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SYNTHESIS AND REACTIONS OF 2-AMINO-5-CARBOMETHOXY-6-PHENYL-6H-1,3,4-THIADIAZINE

V. A. Mamedov, L. V. Krokhina, E. A. Berdnikov, and Ya. A. Levin

Treatment of methyl 3-phenyl-3-chloro-2-oxopropionate with thiosemicarbazide gives 2-amino-5-carbomethoxy-6-phenyl-6H-1,3,4-thiadiazine, the isomeric 2-hydrazino-4-carbomethoxy-5-phenylthiazole, or the corresponding carboxylic acids depending on the acidity of the medium. The intermediate on the way to the thiadiazine proved to be a covalent 4,5-hydrate. These reactions are subject to thermodynamic control. Acetylation of the above thiadiazine occurs either with retention of the thiadiazine structure or via sulfur atom extrusion to give acetylated 3-amino-4-phenyl-5-carbomethoxypyrazole.

The most widely used method for preparing 1,3,4-thiadiazines is the Bose reaction using thiosemicarbazide and α-halocarbonyl compounds [1-3]. We have recently shown [4] that reaction of thiosemicarbazide with the methyl ester of 3-phenyl-3-chloro-2-oxopropionic (phenylchloropyruvic) acid I in acetonitrile (in contrast to that of its close structural analog ethyl bromopyruvate in concentrated hydrochloric acid [5]) gives not the expected thiadiazine II but the cyclic hemihydrazinal III, i.e., the covalent 4,5-hydrate [6] of thiadiazine II. There is every reason to consider it as the immediate precursor of the final product in a variant of the Bose reaction in which closing of the ring is completed by formation of the N_4-C_5 bond [2]. Formation of products analogous to III has not been reported before in the Bose reaction.

In this work we have investigated the mutual relationship of II and III and the conversion of these heterocycles to thiazoles and pyrazoles.

In contrast to condensation of chloroketone I with thiosemicarbazide in neutral solvent [4], the reaction in the presence of an equimolar amount of trifluoroacetic acid occurs smoothly to give thiadiazine II as its hydrochloride from which the free base IV can be prepared by treatment with aqueous sodium bicarbonate. However, condensation in concentrated hydrochloric acid at 0°C (which gives a thiadiazine with a retained carbethoxy group in the case of ethylchloropyruvate [5]) here yields a mixture of the carbomethoxy (II) and carboxy (V) derivatives, i.e., with partial hydrolysis of the substituent. In preparing the thiadiazine II, trifluoroacetic acid functions through dehydration of the intermediate hydroxy compound III, and this is clearly demonstrated by formation of the dehydration product when preparing thiadiazine II by direct condensation of thiosemicarbazide and I. The presence of HCl in the reaction medium as the salt III proves insufficient for acid catalyzed dehydration, at least in the conditions used. The ready and smooth dehydration of III to thiadiazine II is an additional pointer supporting the assignment of the first of these structures as a six and not a five membered ring (made through interpretation of the ^{13}C NMR spectra) despite its ready conversion to thiazole derivatives [4].

With two hour refluxing of II-IV in concentrated hydrochloric acid, the usual recyclization to 2-imino-3-aminothiazolines [1-3] or 2-hydrazinothiazoles [2, 5] does not occur. There occurs instead dehydration (in the case of III) and hydrolysis of the ester function with retention of the thiadiazine ring and formation of compound V. Recyclization does occur with more prolonged refluxing to give 2-hydrazino-thiazole VI, identical to that obtained by us previously through acid hydrolysis of the known 2-hydrazino-4-carbomethoxy-5-phenylthiazole VII [7], i.e. recyclization occurs with fission of the

A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Science Center, Russian Academy of Sciences, Kazan 420083. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1266-1272, September, 1996. Original article submitted June 19, 1996.

