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STRUCTURE OF INTERMEDIATES IN THE HANTZSCH REACTION OF PHENYLCHLOROPYRUVIC ACID DERIVATIVES WITH N,N'-DIPHENYLTHIOUREA

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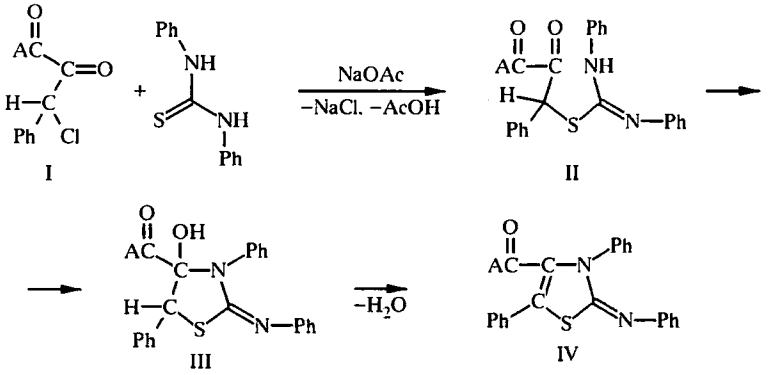
The intermediates in the Hantzsch reaction of the methyl ester and diethylamide of phenylchloropyruvic acid with N,N'-diphenylthiourea are derivatives of 2-phenylimino-3,5-diphenyl-4-hydroxythiazoline-4-carboxylic acid. They exist as an equilibrium mixture of two diastereomers in solution.

We have found previously that methyl phenylchloropyruvate Ia reacts with thiourea to give an intermediate hydroxy compound from the Hantzsch reaction, 2-imino-4-hydroxymethoxycarbonyl-5-phenylthiazoline hydrochloride, which dehydrates in boiling alcohol to produce 2-aminothiazole hydrochloride, the final product [1]. Thus, it behaves like other cyclic intermediates of the Hantzsch reaction that are prepared using other (not I) α-halo ketones [2-11]. Intermediates of the Hantzsch reaction of α-chloro ketone Ia which contain an open-chain isothiourea moiety [12], with thiosemicarbazones convert just as readily into 2-thiazolylhydrazones.

However, we prepared a much more stable intermediate of the Hantzsch reaction by replacing thiourea by N,N'-diphenylthiourea. Only powerful dehydrating agents can dehydrate this intermediate to produce the final product [13]. The present work involves a study of the structure of this intermediate, which was initially identified as the open-chain isothiourea derivative IIa, and of its diethylamide analog, prepared using the diethylamide of phenylchloropyruvic acid IIb.



I II III IV

A = OMe (a), NEt_2 (b)

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TABLE 1. IR and PMR Spectral Characteristics of 2-Phenylimino-3,5-diphenyl-4-hydroxy-4-carboxythiazolidine Derivatives (III)

Compound	IR spectrum (KBr pellet), ν, cm^{-1}	PMR spectrum in DMSO–d_6, δ, ppm, *J*, Hz
IIIa	3517 (O–H); 1741 (C=O); 1647 (C=N) 3066, 3026, 1590, 1493, 733, 693 (Ph) 1242,1103 (C–O–C, C–OH); 2956 1453 (Me)	3.28 (3H, s, OCH_3); 3.71 (3H, s, OCH_3) 5.14 (1H, s, CH); 5.54 (1H, s, CH) 6.97-7.63 (2×15H, m, $2×3C_6H_5$) 9.76 (2×1H, br. s, 2×10H)
IIIb	3284 (O–H); 1633 (C=O, C=N); 3081-3028, 1589, 1493, 734, 695 (Ph) 1105 (C–OH); 2977, 2932, 1452 1383 (Et)	0.75 (6H, t, $2CH_3$, J = 5.7) 0.97 (6H, t, $2CH_3$, J = 5.7) 2.91-3.72 (2×4H, m, $2×2CH_2$) 5.12 (1H, s, CH); 5.39 (1H, s, CH) 6.92-7.52 (2×15H, m, $2×3C_6H_5$) 9.71 (2×1H, br. s, 2×10H)

