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DERIVATIVES OF 4-CARBOXY-3,5-DIPHENYL-2-PHENYLIMINO-THIAZOLINE. SYNTHESIS AND MASS SPECTRAL INVESTIGATION

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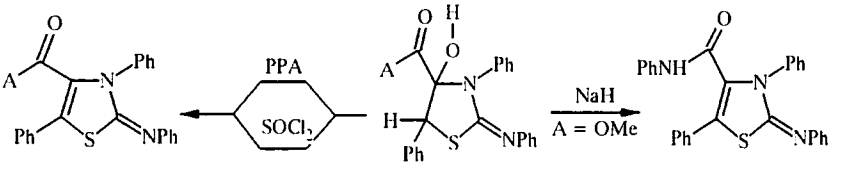
Methods have been developed for dehydrating the unusually stable intermediate products of the Hantzsch reaction of N,N'-diphenylthioureas with derivatives of phenylchloropyruvic acid, viz. 4-hydroxy-4-methoxy (diethylamino)carbonyl-3,5-diphenyl-2-phenyliminothiazolidines, into the corresponding 4-methoxy-(diethylamino)carbonyl-3,5-diphenyl-2-phenyliminothiazolines. Characteristic features of the dissociative ionization of the latter and their anilide analog under the action of electron impact have been clarified.

The intermediate products of the Hantzsch reaction, 4-hydroxy derivatives of thiazolines or thiazolidinimines, if successfully isolated are usually dehydrated to the final products of this reaction under mild conditions, most frequently under the action of acidic agents [1,2]. However in contrast to that the products of the reaction of the methyl ester and diethylamide of phenylchloropyruvic acid with N,N'-diphenylthiourea described by us in [3] were derivatives of 4-carboxy-4-hydroxy-3,5-diphenyl-2-phenyliminothiazolidine I and proved to be extremely stable. They were not converted into the final Hantzsch reaction products II even on boiling in acetic acid or in acetic anhydride and were recovered unchanged. In this respect they are comparable only to 4-hydroxy-3-phenyl-2-phenylimino-4-trifluoromethylthiazolidine, the condensation product of N,N'-diphenylthiourea with 3-bromo-1,1,1-trifluoroacetone [4]. The anomalously high stability of compound I, in the molecule of which there are several electronegative substituents, may be considered as confirmation of the fact that the limiting stage of the dehydration of 4-hydroxythiazolidines to the final Hantzsch reaction products is protonation at the hydroxyl oxygen [4,5].

The use of stronger dehydrating agents such as polyphosphoric acid (PPA) or thionyl chloride is required for the dehydration of 4-hydroxythiazolidines I. The use of a powerful alkaline dehydrating agent (sodium hydride) under mild conditions also offered the possibility of obtaining thiazolinimine system from 4-hydroxy-4-methoxycarbonylthiazolidine Ia but in this case the expected ester IIa was not isolated due to partial destruction of the heterocycle but the amidation product of its ester group, anilide IIc, was obtained.



