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1,2,4-TRIAZINE AND TRIAZOLE DERIVATIVES FROM α-KETO ACIDS AND THIOSEMICARBAZIDES

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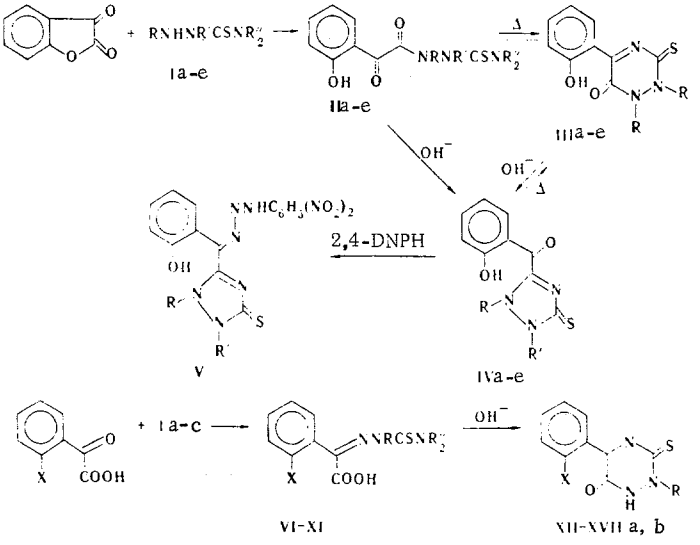
Thiosemicarbazides of 2-hydroxyphenylglyoxylic acid, which, depending on the conditions, undergo cyclization to interconvertible 5-(2-hydroxyphenyl)-6-oxo-1,2,4-triazine-3-thiones or (2-hydroxybenzoyl)-Δ^2-1,2,4-triazoline-5-thiones, are formed by the action of thiosemicarbazide and its homologs on coumarindione. The thiosemicarbazones of 2-hydroxyphenylglyoxlyic and other 2-substituted phenylglyoxylic acids undergo cyclization to 6-(2-hydroxyphenyl)-5-oxo-1,2,4-triazine-3-thiones.

The reaction between α-keto acids and thiosemicarbazide derivatives lies at the foundation of several schemes for the synthesis of heterocyclic structures. One of the unexplored pathways may consist in prior condensation at the carboxyl group to give the corresponding thiosemicarbazides of α-keto acids and their subsequent cyclization to 1,2,4-triazine and triazole derivatives. Because of the high activity of the carbonyl group



I a R=R′=R″=H, b R=R″=H, R′=CH_3, c R=R′=H, R″=CH_3, d R=CH_3, R′=R″=H, e R=p-C_4H_9, R′=R″=H; II a R=R′=R″=H, b R=R″=H, R′=CH_3, c R=R′=H, R″=CH_3, d R=CH_3, R′=R″=H, e R=*n*-C_4H_9, R′=R″=H; III a R=R′=H, b R=H, R′=CH_3, d R=CH_3, R′=H, e R=*n*-C_4H_9, R′=H; IV a R=R′=H, e R=n-C_4H_9, R′=H; V R=R′=H; VI X=H, a R′=R″=H, b R′=CH_3, R″=H, c R′=H, R″=CH_3; VII X=OH, a R′=R″=H, b R′=CH_3, R″=H; VIII X=NH_3, a R′=H; IX X=Br, a R′=R″=H, b R′=CH_3, R″=H; X X=NO_2, a R′=R″=H, b R′=CH_3, R″=H, c R′=H, R″=CH_3; XI X=COOH, a R′=R″=H, b R′=CH_3, R″=H, c R′=H, R″=CH_3; XII X=H, a R=H, b R′=CH_3; XIII X=OH, a R′=H, b R′=CH_3; XIV X=NH_2, a R′=H; XV X=Br, b R′=CH_3; XVI X=NO_2, a R′=H, b R′=CH_3; XVII X=COOH, a R′=H, b R′=CH_3

* Deceased.

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as compared with the carboxyl group, thiosemicarbazides of this sort have remained unknown. Our attempts to obtain them with the aid of dicyclohexylcarbodiimide led to the formation of isomeric thiosemicarbazones (TSC It is known [1] that 2-hydroxyphenylglyoxylic acid thiosemicarbazide is formed by the action of thiosemicarbazide on courmarindione in anhydrous media. We extended this reaction to thiosemicarbazides Ia-e and synthesized the desired 1-acylthiosemicarbazides IIa-e (Table 1).

Their IR spectra contain two intense absorption bands at 1650 (ketone C=O) and 1700 cm^{-1} (amide C=O). In addition to the singlet of a phenolic hydroxyl group (10-11 ppm) and an aromatic multiplet (4H) at 6-8 ppm, the PMR spectra of II contain broad $N_1=H$ and $N_2=H$ singlets (10.5 and 9.0 ppm, respectively) and a characteristic thioamide two-proton signal at 7.1-7.8 ppm, which vanished in the case of substitution of homologs IIb, e.