TABLE 2. ^{13}C NMR Spectral Characteristics of 2-Phenylimino-3,5-diphenyl-4-hydroxy-4-carboxythiazolidine Derivatives (III); DMF + Acetone-d_6 Solution (0.9:0.1); δ, ppm, *J*, Hz

Compound	A	C=O	$C_{(2)}$	$C_{(4)}$	$C_{(5)}$	Ph
IIIa	51.75 (q), $^1J_{CH}$ 147.85; 52.28 (q), $^1J_{CH}$ 148.50	168.35 (br. s); 169.38 (br. s)	158.35 (s) 158.68 (s)	94.27 (s) 96.89 (s)	55.66 (dt), $^1J_{CH}$ 146.81, ^3J 3.85; 57.46 (dt), $^1J_{CH}$ 150.17, ^3J 4.03	121.40; 121.57 123.11; 123.26 123.88; 124.55 126.94; 127.25 128.33; 128.44 128.55; 128.67 128.81; 129.11 129.32; 129.53 129.99; 133.15 135.27; 139.20 139.40; 139.94 151.38; 151.66
IIIb	11.28 (q), CH_3, $^1J_{CH}$ 147.85; 13.43 (q), CH_3, $^1J_{CH}$ 1126.24; 41.58 (t), CH_2, $^1J_{CH}$ 139.37; 42.59 (t), CH_2, $^1J_{CH}$ 135.86	166.60 (s)	158.27 (s)	93.69 (s)	54.90 (br. t), $^1J_{CH}$ 145.04	121.44; 123.23 126.57; 127.65 128.15; 128.26 128.38; 128.59 128.87; 130.07 139.14; 151.48

Elemental analysis data proved that we are working not with the final thiazolinimines IV but with their hydrates. The ^1H and ^{13}C NMR spectra (Tables 1 and 2) clearly exhibit peaks of the methine moiety, which occurs in structures II and III but not in IV. Thus, the obtained product are unambiguously covalent 4,5-hydrates [14] III or their open-chain isothiourea isomers II and not the crystal hydrates of thiazolinimines IV.

Absorption bands in the 3400 cm^{-1} region, which are characteristic of ν_{N-H} vibrations of the diphenylamidine moiety [15] and could be assigned to the structure II, are absent in the IR spectra of crystalline samples (Table 3). On the other hand, the spectra contain broad bands in the 3500 cm^{-1} (IIIa) and 3300 cm^{-1} (IIIb) regions, which can be assigned to ν_{O-H} of bound hydroxyl groups. Thus, like the earlier described intermediate of the Hantzsch reaction of ketone Ia with thiourea [1], the intermediates in the reaction of N,N'-diphenylthiourea are products possessing the cyclic structure in the crystalline phase, 4-hydroxythiazolidines III.

The IR spectra of compounds III in CCl_4 solution are practically identical to those for the crystalline phase. In addition to absorption bands ν_{O-H} of bound hydroxyl groups, those of free hydroxyls are also seen (see below). This is consistent with the fact that the IR spectra of the studied compounds in both the crystalline and phase solution exhibit only one symmetric $\nu_{C=O}$ band whereas two $\nu_{C=O}$ bands would be expected for structure II, the ketone

TABLE 3. Ratio of Diastereomers of 2-Phenylimino-3,5-diphenyl-4-hydroxy-4-methoxycarbonylthiazolidine (IIIa) in DMSO-d_6

Temperature, °C	Ratio
30*	≈1 : 0
30*[2]	0.85 : 0.15
60*[2]	0.75 : 0.25
120*[2]	0.65 : 0.35
150*[2]	0.60 : 0.40

* Immediately after dissolution.

*[2] After one hour heating at the indicated temperature.

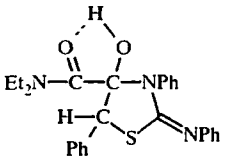
and the methoxycarbonyl (diethylamide) bands. Thus, for starting material Ia, which has two carbonyl groups, absorption bands at 1726 and 1745 cm^{-1} in the crystalline phase and at 1741 and 1753 cm^{-1} in CCl_4 solution appear, for an intermediate of the Hantzsch reaction of that compound with a acetone thiosemicarbazone [12] bands at 1740 and 1770 cm^{-1} are characteristic. The UV spectra of the studied compounds in CCl_4 (Table 3) lack absorption bands of keto groups of the fragment C(O)–COA [~350-360 nm, for example, Ia has λ_{max} at 356 nm ($\log \varepsilon = 2.06$)].