IIa,b I IIc

a A = OMe, b A = NEt_2, c A = PhNH

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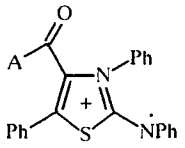
The characteristics of the compounds obtained are given in Table 1. The data of elemental analysis, ^{1}H NMR and IR spectra corresponded completely to structures IIa-c. In particular, characteristics for the 4-hydroxy and methine ($C_{(5)}H$) groups of the initial 4-hydroxythiazolidines I were absent from both types of spectra [3], which directly indicates on dehydration. The nonequivalence of the two ethyl groups observed in the ^{1}H NMR spectrum of diethylamide IIb, as in the spectrum of the initial 4-hydroxythiazolidine Ib [3] is probably explained by hindrance (in the ^{1}H NMR time scale) to rotation about the partially double amide C–N bond. Furthermore, in the spectrum of 4-hydroxythiazolidine Ib the methyl protons of the ethyl groups give two triplets and the methylene protons – a poorly resolved multiplet. In the spectrum of its dehydration product, thiazoline IIb, the methylene protons appear as two distinct $AA'X_3$ and $BB'X_3$ systems, i.e., nonequivalence is observed not only for the ethyl substituents at the amide nitrogen atom but also for the geminal protons in each of the methylene groups $CH^ACH^{A'}$ and $CH^BCH^{B'}$. This indicates the high inhibition of rotation about the amide C–N bond in thiazolinimine IIb in comparison with the initial 4-hydroxythiazolidine Ib. On increasing the temperature of solution of diethylamide Ib in DMSO-d_6 a gradual coalescence was observed for the peaks of the methylene protons and the spectrum in this region approached the shape of the spectrum of 4-hydroxythiazolidine Ib. However complete coalescence of the peaks was not observed since the relevant temperature lies above the boiling point of DMSO.

Continuing our investigations in the field of the mass spectrometry of 5-phenylthiazoles [6,7] obtained from esters and amides of phenylchloropyruvic acid, we extended them to esters and amides of 4-carboxy-3,5-diphenyl-2-phenyliminothiazolidine II. The results obtained are given in Table 2.

The molecular ion peaks were intense in the mass spectra of compounds II [for ester IIa and diethylamide IIb they were the most intense], as for the majority of types of thiazoles. This may indicate the aromatic stabilization of cation-radicals of 2-phenyliminothiazolines as a type of diarylaminyl where one of the aryls is a stable thiazolium residue.



An intense peak with m/z 121 $[C_7H_5S]^+$ was observed in the mass spectra of the derivatives of 4-carboxy-3,5-diphenyl-2-phenyliminothiazoline II, as for 4-substituted 5-phenylthiazoles [6,7]. This peak was practically absent from the spectra of 5-phenylthiazole itself and 5-phenyl-2-propylthiazole [8] and thiazoles with a substituent other than phenyl at position 5 [9]. Consequently it may be considered to be characteristic for 4-substituted derivatives of 5-phenylthiazole and 5-phenylthiazoline heterocyclic systems. A general feature of the mass spectra of compounds II is the presence of intense $[M-1]^+$ peaks the appearance of which is due to elimination of hydrogen atom from the molecular ion M^+. Finally compounds II, like derivatives of 4-substituted 5-phenylthiazoles [6,7], are characterized by a significantly high intensity for the dehydrotropylium cation $C_7H_5^+$ peak, compared with 5-phenylthiazoles containing no substituent at position 4 [8].

The main routes of fragmentation of the molecular ions and the origin of the more intense peaks in the mass spectra of 4-carboxy-3,5-diphenyl-2-phenyliminothiazoline derivatives IIa-c are represented as follows.

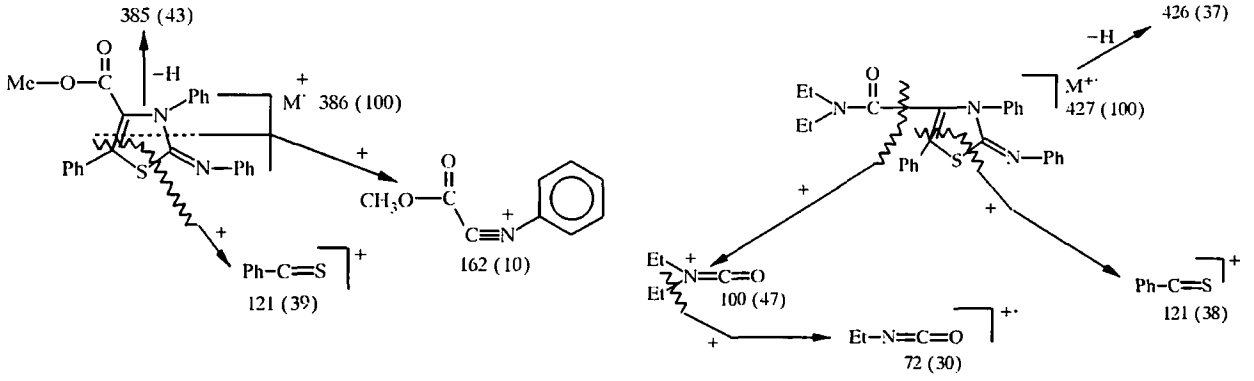


TABLE 1. Characteristics of the Synthesized Derivatives of 4-Carboxy-3,5-diphenyl-2-phenylaminothiazoline (II)

