SYNTHESIS AND SOME PROPERTIES OF THE METHYL ESTER AND N,N-DIETHYLAMIDE OF 2-AZIDO-5-PHENYL-4-THIAZOLECARBOXYLIC ACID

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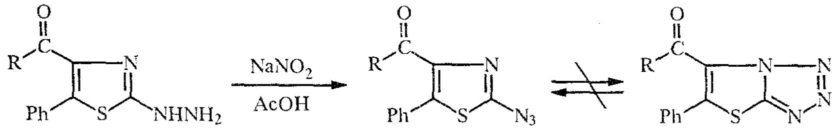
The methyl ester and N,N-diethylamide of 2-azido-5-phenyl-4-thiazolecarboxylic acid were obtained by the reaction of the corresponding 4-substituted 2-hydrazino-5-phenylthiazole with $NaNO_2$ *in acid media. IR and UV spectroscopy were used to show that the compounds synthesized retain azide form in both the crystalline state and in solution. The reaction of azides with dicarbonyl compounds gave derivatives of 2-[5'-methyl-4'-acetyl- or 2-[5'-methyl-4'-ethoxycarbonyl-1',2',3'-triazol-1'-yl]-5-phenylthiazole-4-carboxylic acid.*

In a continuation of work on the synthesis of functionally substituted thiazoles and an investigation of the reactivity of these compounds [1, 2], we carried out an IR and UV spectral study of the structural features of 2-azidothiazoles and examined the behavior of these compounds in dipolar cycloaddition reactions.

The methyl ester (IIa) and N,N-diethylamide (IIb) of 2-azido-5-phenyl-4-thiazolecarboxylic acid were obtained in high yield by the reaction of the corresponding 4-substituted 2-hydrazino-5-phenylthiazoles Ia and Ib with sodium nitrite in acid medium at 0-5°C.



Ia,b IIa,b

I, II a R = MeO; b R = Et_2N

Thiazoles [3-6] as well as other nitrogen heterocycles [7-10] having an azide group in the α-position relative to the ring nitrogen may exist either in the azide (A) or tetrazole (T) form or in an azide–tetrazole equilibrium (A ⇄ T) depending on the phase state and polarity of the medium. Thus, Fig. 1 shows that there are strong azide bands at 2100-2200 cm^{-1} ($\nu_{N_3}{}^{as}$) in the IR spectra of the crystals, melts, and solutions of IIa and IIb in CCl_4, dioxane, pyridine, and DMF. These bands, along with the $\nu_{N_3}{}^{s}$ bands (1260-1270 cm^{-1}) and carbonyl bands $\nu_{C=O}$ at 1730 (IIa) and 1630 cm^{-1} (IIb) are the strongest signals in these spectra, which indicates predominance of the azide form for these compounds.

We should note that bands at 1216 and 760 cm^{-1}, which are lacking in the spectra of the crystals, appear in the spectrum of the melt of IIb. These bands may indicate the tetrazole form [3]. Also, a shoulder is retained in the spectrum of the melt at 780 cm^{-1}, which is a band for the crystalline form. Subsequent crystallization of the melt leads to a redistribution of the doublet components such that the band at 780 cm^{-1} becomes predominant. On the other hand, we should note that complete reversibility of the spectral behavior upon crystal–melt–crystal phase transitions is not observed and, in addition to indications of a reversible process, there is also evidence for an irreversible process, probably decomposition (Fig. 2). Product IIa does not display such behavior upon crystal–melt–crystal phase transitions.

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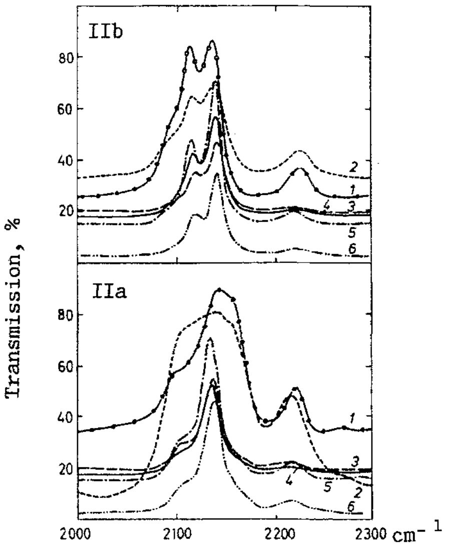

Fig. 1. IR spectra of IIa and IIb at 2100-2300 cm^{-1} ($\nu_{N_3}{}^{as}$): 1) Vaseline mull; 2) melt; 3) solution in DMF; 4) solution in pyridine; 5) solution in CCl_4, and 6) solution in dioxane.