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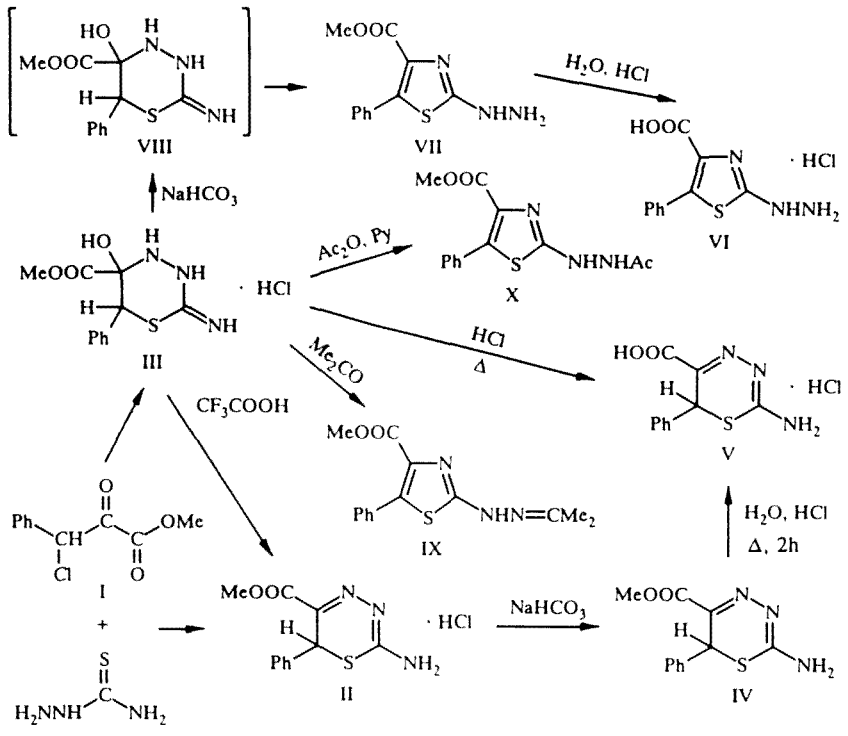
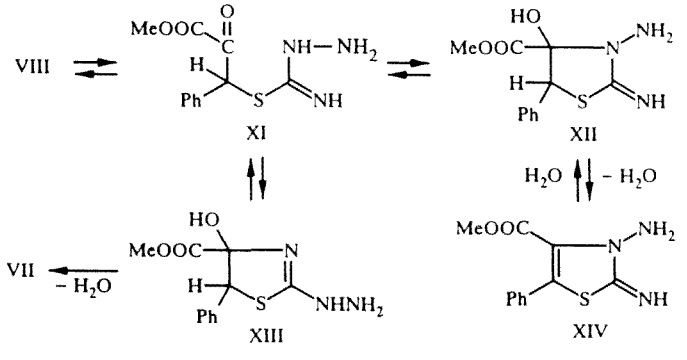


N_4-C_5 bond and subsequent attack of this carbon atom on the non-hydrazino nitrogen atom. These observations support those on the inhibition of the recyclization of 2-amino-6H-1,2,4-thiadiazines by 5-carbalkoxy or carboxy groups and also that these substituents direct the cyclization to formation of 2-hydrazinothiazoles [2-5] but contradict the general observations about the negative effect of a 6-phenyl substituent on the stability of the thiadiazine ring [2].



Attempts to prepare the free base VIII from its hydrochloride III (even under such mild conditions as treatment with an aqueous solution of sodium bicarbonate at room temperature) lead to formation of the hydrazinothiazole isomer VII, i.e., recyclization occurs much more rapidly even than when refluxing with concentrated hydrochloric acid. Hence the relatively rare recyclization route (not involving formation of a 2-imino-3-aminothiazole XIV [1-3]) comes about much more rapidly than in acids. Evidently recyclization of base VIII occurs more rapidly than the possible dehydration VIII – IV since compound IV is completely stable.

Other examples of ring contraction of III when converting to 2-hydrazinothiazole derivatives are the preparation of the hydrazone IX via refluxing in acetone and of the acetylhydrazine X by the action of acetic anhydride in pyridine [4].

We believe that the presence of two electron acceptor groups (Ph; COOMe or COOH) in the thiadiazines II and IV hinders their diprotonation and correspondingly decreases the velocity of transannular attack of the positive C_5 atom in the dication on N_3, being key in formation of 2-imino-3-aminothiazoles [3, 8]. There also arises another competitive recyclization route via hydration of N_4-C_4 in II, IV to form the covalent hydrates III, VIII (similarly for acid V). These covalent hydrates (III, VIII) can exist as ring-chain tautomers with isothiosemicarbazides (XI) and, through the latter, with the covalent hydrates of 2-imino-3-aminothiazolines and 2-hydrazinothiazoles, e.g. XII, XIII. Since the thiadiazines and thiazolines are nonaromatic