Compound	Empirical formula	Found, % / Calculated, %				mp, °C (solvent)	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm, J, Hz (solvent)	Yield, % (method)
		C	H	N	S				
IIa	$C_{23}H_{18}N_2O_2S$	71.45 / 71.50	4.53 / 4.64	7.21 / 7.25	8.65 / 8.30	138–140 (*i*-PrOH)	705, 775, 835, 1180, 1220, 1340, 1565, 1630, 1740, 3060	3.40 (3H, s, MeO); 6.70-7.22 (5H, m, Ph-N=); 7.26 and 7.33 (5H and 5H, 2s, Ph-C, Ph-N=) (CD_3CN)	86 (A) (77 (B)
IIb	$C_{26}H_{25}N_3OS$	72.98 / 73.07	5.83 / 3.83	9.80 / 9.84	7.76 / 7.50	213–214 (*i*-PrOH)	700, 775, 1080, 1150, 1220, 1360, 1485, 1585, 1630, 3060	0.59 and 0.76 (3H and 3H, 2t, 2Me, $^3J_{НАССН_3} = {}^3J_{НАССН_3} = J_{НИССН_3} = J_{НИССН_3} = 7.0$); 2.99; 3.14; 3.45; 3.50 (4 x 1H, 2 q all $^2J = 14.0$); 6.97–7.49 (15H, m, 3Ph) (DMSO-d_6)	69 (A) 68 (B)
IIc	$C_{28}H_{21}N_3OS$	75.02 / 75.17	4.66 / 4.70	9.38 / 9.40	7.21 / 7.16	180–181 (*i*-PrOH MeOH, 1:1)	705, 765, 1195, 1495, 1565, 1590, 1625, 1655, 1675, 3090, 3145, 3200, 3270	6.67–7.63 (20H, m, 4Ph) (DMSO-d_6)	62

TABLE 2. Mass Spectra of 4-Carboxy-3,5-diphenyl-2-phenyliminothiazoline (II) Derivatives

Compound	Elemental composition *2	Found / Calculated	m/z*	Intensity ($I : I_{max}$)·100, %
IIa		386.107	388	9
		386.1089	387	26
	$C_{23}H_{18}N_2O_2S$		386	100
	$C_{23}H_{17}N_2O_2S$		385	43
	$C_{15}H_9NOS$		251	5
	$C_{10}H_9OS$		177	11
	$C_9H_8NO_2$		162	10
	C_7H_5S		121	39
	$C_6H_{11}N$		118	9
	C_7H_5		89	12
	C_6H_5		77	32
			59	5
			51	5
IIb		427.171	429	9
		427.1718	428	30
	$C_{26}H_{25}N_3OS$		427	100
	$C_{26}H_{24}N_3OS$		426	37
	$C_{22}H_{15}N_2OS$		355	6
	$C_{13}H_{11}N_2$		195	4
	$C_{14}H_{11}N_2$		193	5
	$C_{10}H_9OS$		177	5
			122	5
	C_7H_5S		121	38
	$C_5H_{10}NO$		100	47
	C_7H_5		89	14
	C_6H_5		77	9
	$C_4H_{10}N$		72	4
	C_3H_6NO		72	30
			44	11
	C_2H_5		29	25
IIc		447.140	449	10
		447.1405	448	37
	$C_{28}H_{21}N_3OS$		447	97
	$C_{28}H_{20}N_3OS$		446	46
	$C_{22}H_{15}N_2OS$		356	4
	$C_{22}H_{15}N_2OS$		355	24
	$C_{21}H_{15}N_2S$		327	7
	$C_{14}H_{11}NS$		225	20
	$C_{13}H_{10}N$		192	4
	$C_{13}H_9$		165	4
	C_7H_6S		122	14
	C_7H_5S		121	100
	C_7H_6N		104	41
	C_7H_5N		103	5
	C_6H_5N		92	5
	C_7H_5		89	41
	C_6H_5		77	47
			68	8
			51	9