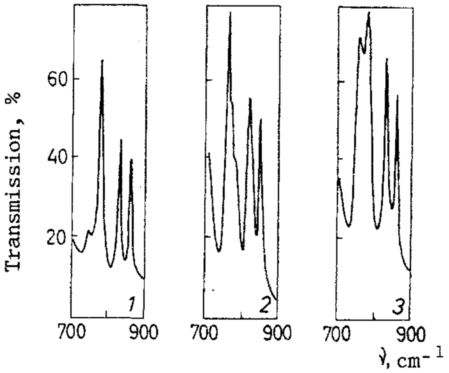

Fig. 2. IR spectrum of IIb at 700-800 cm^{-1}: 1) crystal; 2) melt; 3) crystal after melting.

Figure 1 shows that the azide form predominates in solutions of IIa and IIb, independently of the nature of the solvent. Judging from the relative intensity of the $\nu_{N_3}{}^{as}$ band (Table 1), the fraction of this form for similar solutions is somewhat higher for IIa. Direct evidence could not be obtained for the presence of the tetrazole form in solution or for the complete absence of this form. The UV spectra of solutions of IIa and IIb have bands characteristic for the azide group [4-6] at 291 nm for IIa and 302 nm for IIb along with phenyl bands.

Thus, the results of the spectral study unequivocally indicate that these compounds both in the crystalline state and in solution exist predominantly in the azide form. No spectral evidence is obtained for the tetrazole form even when the polarity of the medium or phase state are varied. The destabilization of the tetrazole form on the basis of the data of Boyer [4] and Temple [6] may be attributed to the electron-withdrawing nature of substituent R, which is more pronounced for IIa.

Support for this hypothesis was found in the reactions of IIa and IIb with acetylacetone (IIIa) and ethyl acetoacetate (IIIb) in DMF in the presence of triethylamine. These reactions were carried out at room temperature. The completion of these reactions was indicated by the complete disappearance of the $\nu_{N_3}{}^{as}$ band in the IR spectrum of the reaction mixture.

TABLE 1. Relative Intensity of the Azide Band $\nu_{N_3}{}^{as}$ $(I_{N_3}{}^{max}/I_{C=O}{}^{max})$* in the IR Spectra of Solutions of IIa and IIb

Compound	$I_{N3}{}^{max}/I_{C=O}{}^{max}$		
	in CCl_4	in C_5H_5N	in DMF
IIa	1,23	1,06	1,16
IIb	1,06	0,94	—

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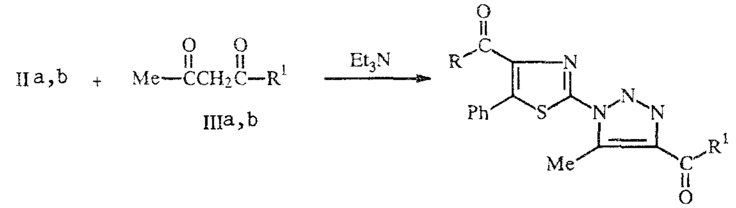
*The $\nu_{C=O}$ band was used as an internal standard.

TABLE 2. Spectral Indices of Derivatives of Triazolylthiazolecarboxylic Acids IVa-IVd

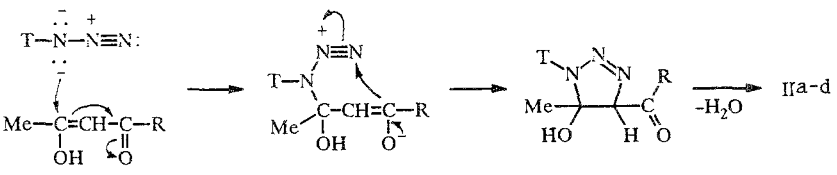
Compound	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm (solvent)
IVa	1725, 1735, 1570, 1345, 1210, 1025, 980, 790, 770	1,36 (3H, t, $OCH_2C\underline{H}_3$), 2,93 (3H, s, CH_3), 3,70 (3H, s, OCH_3), 4,33 (2H, q, $OC\underline{H}_2CH_3$), 7,40 (5H, s, C_6H_5); (DMSO-d_6)
IVb	1730, 1690, 1560, 1520, 1465, 1380, 1210, 1190, 1105, 1025, 800, 775	2,93 (3H, s, CH_3), 3,10 (3H, s, $C(O)CH_3$), 3,90 (3H, s., OCH_3), 7,50 (5H, s, C_6H_5); (CF_3COOH)
IVc	1715, 1640, 1575, 1430, 1375, 1345, 1250, 1130, 1030, 1010, 770, 700	0,90...1,66 (6H, m, $N(CH_2C\underline{H}_3)_2$), 1,53 (3H, t, $OCH_2C\underline{H}_3$), 3,10 (3H, s, CH_3), 3,26...4,00 (4H, m, $N(C\underline{H}_2CH_3)_2$), 4,53 (2H, q, $OC\underline{H}_2CH_3$), 7,46 (5H, s, C_6H_5); (CF_3COOH)
IVd	1685, 1635, 1545, 1520, 1460, 1380, 1365, 1260, 1220, 1100, 1010, 840, 770	0,90...1,53 (6H, m, $N(CH_2C\underline{H}_3)_2$), 2,93 (3H, s, CH_3), 3,10 (3H, s, $C(O)CH_3$), 3,26...3,90 (4H, m, $N(C\underline{H}_2CH_3)_2$), 7,50 (5H, s, C_6H_5); (CF_3COOH)



