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SYNTHESIS OF SOME NEW ANNELLATED 1,2,4-TRIAZOLE SYSTEMS FROM METHYL 5-PHENYL-2-HYDRAZINOTHIAZOLECARBOXYLATE

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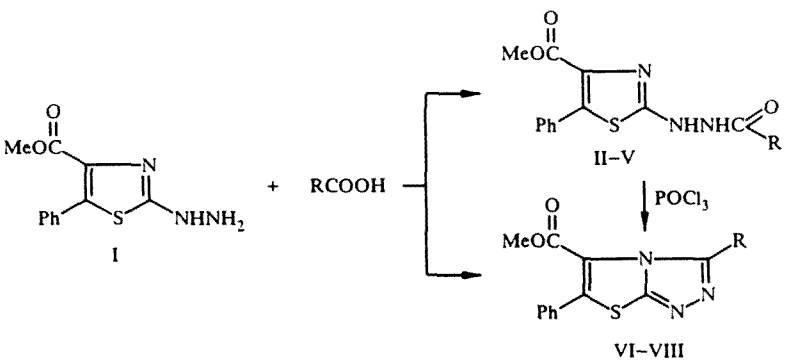
The heterocyclization of hydrazides, prepared from methyl 5-phenyl-2-hydrozinothiazole-4-carboxylate and organic acids or their anhydrides, leads to the production of thiazolo[2,3-c]triazoles which do not undergo rearrangement to the corresponding thiazolo[3,2-b]triazoles under the action of mineral acids. The 2-trifluoroacetylhydrazine derivative does not cyclize, even under severe conditions.

Previously, we have shown that when electron acceptor groups are introduced into the 2-azidothiazole molecule, the product of the annellation of a tetrazone ring to the thiazole is not formed [1]. In order to elucidate the possibility of synthesizing condensed, thiazole-containing systems, this paper gives the results of an investigation into the reaction of methyl 2-hydrazino-5-phenylthiazolecarboxylate (I) [2] with various acidic reagents. There are numerous data in the literature concerning the annellation of 1,2,4-triazole systems from 2-hydrazine-substituted heterocycles according to the nature of the structure [3] — in one case, successful cyclization depends on the nature and location of the substituents [4, 5], and in another, on the cyclization reagent [6], in a number of cases the intermediate hydrazines that form must be boiled in high-boiling solvents with phosphoryl chloride [7] or polyphosphoric acid [8].

2-Hydrazinothiazole I reacts with boiling formic acid. Unlike the case with acetic or trifluoroacetic acids, which lead to the acetyl (III) and trifluoroacetyl (V) derivatives of hydrazine I, respectively, this leads to the formation of N-formyl-N'-thiazolylhydrazine II, or thiazolyl[2,3-c]-s-triazole V, depending on the reaction time.



II, VI R = H; III, VII R = Me, IV, VIII R = Ph, V R = CF_3

The absence from the IR spectrum of compound VI of the absorption bands from a primary amine (3265, 3170 cm^{-1}) and a formyl group (1685 cm^{-1}), as well as the presence in its PMR spectrum of the 3-H proton singlet at 9.33 ppm, is evidence of the formation of thiazolo[2,3-c]-s-triazole, and the presence in its PMR spectrum of the 3-H proton singlet at 9.33 ppm is evidence of the formation of thiazolo[2,3-c]-s-triazole. When a sample of compound VI is diluted in DMSO-D_6, the

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TABLE 1. Spectral Characteristics of the Compounds Synthesized

Compound	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm (solvent)
II	3265, 3170, 3080 (NH), 1730, 1680 (C=O), 1585 (C=N)	3,90 (3H, s, CH_3O), 7,43 (5H, m, C_6H_5), 8,40 (1H, s, CHO) (CF_3COOH)
III	3290, 3170, 3085 (NH), 1720, 1670 (C=O), 1580 (C=N)	2,33 (3H, s, CH_3CO), 3,9 (3H, s, CH_3O), 7,43 (5H, m, C_6H_5) (CF_3COOH)
IV	3260, 3165, 3085 (NH), 1720, 1665 (C=O), 1580 (C=N)	3,63 (3H, s, CH_3O), 7,26 (5H, m, 5H-C_6H_5), 7,33...8,00 (5H, m, C_6H_5CO), 9,7 (1H, ex.b.s. NH) (DMSO-D_6)
V	3280, 3160, 3090 (NH), 1730 (C=O), 1580 (C=N)	3,90 (3H, s, CH_3O), 7,46 (5H, m, C_6H_5) (CF_3COOH)
VI*	1725 (C=O), 1605, 1570 (C=N)	3,73 (3H, s, CH_3O), 7,43 (5H, m, C_6H_5), 9,13 (1H, s, 3-H) (DMSO-D_6)
VII	1725 (C=O), 1600, 1570 (C=N)	2,76 (3H, s, 3-CH_3), 3,73 (3H, s, CH_3O), 7,4 (5H, s, C_6H_5) ($CDCl_3$)
VIII	1735 (C=O), 1575 (C=N)	3,96 (3H, s, CH_3O), 7,53 (5H, m, 6-C_6H_5), 7,66...8,16 (5H, m, 3-C_6H_5) (DMSO-D_6)
IX	1735, 1715, 1710, 1690 (C=O)	2,43 (3H, s, $COCH_3$), 2,66 (6H, s, $[COCH_3]_2$), 3,8 (3H, s, CH_3O), 7,43 (5H, m, C_6H_5) (CF_3COOH)
X	—	7,56 (5H, m, C_6H_5), 9,8 (1H, s, 3-H) (CF_3COOH)