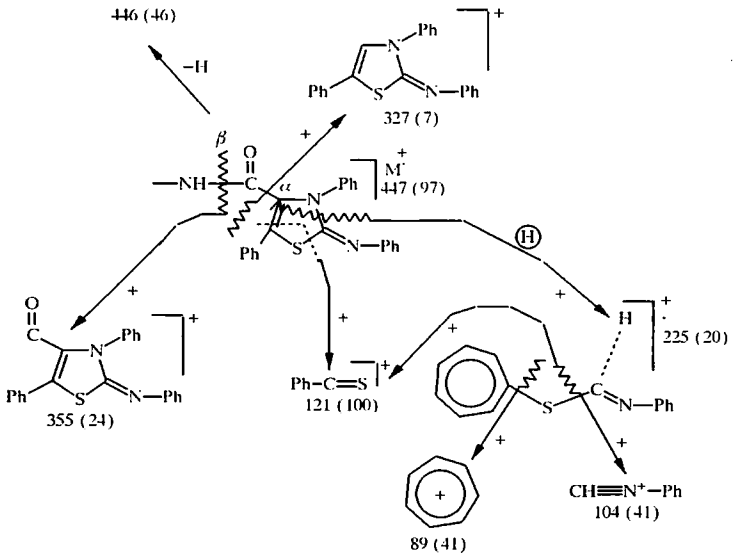
* Ion peaks of intensity less than 4% are not given.

*2 Elemental compositions of ions formed by ^{13}C are not given.

Their general features, as already stated, are elimination of hydrogen atom from M^+ leading to the $[M-1]^+$ ion, and fission of M^+ at the S–$C_{(2)}$ and $C_{(4)}$-$C_{(5)}$ bonds of the heterocycle leading to the $[PhC{=}S]^+$ ion. In all cases phenyl ions $C_6H_5^+$ (*m/z* 77) were formed, and were particularly intense for IIa and IIc and the dehydrotropylium ion (*m/z* 89) was most characteristic for anilide IIc. The presence of three to four phenyl groups at various positions in the structures being considered makes probable the generation of $C_6H_5^+$ ions by several channels. Two possible routes of forming dehydrotropylium from compound IIc are shown in its fragmentation scheme.

The mass spectrum of ester Ia is characterized by the small number of abundant (more than 10%) ions. In addition to the fragmentation routes described for this compound the appearance must be noted of an ion with *m/z* 162 formed from M^+ by cleavage of the N–$C_{(2)}$ and $C_{(4)}$–$C_{(5)}$ bonds of the thiazole ring. The formation of ions with *m/z* 177 and 118 may only be explained by profound rearrangement processes. In addition to those indicated in Table 2 and in the diagram, low intensity peaks were recorded in the heavy ion region formed by removal from M^+ of Me (*m/z* 371), MeO (*m/z* 355), MeOCO (*m/z* 327), and Ph (*m/z* 309).

The dissociative ionization of diethylamide Ib has a complex character. Here an intense peak is observed at *m/z* 100, belonging to the diethylaminocarbonyl ion formed as a result of localization of the charge on the diethylamide nitrogen atom with cleavage of the $C_{(0)}$–$C_{(4)}$ bond (β decomposition in relation to this atom). Probably the indicated ion is the mother ion of the intense *m/z* 72 ion. In the heavy ion region of the spectrum of diethylamide IIb low intensity (2-6%) peaks were recorded for ions formed by fission from M^+ of Et (*m/z* 398), Et_2N (*m/z* 355), and Et_2NCO (*m/z* 327).