IVa-d

IV a R = MeO, R^1 = COOEt; b R = Et_2N, R^1 = COOEt; c R = MeO, R^1 = COMe;
d R = Et_2N, R^1 = COMe

The spectral data given in Table 2 and the elemental analyses served as the basis for assignment of the structure of triazolylthiazolecarboxylic acid derivatives (IVa-IVd) to the final products. The formation of these products may be explained using the mechanism for the Mannich reaction [11] as shown below.



The yield of the reaction products, as seen in the above mechanism, depends not only on the nucleophilicity of the nitrogen atom of the azide group directly bound to the thiazole ring but also the electrophilicity of the carbon atom in the dicarbonyl compound. Electron-withdrawing methoxycarbonyl and N,N-diethylamide groups, which presumably reduce the nucleophilicity of the thiazole nitrogen, hinder the formation of the tetrazole form. The ethoxycarbonyl group has a greater effect for enhancing the electrophilicity of the carbon atom than the acetyl group in IIIa and IIIb. This affects the yields and times of the reactions of 2-azidothiazoles (IIa and IIb) with these dicarbonyl compounds (Table 3).

TABLE 3. Indices of Compounds Obtained

Compound	Chemical formula	mp, °C	Yield, %	Reaction time
IIa*	$C_{11}H_8N_4O_2S$	89...90	96	—
IIb	$C_{14}H_{15}N_5OS$	103...104	90	—
IVa	$C_{17}H_{16}N_4O_4S$	131...132	70	15 min
IVb	$C_{20}H_{23}N_5O_3S$	144...145	65	4 min
IVc	$C_{16}H_{14}N_4O_3S$	163...164	58	24 h
IVd	$C_{19}H_{21}N_5O_2S$	150...151	55	7 days

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*IIa was recrystallized from 1:9 water–2-propanol and the other compounds were recrystallized from 2-propanol.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer for solutions in DMF, pyridine, CCl_4, and dioxane. The path length was 0.107 mm. The UV spectra were taken in absolute ethanol on a Karl Zeiss (Jena) Specord M-40 spectrometer under standard conditions for $1 \cdot 10^{-3}$ M solutions. The path length was 0.2 mm. The PMR spectra were taken on a Varian T-60 spectrometer with TMS as the internal standard.

The indices of IIa, IIb, and IVa-IVd are given in Tables 2 and 3.

The elemental analysis data for C, H, Cl, N, and S corresponded to the calculated values.

The hydrochloride salt of 2-hydrazino-4-(N,N-diethylaminocarbonyl)-5-phenylthiazole (Ib, $C_{14}H_{18}N_3OS \cdot HCl$) was obtained analogously to Ia [2] from 15 g (0.11 mole) acetone thiosemicarbazone and 30 g (0.11 mole) N,N-diethylamide of 3-phenyl-3-chloro-2-oxopropionic acid. The yield of Ib was 38%, mp 100-102°C. PMR spectrum in CF_3CO_2H: 1.01 (6H, m, CH_3), 3.43 (4H, m, CH_2), 7.33 (5H, s, C_6H_5). IR spectrum: 3475, 3150, 3050-2400, 2380, 1610, 1575, 1505, 1465, 765 cm^{-1}.

2-Azido-4-methoxycarbonyl-5-phenylthiazole (IIa). A solution of 1.27 g (0.018 mole) sodium nitrite in 3 ml water was added to a solution of 2 g (0.008 mole) hydrazine Ia in 10 ml water, 10 ml acetic acid, and 1.5 ml trifluoroacetic acid at 0°C, maintained for 5 min at 0°C, and poured into ice water. The precipitate formed was filtered off and washed with water to give 2 g IIa.

2-Azido-4-(N,N-diethylaminocarbonyl)-5-phenylthiazole (IIb) was obtained analogously to IIa.

Method for the Preparation of 2-[5′-methyl-4′-acetyl- or 2-[5′-methyl-4′-ethoxycarbonyl-1′,2′,3′-triazol-1′-yl]-5-phenylthiazole-4-carboxylic Acid Derivatives (IVa-IVd). A sample of 0.01 mole dicarbonyl compound and 0.01 mole triethylamine were added to a solution of 0.005 mole of the corresponding azide in 2 ml DMF at 20°C. The precipitate formed was filtered off and crystallized from 2-propanol. The reaction times and yields of products IVa-IVd are given in Table 3.

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