TABLE 1. Parameters for Compounds Synthesized

Compound	Found, % / Calculated, %				Empirical formula	mp, °C (solvent)	Yield, %
	C	H	N	S(Cl)			
II	46,25 46,32	4,20 4,17	14,71 15,04	11,22 11,19 (12,41) (12,44)	$C_{11}H_{11}N_3O_2S \cdot HCl$	157...159 (MeCN)	86 (A), 90 (B)
IV	53,02 53,06	4,41 4,41	16,87 16,84	12,87 12,91	$C_{11}H_{11}N_3O_2S$	140...142 (*i*-PrOH)	100
V	44,21 44,17	3,31 3,30	15,46 15,50	11,81 12,01	$C_{10}H_8N_3O_2S \cdot HCl$	282...284 (DMF)	87 (A), 71 (B) 62 (B)
XV	53,62 53,34	4,46 4,47	14,43 13,98	11,01 11,08	$C_{13}H_{13}N_3O_3S$	164...166 (*i*-PrOH)	79 (A), 83 (C)
XVI	60,25 61,14	5,02 5,01	16,22 16,08	(13,05) (13,17)	$C_{13}H_{13}N_3O_3$	226...227,5 (DMSO)	88 (A), 5 (B)

TABLE 2. IR and PMR Spectra of Compounds Synthesized

Compound	IR Spectrum, ν, cm^{-1}	PMR Spectrum, δ, ppm (solvent)
II	3400...2500 (NH), 1735 (C=O), 1650, 1635 (C=N, NH)	3,83 (3H, s, MeO), 5,93 (1H, s, CH), 7,0...7,5 (5H, m, Ph), 8,9 (3H, br. s, NH); (DMSO-D_6)
IV	3400...2600 (NH), 1715 (C=O), 1650 (C=N, NH)	3,76 (3H, s, MeO), 5,46 (1H, s, CH), 6,2 (2H, br. s 2H); 6,9...7,4 (5H, m, Ph); (DMSO-D_6)
V	3300...2550 (NH, OH), 1710 (C=O)	6,00 (1H, s, CH), 7,53 (5H, s, Ph); (DMF-D_7)
XV	3380...3100 (NH), 1740 (OC=O), 1710, 1705, 1695 (MeC=O)	2,00 (3H, s, MeCO), 3,80 (3H, s, MeO), 5,33 (1H, s, CH), 6,7...7,4 (6H, m, Ph, NH); (DMSO-D_6)
XVI	3345...3275, 3380 (NH), 1735 (OC=O), 1710, 1705, 1695, 1685 (MeC=O), 1615 (C=N, NH)	1,95 (3H, br. s MeCO), 3,75 (3H, s, MeO), 7,37 (5H, s Ph), 9,69 (1H, br. s, NH); (DMSO-D_6)

TABLE 3. ^{13}C NMR Spectra for Thiadiazines II*, IV*†

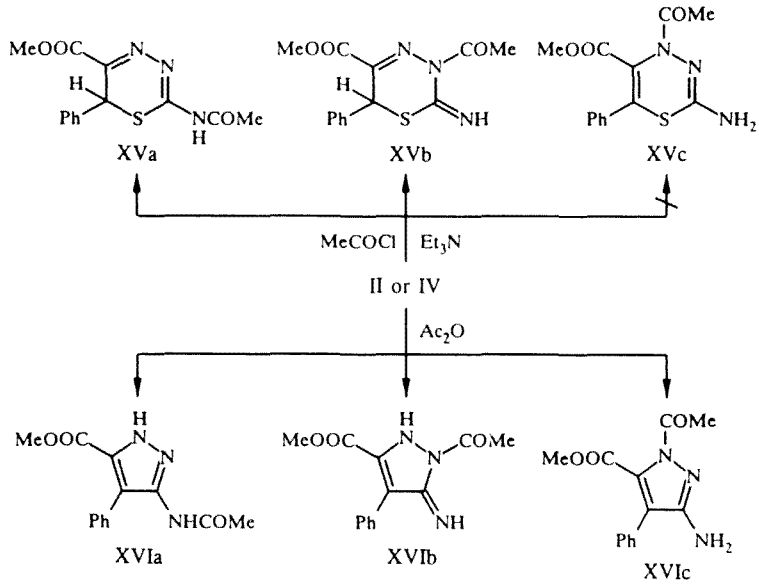
Compound	$C^{2,7}$	C^5	C^6	C^8
II	165,74 (s), 166,15 (s),	144,82 (d), $^2J_{CH}$ 6,6	41,09 (d), $^1J_{CH}$ 145,2	57,43 (кв), $^1J_{CH}$ 148,3
V	165,93 (s), 166,08 (s),	145,69 (d), $^2J_{CH}$ 6,9	40,52 (d), $^1J_{CH}$ 150,3	—
Compound	C^i	C^o	C^m	C^p
II	139,51 (t), $^3J_{CH}$ 7,3	130,18 (dt), $^1J_{CH}$ 156,2, $^3J_{CH}$ 5,3	133,45 (dd), $^1J_{CH}$ 163,00 $^3J_{CH}$ 7,3	133,08 (dt), $^1J_{CH}$ 169,1, $^3J_{CH}$ 7,1
V	139,06 (t), $^3J_{CH}$ 6,6	130,19 (dt), $^1J_{CH}$ 156,2, $^3J_{CH}$ 6,6	132,88 (dd), $^1J_{CH}$ 163,0 $^3J_{CH}$ 6,6	133,08 (dt), $^1J_{CH}$ 169,1, $^3J_{CH}$ 6,6