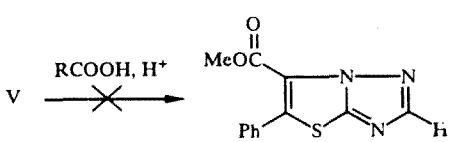
*PMR spectrum of compound VI in CF_3COOH: 3.96 (3H, s, CH_3O), 7.53 (5H, m, C_6H_5), 9.86 (1H, s, 3-H).

3-H proton signal in the PMR spectrum is shifted to a stronger field (9.33 → 9.13 ppm), which obviously is explained by the rupture of an intermolecular hydrogen bond between this proton and one of the basic heteroatoms [9]. On the other hand, this signal is shifted to a weaker field (9.13 → 9.86 ppm) in the PMR spectrum of compound VI in CF_3COOH because of the protonation of the ring.

Compounds III and IV are also easily obtained by the reaction of 2-hydrazinothiazole I with acetic or benzoic anhydride in the presence of pyridine. The conversion of the acetyl and benzoyl derivatives to the corresponding thiazolotriazoles is accomplished by the action of $POCl_3$ in boiling dioxane. Even on prolonged boiling (40 h), trifluoroacetyl derivative IV remains unchanged under these conditions.

An attempt to convert 2-hydrazinothiazole I and its monoacetyl derivative, III, to thiazolo[2,3-c]-s-triazoles in a boiling solution of acetic anhydride by the method in [10] proved unsuccessful. Instead of the expected product, the triacetyl derivative of hydrazinothiazole IX was formed, having the absorption bands of three amide groups at 1710, 1690, and 1680 cm^{-1} and of an ester group at 1725 cm^{-1} in the IR spectrum, and three methyl group singlets at 2.43, 2.66, and 3.80 ppm in the PMR spectrum.

It is known that condensed systems containing a triazole ring undergo a Dimroth rearrangement [11] in an acid medium under severe conditions to form thiazole[3,2-b]triazole derivatives. The existing literature data show that in a number of cases the products of a Dimroth rearrangement are formed together with the basic annellation product. Because of this, we have studied the behavior of triazolo[2,3-c]triazole VI with respect to organic acids in the presence of mineral acid (H_2SO_4) in order to elucidate the possibility of a Dimroth rearrangement taking place. Experiments showed that the prolonged boiling of compound VI in CF_3COOH or HCOOH in the presence of 0.1 ml of H_2SO_4 gives no results; a tenfold increase in the amount of mineral acid leads to the hydrolysis of the ester group and the formation of acid X.



XI

It is not precluded that the [2,3-c] → [3,2-b] rearrangement occurs at the moment of thiazolotriazole formation in acid medium, therefore, in order to elucidate the structure of the end product, triethoxymethane was used as an annellating reagent in which, according to the literature [12, 13], rearrangement to form a [3,2-b]-structure is impossible. It was shown that the

reaction of 2-hydrazinothiazole I with triethoxymethane takes place with the formation of structure VI, not XI, as indicated by the identity of the spectra of this product and VI, and the lack of a melting point depression of a mixed sample of this compound and VI.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument (in mineral oil), the PMR spectra on a Varian-60 spectrometer, TMS internal standard. The melting points were determined on a heated Boetius column. The spectral characteristics of the compounds synthesized are given in Table 1.

Elementary analyses of the compounds for C, H, N, and S agreed with the calculated values.

N-Formyl-N'-[2-(4-methoxycarbonyl-5-phenyl)triazolyl]hydrazine (II, $C_{12}H_{11}N_3O_3S$). A solution of 2.0 g (0.008 moles) of compound I in 20 ml of formic acid is boiled for 3 h, the acid evaporated off under vacuum, and the residue washed with water and dried in air. After recrystallization from MeOH, compound II is obtained in a 1.9 g yield (86.3%), mp 214-215°C.