These data suggest that the intermediates of the Hantzsch reaction of N,N'-diphenylthiourea with the methyl ester and diethylamide of phenylchloropyruvic acid are 4-hydroxythiazolidine derivatives IIIa and -b and not their open-chain isomers IIa,b.

Certain additional features of the IR spectra of 4-hydroxythiazolidines III should be noted.

First, the ν_{O-H} stretching vibrations in diethylamide IIIb (3284 cm^{-1} in the crystalline phase) occur at much lower frequency than in ester IIIa (3517 cm^{-1}). Second, in contrast with the ester, the spectrum of which has two intense bands in the region of vibration frequences characteristic of multiple bonds, $\nu_{C=O}$ at 1741 and $\nu_{C=N}$ at 1646 cm^{-1}, the spectrum of the diethylamide has only one practically symmetric strong band at 1633 cm^{-1}.

Spectra of dilute solutions of the 4-hydroxythiazolidines III in CCl_4 were recorded in order to resolve this discrepancy. As it turned out, symmetric absorption bands at frequencies 66 cm^{-1} greater (3583 cm^{-1} for IIIa and 3340 cm^{-1} for IIIb) are seen after dilution in addition to the ν_{O-H} bands present in the spectra of the crystalline samples. These bands become the only ones in the ν_{O-H} frequences region at concentrations of $2 \cdot 10^{-4}$ mole/liter and lower. Hence, the crystalline phase of III exhibits vibrations of hydroxyl groups bound by intermolecular hydrogen bonds. On going to the dilute solutions of compound IIIa, these bonds break. The band at 3583 cm^{-1} corresponds to valence vibrations ν_{O-H} of free hydroxyl groups, which are typically observed near 3600 cm^{-1} [16] for various types of hydroxyl-containing compounds. The band at 3340 cm^{-1} in the spectrum of IIIb should be assigned to ν_{O-H} of hydroxyl group bound by intramolecular hydrogen bond.

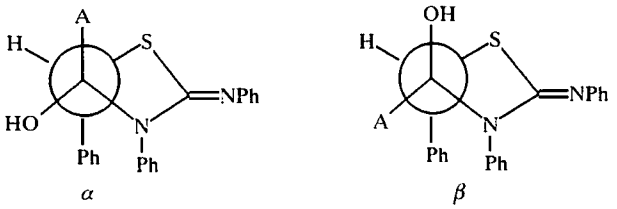


The hydroxyl groups in dilute solutions of ester IIIa and diethylamide IIIb exist in different states owing to the much greater basicity of the carbonyl group in amides compared with esters [17].

The integral intensity of the band at 1646 cm^{-1} in the dilute solution of amide IIIb was measured as $5.3 \cdot 10^{-4}$ liter·mol^{-1} whereas $\nu_{C=O}$ at 1740 cm^{-1} and $\nu_{C=N}$ at 1644 cm^{-1} in the spectrum of ester IIIa each were measured as $1.6 \cdot 10^{-4}$ liter·$mol^{-1} \cdot s^{-2}$, i.e., the total is practically the same as for the band at 1646 cm^{-1} in the spectrum of amide IIIb. This can be considered as evidence that this band is the composite ($\nu_{C=O} + \nu_{C=N}$). The decrease of the $\nu_{C=O}$ frequence from 1750 to 1646 cm^{-1} on going from the ester to the amide is completely consistent with the lower frequencies of carbonyl absorption of amides compared with esters owing to decrease in the double-bond nature of the C=O bond in amides [16].

Tables 1 and 2 list the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of the studied stable intermediates of the Hantzsch reaction. They agree completely with the proposed hydroxythiazolidine structures III because they contain peaks of all expected molecular fragments and no extraneous ones. However, all peaks are doubled for ester IIIa. This suggests that it exists in solution as a mixture of two forms of similar structure. Judging from the intensities of the components, these species are present in approximately equal amounts. This cannot be a mixture of isomers IIa and IIIa because the $^{13}C\{^{1}H\}$ NMR spectrum in this instance would have at least three and not two carbonyl peaks.

