-1,3-thiazolidine (VI). To a solution of 14.7 g (0.1 mole) of the ester II in 50 ml of methanol, 7.4 g (0.1 mole) of the methyl ester of acetylenecarboxylic acid was added. The mixture was held for 6 h at 65°C. After driving off the solvent, the residue was distilled at 150°C/1×10^{-2} mm Hg. Obtained 2.1 g (95%) of the product VI (viscous oil); see Table 1 for PMR spectrum.

General Procedure for Obtaining 4-(Alkoxycarbonyl)-3,5-dimethoxycarbonyltetrahydro-1,4-thiazines (XIV-XIX). A mixture of 0.01 mole of the cis isomer of the diester XIIIa with an equimolar quantity of an acetylenecarboxylic ester in 10 ml of methanol was held at 20°C until the original ...* had disappeared (20-30 h). The solvent was removed, obtaining the addition products XIV-XVI in the form of viscous oils.

The reactions of the trans isomer of the diester XIIb were completed in 10 min at 20°C, forming the compounds XVII-XIX with quantitative yields; see Table 1 for PMR spectra.

3,4-Bis(methoxycarbonyl)tetrahydro-1,4-thiazine (XXV). A solution of 8.0 g (50 mmoles) of the ester IV and 8.4 ml (60 mmoles) of triethylamine in 50 ml of dry THF was chilled to 0°C and stirred while adding a solution of 5.7 g (60 mmoles) of methyl chloroformate in 10 ml of dry THF, after which the solution was warmed to room temperature and stirred for an additional 1 h. The precipitated triethylamine salt was filtered off. The filtrate was evaporated to dryness, and the oily residue was distilled at 140°C/0.02 mm Hg. Obtained 10.6 g (96%) of the product XXV in the form of a yellow oil. IR spectrum: 1733 cm^{-1} (CO). Mass spectrum: 219(11), 187(4), 162(6), 161(9), 160(100), 159(4), 146(4), 145(4), 144(25), 132(5), 129(35), 115(5), 114(14), 112(6), 104(4), 103(5), 102(40), 101(25), 100(20).

N-Alkoxycarbonyl Esters of Cyclic α-Iminocarboxylic Acids (XXII-XXIV). These were obtained in the same manner as the diester XXV, from esters of cyclic α-iminocarboxylic acids and chloroformic esters, with yields of 95-100%.

1,2-Bis(methoxycarbonyl)pyrrolidine (XX), bp 100-104°C/0.1 mm Hg. PMR spectrum ($CDCl_3$): 1.2-2.2 (4H, *m*, β-CH_2, γ-CH_2), 3.3-3.5 (2H, *m*, δ-CH_2), 3.71 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.0 ppm (1H, t, α-CH).

1-Benzoxycarbonyl-2-methoxycarbonylpyrrolidine (XXI), bp 178-183°C/0.1 mm Hg. PMR spectrum ($CDCl_3$): 1.08-2.23 (4H, m, α-CH_2, γ-CH_2), 3.28 (2H, d, NCH_2Ph), 3.34-3.55 (2H, m, δ-CH_2), 4.01 (1H, t, α-CH), 7.1-7.6 ppm (5H, m, C_6H_5).

3,4-Bis(methoxycarbonyl)-1,3-thiazolidine (XXII). Viscous oil, bp 110-112°C/0.1 mm Hg. PMR spectrum ($CDCl_3$): 3.21 (2H, dd, S-CH_2), 3.71 (3H, s, CO_2CH_3), 3.80 (3H, s, CO_2CH_3), 4.33 (2H, d, SCH_2N) 4.50 ppm (1H, t, α-CHCO).

1,2-Bis(methoxycarbonyl)piperidine (XXIII), bp 116-121°C/0.1 mm Hg. PMR spectrum ($CDCl_3$): 1.20-4.2 (9H, m, ring protons), 3.76 (3H, s, OCH_3), 3.81 ppm (3H, s, OCH_3).