N-Acetyl-N'-[2-(4-methoxycarbonyl-5-phenyl)thiazolyl]hydrazine (III, $C_{13}H_{13}N_3O_3S$). A. A solution of 1.5 g (0.006 moles) of compound I in 20 ml of acetic acid is boiled for 3 h, the acid evaporated off under vacuum, and the residue washed with water and dried in air. After recrystallization from MeOH, compound III is obtained in a 0.9 g yield (60%), mp 240-241°C.

B. A mixture of 1.0 g (0.004 moles) of compound I and 0.7 g (0.005 moles) of acetic anhydride in 8 ml of anhydrous pyridine is held at room temperature for 2 h. The crystals that precipitate are filtered off and dried in air. After recrystallization from MeOH, compound III is obtained in a 0.5 g yield (45.5%).

N-Benzoyl-N'-[2-(4-methoxycarbonyl-5-phenyl)thiazolyl]hydrazine (IV, $C_{18}H_{15}N_3O_3S$). A mixture of 1.5 g (0.006 moles) of compound I and 1.3 g (0.006 moles) of benzoic anhydride in 5 ml of anhydrous pyridine is held at room temperature for 72 h. The crystals that precipitate are filtered off and dried in air. After recrystallization from a 1:1 MeCN/dioxane mixture, compound IV is obtained in a 1.3 g yield (61.9%), mp 212-214°C.

N-Trifluoroacetyl-N'-[2-(4-methoxycarbonyl-5-phenyl)thiazolyl]hydrazine (V, $C_{13}H_{10}F_3N_3O_3S$). A solution of 2.0 g (0.008 moles) of compound in 15 ml of trifluoroacetic acid is boiled for 40 h, the acid evaporated off under vacuum, and the residue dissolved in ether. The crystals that form are filtered off and recrystallized from i-PrOH to obtain compound V in a 1.6 g yield (57.1%), mp 207-208°C.

5-Methoxycarbonyl-6-phenylthiazolyl[2,3-c]-triazole (VI, $C_{12}H_9N_3O_2S$). A. Two grams (0.008 moles) of compound I in 20 ml of formic acid is boiled for 70 h and the acid evaporated off under vacuum. The residue is recrystallized from i-PrOH to obtain compound VI in a 1.0 g yield (48.1%) mp 155-156°C.

B. One gram (0.004 moles) of compound I in 10 ml of triethoxymethane is boiled for 60 h. The excess triethoxymethane is evaporated off under vacuum, and the residue recrystallized from i-PrOH to obtain compound VI in a 0.6 g yield (60%).

5-Methoxycarbonyl-6-phenylthiazolyl[2,3-c]-s-methyltriazole (VII, $C_{13}H_{11}N_3O_2S$). To a solution of 5.0 g (0.017 moles) of compound III in 85 ml of absolute dioxane is added 42.5 ml of freshly distilled $POCl_3$. The reaction mixture is boiled for 3 h, cooled to 20°C, cautiously poured onto ice, and allowed to stand overnight. It is then extracted with chloroform (3 × 150 ml), and the extract dried with $CaCl_2$. After the solvent has been evaporated off, the residue is recrystallized from hexane to obtain compound VII in a 0.9 g yield (20.4%), mp 131-133°C.

5-Methoxycarbonyl-6-phenylthiazolyl[2,3-c]-s-phenyltriazole (VIII, $C_{18}H_{13}N_3O_2S$). To a solution of 1.2 g (0.003 moles) of compound IV in 80 ml of absolute dioxane is added 42.5 ml of freshly distilled $POCl_3$. The reaction mixture is boiled for 3 h, cooled to 20°C, cautiously poured into ice, allowed to stand overnight and the crystals that precipitate filtered off. After recrystallization from hexane, compound VIII is obtained in a 0.3 g yield ((27.3%), mp 84-86°C.

2-(N,N,N'-Triacetylhydrazino)-4-methoxycarbonyl-5-phenylthiazole (IX, $C_{17}H_{17}N_3O_2S$). Two grams (0.004 moles) of compound I in 40 ml of acetic anhydride is boiled for 48 h. The excess acetic anhydride is evaporated off, the residue treated with ether, and the crystals that form filtered off and recrystallization from i-PrOH to obtain compound IX in a 2.8 g yield (93.3%), mp 169-170°C.

6-Phenylthiazolyl[2,3-c]-s-triazole-5-carboxylic Acid (X, $C_{11}H_7N_3O_2S$). A solution of 1.0 g (0.004 moles) of compound VI in 5 ml of formic (or acetic) acid is boiled for 5 h in the presence of 1 ml of concentrated H_2SO_4. The excess acid is evaporated off under vacuum, and the residue washed with water. The crystals that form are filtered off and after being dried in air give a 0.6 g yield (60%) of compound X, mp 178-180°C.

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