The two forms of hydroxythiazolidine IIIa that are observed in the NMR spectra of solutions may be the two diastereomers α and β, analogous to certain other intermediates of the Hantzsch [7-9] and Boze [1] reactions but not to the intermediate of the Hantzsch reaction of ester Ia and unsubstituted thiourea [1].



Doubled peaks are also observed in the PMR spectrum of the diethylamide IIIb. It also is probably a mixture of diastereomers. However, only the peaks of of carbon nuclei of the ethyl groups are doubled in the ^{13}C and $^{13}C\{^{1}H\}$ NMR spectra of this compound. Evidently, in contrast with ester IIIa, the relaxation times of the carbon nuclei of the thiazolidine and phenyl rings in amide IIIb are so long that the chemical shifts of these nuclei are averaged. In the PMR spectra, owing to the much shorter proton relaxation times, the diastereomers can be resolved. It is noteworthy that the diethylamide moieties in both spectra may be nonequivalent owing to hindered rotation around the partially double amide C–N bond.

It is interesting that peaks are not doubled if the NMR spectra of thiazolidines III are recorded immediately after dissolution (in Tables 1 and 2 spectra of solutions held for several days at room temperature are given). Consequently, only one diastereomer is apparently present initially in solution, apparently that in the form of which thiazolidine exists in the crystalline phase. In the course of time or at heating the diastereomers reach equilibrium, most probably owing to the ring–chain tautomerism

$$\alpha\text{-III} \rightleftharpoons \text{II} \rightleftharpoons \beta\text{-III}$$

According to Table 3, where the relative contents of the two diastereomers are listed estimated from the integral intensities of the methine group peaks of both species in the PMR spectrum, the establishment of equilibrium upon heating a DMSO solution of thiazolidine IIIa can be followed. Additional research, especially the determination of X-ray crystal structures, is needed in order both to assign peaks in NMR spectra to one or the other diastereomer of thiazolidine III, as was done for their 1,3,4-thiadiazine analog [1], and to determine in which of the diastereomeric forms they crystallize.

Another possible explanation of the signal doubling in the NMR spectra of thiazolidine III is the coexistence of *Z*- and *E*-stereoisomers that differ in the position of the phenyl substituent on the exocyclic nitrogen atom. This explanation is less probable because it is not consistent with large differences in the chemical shifts of the nuclei situated far from the imino group.

EXPERIMENTAL

Melting points were determined on a Boetius stage. ^{1}H, $^{13}C\{^{1}H\}$, and ^{13}C NMR spectra were recorded on a Bruker MSL-400 instrument at working frequency of 400.13 MHz (^{1}H) and 100.6 MHz (^{13}C). IR spectra were recorded in KBr pellets and in solutions on a IFS-113 Fourier-transform instrument. UV spectra were taken on a Specord M-40 UV-vis instrument.

The methyl ester of phenylchloropyruvic acid Ia was prepared according to [18] and diethylamide Ib - according to [19].

2-Phenylimino-3,5-diphenyl-4-hydroxythiazolidines (III). Solution of N,N'-diphenylthiourea (4.56 g, 20 mmol) in CH_2Cl_2 (100 ml) is treated with sodium acetate (4.10 g, 50 mmol). The mixture is cooled to -(15-20)°C. The ester Ia (4.2 g, 0.02 mol) is carefully added. The mixture is stirred for 3 h and gradually brought to room temperature, then poured into water. The organic layer is separated. The aqueous layer is extracted three times with CH_2Cl_2 (50 ml). The organic layer is dried over $MgSO_4$. The solvent is evaporated. The formed crystals are recrystallized. The product is 2-phenylimino-3,5-diphenyl-4-methoxycarbonyl-4-hydroxythiazolidine (IIIa).

The diethylamide Ib is used to prepare analogously 2-phenylimino-3,5-diphenyl-4-diethylamidocarbonyl-4-hydroxythiazolidine (IIIb).

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