*II, R = Me; V, R = H.

†As in Russian original — Publisher.

heterocycles and the thiazoles are aromatic, the dehydration of compounds III and XII is reversible for the first two types of rings [3, 8] and irreversible for type XIII giving 2-hydrazinothiazoles. This also shows that the rearrangement described here and in [4] are under thermodynamic control. It is significant that the 4-hydroxythiazoline analogs III, VIII have been separated and characterized as key intermediates in the Bose related synthesis of thiazoles by Hantzsch. The problems of ring-chain isomers and tautomers are similar to those considered here, e.g., see [4. 9-11].

The structure and composition of thiadiazines II, IV, V are proved by the data in Tables 1-3. In particular, the number, chemical shifts and multiplicities of the ^{13}C NMR spectral peaks correspond exactly, and it was possible to assign all of the peaks corresponding to the carbon atoms of the thiadiazine ring (Table 3). Attention is drawn to the strong deshielding of all protons in the PMR spectrum of hydrochloride II when compared with the spectrum of the corresponding base IV, being especially marked for protons on the nitrogen atom.



It is known that acylation of 1,3,4-thiadiazines and 2-amino derivatives (depending on their structure, the nature of the acylating agent, and the reaction conditions) can occur at different nitrogen atoms and sometimes (with ring contraction) at the sulfur atom but more frequently with extrusion of the latter [2, 3]. The current thiadiazine IV or its hydrochloride II react with acetyl chloride in the presence of triethylamine to form a mono acetylated derivative of the starting heterocycle without loss of the sulfur atom. It shows a PMR singlet spectral peak (Table 1) at 5.33 ppm, i.e., in the region for the methine proton of the PhCH in a thiadiazine ring (compound II, IV, V in Table 1; III in report [4]). This component cannot be present in either the thiazole or thiazoline structures. Hence acylation is not accompanied by recyclization in these conditions. Of the three possible mono acetyl thiadiazine structures XVa-c, the 4H structure XVc can be eliminated in view of the absence of the methine group but a choice between the two 6H structures XVa, b cannot be made with certainty.

Acetylation of thiadiazines II, IV gave a minor product (not containing sulfur) as well as compound XV. It was obtained as the only product when acetylating with acetic anhydride in the presence or the absence of triethylamine. Its composition corresponded to a mono acetyl derivative of the 3-amino-4-phenyl-5-carbomethoxypyrazoles XVIa-c. The ^{1}H and ^{13}C NMR spectra show features which can be interpreted as evidence for acylotropic exchange processes. The ^{13}CNMR spectrum shows marked broadening or indeed the absence of peaks for two of the three pyrazole nuclear carbons with a broadened acetyl group carbonyl carbon and, in the PMR spectrum, the protons of the latter group. Hence a choice between them must be the subject of special investigation.

For compounds described previously, the structural formulae are given with the exact prototropy in the original form.