The fragmentation of the most complex compound – of anilide IIc was characterized by high diversity. In addition to that already indicated, fission of the thiazoline ring at the N–$C_{(2)}$ and $C_{(4)}$–$C_{(5)}$ bonds with migration of hydrogen atom to the charged fragment must be mentioned. This gives rise to an ion of *m/z* 225 in the mass spectrum which in our opinion is subjected to further decomposition at the C–S bond. Depending on the charge localization on one fragment or the other either phenylnitrilium type ion of *m/z* 104 is formed or the most intense ion of *m/z* 121, already considered in the mass spectrum of this substance, is formed. The stability of the anilinium free radical leads to the appearance of an ion with *m/z* 355. As in the case of diethylamide IIb fission occurred at the $C_{(0)}$–$C_{(4)}$ bond in the molecular ion of anilide IIc. The charge is not localized on the anilide functional group split off, which is less nucleophilic than the diethylamide group, but on the strongly conjugated heterocyclic residue bearing three phenyl substituents.

EXPERIMENTAL

Melting points were determined on a Boetius-type stage. The IR spectra were taken on an UR 20 spectrophotometer in Nujol. The ^{1}H NMR spectra of compounds IIa,b were recorded on a Varian 60 (60 MHz) instrument, and of compound IIc on a Bruker 250 (250.13 MHz). Electron impact mass spectra were obtained on MX 1310 mass spectrometric equipment at R = 15000, ionizing voltage was 70 eV, electron collector current 60 μA, temperature of the outer heater of the ion source was 120 °C. Samples were inserted directly with an SVP 5 input device, evaporator temperature for compounds Ia,b was 150 °C, and for compound Ic 230°C.

Phenylchloropyruvic acid methyl ester Ia was obtained by the procedure [10], and diethylamide Ib according to [11].

4-Methoxycarbonyl-3,5-diphenyl-2-phenyliminothiazoline (IIa). A. Phosphoric anhydride (10 g) and 85% phosphoric acid (5 ml) were stirred together at 90°C until homogeneous. The temperature was reduced to room temperature, 4-hydroxythiazolidine Ia (1.00 g, 26 mmol) was added, the mixture was stirred for 1 h at 20°C, then 3 h at 60°C. The reaction mixture was cooled to room temperature, and poured into ice water. The precipitated crystals were filtered off, dried, and recrystallized.

B. Thionyl chloride (6 ml, 83 mmol) was added to suspension of 4-hydroxythiazolidine Ia (3.00 g, 7 mmol) in benzene (100 ml). The resulting solution was boiled under reflux for 4 h, and the excess of $SOCl_2$ and solvent were evaporated. The residue was triturated with saturated aqueous sodium carbonate solution (50 ml). The crystals formed were filtered off, dried, and recrystallized. The product obtained by this method was identical to the product obtained by method A. A mixed melting point gave no depression.

4-Diethylaminocarbonyl-3,5-diphenyl-2-phenyliminothiazoline (IIb) was obtained analogously from 4-hydroxythiazolidine Ib by methods A and B.

3,5-Diphenyl-4-phenylamino-2-phenyliminothiazoline (IIc). Sodium hydride (0.17 g, 7 mmol) was added in portions with stirring at -15°C to suspension of 4-hydroxythiazolidine Ia (3.00 g, 7 mmol) in ether (200 ml) in atmosphere of dry argon. The reaction temperature was gradually brought up to room temperature. The mixture was left overnight, then filtered. The filtrate was treated with ice water, and the aqueous phase extracted three times with $CHCl_3$ (75 ml portions). The organic phases were combined, dried over $MgSO_4$, the solvent evaporated, and the residue recrystallized.

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