1-Benzoxycarbonyl-2-methoxycarbonylpiperidine (XXIV). Viscous oil, distills with decomposition at 152-160°C/0.01 mm Hg. PMR spectrum ($CDCl_3$): 1.21-4.8 (9H, m, ring protons), 3.60 (2H, d, NCH_2Ph), 3.80 (3H, s, OCH_3), 7.1-7.5 ppm (5H, m, C_6H_5).

8-Amino-7,9-dioxo-4-thia-1,8-diazabicyclo[4.3.0]nonane (XXVI). A solution of 2.19 g (10 mmoles) of the thiazine XXV and 0.6 g (10 mmoles) of hydrazine hydrate in 15 ml of methanol was held for 3 days at 25°C. The precipitated colorless crystals were filtered off and washed with dry ether. Obtained 1.6 g of the product XXVI, mp 68-70°C (from methanol). IR spectrum: 1677 and 1670 (amide CO), 3320 cm^{-1} (NH_2). PMR spectrum ($CDCl_3$): 2.57 (1H, dd, 5-He, J_{5e5a} = 13.0, J_{5e6a} = 3.6), 2.62 (1H, dd, 5-H_a, J_{5a5e} = 13.0, J_{5a6a} = 10.8), 2.71 (1H, m, 3-H_a, J_{3a2a} = 10.6, J_{3a2e} = 2.8, J_{3a3e} = 13.2), 2.90 (1H, m, 3-H_e, J_{3e3a} = 13.2, J_{3e2a} = 3.2, J_{3e2e} = 2.4), 3.15 (1H, m, 2-H_a, J_{2a2e} = 13.0, J_{2a3e} = 10.6, J_{2a3e} = 3.2), 4.07 (1H, dd, 6-H_a, J_{6a5a} = 10.8, J_{6a5e} = 3.6), 4.01 (2H, br.s, NH_2), 4.45 ppm (1H, m, 2-H_e, J_{2e2a} = 13.0, J_{2e3a} = 2.8, J_{2e3e} = 2.4). Mass spectrum: 187(1000) $[M]^+$, 171(11) $[M-NH_2]^+$, 159(76), 149(10), 144(11), 128(9), 121(7), 104(14), 103(12), 102(86), 101(36), 100(14).

8-Benzylidenamino-7,9-dioxo-4-thia-1,8-diazabicyclo[4.3.0]nonane (XXVII). A solution of 0.2 g (1.07 mmoles) of the bicyclic compound XXVI and 0.2 g (1.88 mmoles) of benzaldehyde in 2 ml of methanol was heated for 30 min at 50°C, and the mixture was left overnight. The solvent was evaporated, and the residue was washed with ether. Obtained 0.26 g

*As in Russian original; a word has apparently been omitted — Translator.

(95%) of colorless crystals of the hydrazone XXVII, mp 158-160°C (from methanol). IR spectrum: 1638 (CN), 1662 and 1671 cm^{-1} (amide CO). PMR spectrum ($CDCl_3$): 2.69 (1H, dd, 5-H_a, J_{5a5e} = 13.2, J_{5a6a} = 11.2), 2.76 (1H, m, 3-H_a, J_{3a3e} = 13.4, J_{3a2a} = 11.9, J_{3a2e} = 3.4), 2.82 (1H, dd, 5-H_e, J_{5e5a} = 13.2, J_{5e6a} = 3.8), 2.94 (1H, m, 3-H_e, J_{3e3a} = 13.4, J_{3e2e} = 2.8, J_{3e2a} = 3.4), 3.13 (1H, m, 2-H_a, J_{2e2a} = 13.4, J_{2a3a} = 11.9, J_{2a3e} = 3.4), 4.12 (1H, dd, 6-H_a, J_{6a5a} = 11.2, J_{6a5e} = 3.8), 4.49 (1H, m, 2-He, J_{2e2a} = 13.4, J_{2e3e} = 3.4, J_{2e3e} = 2.8), 7.1-7.6 (5H, m, C_6H_5), 7.78 ppm (1H, s, NCH). Mass spectrum: 275(12), 174(6), 173(9), 172(100), 159(9), 158(9), 157(82), 149(12), 144(32), 126(13), 125(53), 116(24), 113(59), 112(21), 104(15), 103(21), 102(35), 101(24).

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