EXPERIMENTAL

Melting points were determined on a Boetius microscope stage. IR spectra were recorded on a UR-20 spectrophotometer using Vaseline oil. PMR spectra for II, IV, V were recorded on a Varian-60 (60 MHz) instrument and XV,

XVI on a Bruker-250 (250.13 MHz). ^{13}C NMR spectra were taken on a Bruker MSL-400 spectrometer (100.6 MHz) using DMSO-D_6 solvent and TMS internal standard.

2-Amino-5-carbomethoxy-6-phenyl-6H-1,3,4-thiadiazine Hydrochloride (II). A. Chloroketone I (21.2 g, 0.1 mole) was added with vigorous stirring to a solution of thiosemicarbazide (9.1 g, 0.1 mole) and trifluoroacetic acid (11.4 g, 0.1 mole) in acetonitrile (150 ml), and the product was refluxed with stirring for 4 h. After 2.5-3 h the crystalline thiadiazine II began to crystallize. After cooling, the precipitate was filtered and washed with cold acetonitrile.

B. A suspension of hydroxy compound III (3.0 g, 9.9 mmole) in trifluoroacetic acid (1.2 g, 10.5 mmole) and acetonitrile (35 ml) was stirred for 1 h at 55-60°C and then treated as described above.

2-Amino-5-carbomethoxy-6-phenyl-6H-1,3,4-thiadiazine (IV). A suspension of II hydrochloride in an excess of 0.5% aqueous sodium bicarbonate was stirred for 2 h at room temperature and the precipitate was filtered off and washed with water.

2-Amino-5-carboxy-6-phenyl-6H-1,3,4-thiadiazine Hydrochloride (V). A. A solution of hydroxy compound III (3.0 g, 9.9 mmole) in concentrated hydrochloric acid (15 ml) was refluxed for 2 h. The precipitate was filtered after cooling and washed with water.

The carboxythiadiazine hydrochloride V was obtained similarly from the thiadiazine II hydrochloride (B) and its free base IV (C).

2-Hydrazino-5-phenyl-4-carboxythiazole Hydrochloride (VI). A solution of hydroxy compound III (3.0 g, 9.9 mmole) in concentrated hydrochloric acid (15 ml) was refluxed for 6 h. After 20-30 min, precipitation of thiadiazine V began and this gradually redissolved. After cooling, the new precipitate was filtered, washed with water, and recrystallized from DMF to give VI (1.5 g, 53%), identical to that reported in [6].

2-Hydrazino-5-phenyl-4-carbomethoxythiazole (VII). An aqueous solution of sodium bicarbonate (5%, 25 ml) was added with stirring to a solution of hydroxy compound III (2.0 g, 7 mmole) in water (50 ml). The precipitated crystals were filtered and washed with water to give VII (0.7 g, 40%), which was identical to that reported in [6].

Mono Acetylated 2-Amino-5-carbomethoxy-6-phenyl-6H-1,3,4-thiadiazine (XV). A. Acetyl chloride (2.2 g, 28 mmole) was added with stirring to a solution of hydrochloride II (8.0 g, 28 mmole) and triethylamine (5.7 g, 56 mmole) in acetonitrile (50 ml) under argon at 0-5°C. Solvent was evaporated and the residue treated with water. The precipitated crystals were filtered, washed with water and, after drying, were recrystallized from isopropanol.

B. Compound XV was prepared similarly from the free base IV using equimolar amounts of reagents.

Mono Acetylated 3-Amino-5-carbomethoxy-4-phenylpyrazole (XVI). A. Hydrochloride II (3.6 g, 13 mmole) and acetic anhydride (5.0 g, 49 mmole) in benzene (30 ml) were refluxed for 4 h. Excess anhydride and solvent were distilled off and the residue was crystallized from DMSO. ^{13}C NMR spectrum: 26.45, $^1J_{CH}$ 128.1 (q, MeCO); 55.47, $^1J_{CH}$ 147.7 (q, MeO); 130.96, $^1J_{CH}$ 160.7, $^3J_{CH}$ 7.2 (dt, C_p); 131.60, $^1J_{CH}$ 160.4, $^3J_{CH}$ 6.2 (dd, C_m); 133.61, $^1J_{CH}$ 160.3 (dm, C_o); 134.68 $^3J_{CH}$ 6.0 (t, C_i); 173.83 (s, MeOCO); 99.35 (s, C_4); 123.63 ppm (br s, $C_{3,5}$).

B. The residue insoluble in isopropanol on crystallization of XV using acetyl chloride (see above) proved to be compound XVI and is identical to that obtained by method A.

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