When thiosemicarbazides IIa, b, d, e are heated briefly in polar solvents, they lose water and are converted to 6-oxo-1,2,4-triazine-3-thiones (IIIa, b, d, e) (Table 2). Their IR spectra have C=N (1630) and C=O (1670-1700 cm^{-1}) absorption. On passing from II to triazines III, the signal of the thioamide group vanishes in the PMR spectrum, but the multiplets of four aromatic protons (6.2-8.6 ppm) and the hydroxyl singlet ($\sim$ 11.5 ppm) are retained. The signal of a proton attached to N_1 (13.5 ppm), is present only in the case of IIIa, c, whereas the N_2-H proton is not observed in the spectra of any one of the compounds, although the results of integration of the spectra indicate that it is present.

When IIa, e are heated in alkaline media, they are rapidly converted to the isomeric 3-acyl-Δ^2-1,2,4-triazoline-5-thiones (IVa, e), which are also readily obtained by treatment of starting thiosemicarbazides IIa, e with alkali. Like III, these substances have bands of C=N and C=O bonds (1630 and 1700 cm^{-1}) in their IR spectra but differ markedly from them with respect to their UV absorption and chromatographic behavior (Table 2). The PMR spectra of IVa, e at weak field are characterized by an aromatic multiplet (4H) at 6.5-8.6 ppm, and the labile protons of the five-membered ring and the phenolic hydroxyl group give an averaged broad signal at $\sim$14.5 ppm.

Chemical proof of the structure of triazolines IV is their ability to form derivatives involving the carbonyl group; this ability distinguishes them from the isomeric triazines III [2,4-dinitrophenylhydrazone V (Table 2) was isolated and characterized].

It is interesting to note that triazolines IVa, e are reconverted to triazines III even on brief standing in polar solvents. Thus the III$\rightleftharpoons$IV recyclization is reversible. It can be considered to be intramolecular transamination that proceeds in neutral media at the more active ketone carbonyl group and in alkaline media at the amide carbonyl group, which is also in agreement with the cyclization of starting thiosemicarbazides II.*

Another scheme consists in cyclization of the TSC of α-keto acids – products of condensation at the carbonyl group rather than at the carboxyl group. This scheme, which leads to the corresponding 5-oxo-1,2,4-triazine-3-thiones, is well known [3, 4], and we examined it in part as applied to the TSC of 2-substituted phenylglyoxylic acids [5-7].

Our correlated data, which are necessary for comparison of the characteristics of the isomeric TSC and thiosemicarbazides II, as well as their derivatives – triazoles IV and triazines III – with the isomeric products of cyclization of the TSC, are presented below. Thiosemicarbazones VI-XIa-c (Table 3) were synthesized for this purpose. Their UV spectra are of the same type but differ substantially from the UV spectra of thiosemicarbazides II. Intense C=O absorption at 1700-1740 cm^{-1} and a band of medium intensity at 1560-1600 cm^{-1} (C=N) are present in the IR spectra of TSC VI-XI. In addition to an aromatic multiplet at 6.8-8.0 ppm, their PMR spectra contain a signal of a $CSNH_2$ grouping (2H) at 8-9 ppm, which vanishes when it is replaced by a $CSN(CH_3)_2$ grouping. The signals of COOH and NH protons, as well as of a hydroxyl group in the 2 position (for VIIa, b) and a COOH group (for TSC XIa-c), because of exchange processes, do not show up or give broad unreliably identifiable resonance bands at weak field.

Thiosemicarbazones VI-XIa, b undergo cyclization to 1,2,4-triazines XII-XVIIa, b (Table 4) when they are heated in alkaline media. In contrast to the starting TSC, the signal of a ring thioamide group (2H) vanishes in the PMR spectra of the cyclization products, and the labile protons of the triazine ring and of the substituent in the 2 position of the benzene ring resonate in the form of an averaged signal at 13.8-14.0 ppm, which, when the solution is heated, is shifted to strong field, undergoes broadening, and finally vanishes as the temperature is raised. The presence of this sort of temperature-sensitive signal in this region can be assumed to be a characteristic feature of the PMR spectra of triazines XII-XVII that distinguishes them from isomeric triazines

*Closing to a 1,2,4-triazole ring in alkaline media is a characteristic property of 1-acylthiosemicarbazides [2].

TABLE 1. 2-Hydroxyphenylgyloxylic Acid Thiosemicarbazides IIa-e

Compound	mp, °C	Empirical formula	Found, %		Calc., %		TLC data			UV spectra in dioxane		Yield, %
			N	S	N	S	adsorbent	eluent	R_f	λ_{max}, nm	lg ε	
IIa	181[1]	$C_9H_9N_3O_3S$	17,9	13,4	17,6	13,4	B	Acetone–acetic acid, 15:1	0,14	255 354	4,26 3,55	78
IIb	150	$C_{10}H_{11}N_3O_3S$	16,7	12,7	16,6	12,7	A	Chloroform–methanol, 10:1	0.40	252 354	4,27 3,52	78
IIc	153	$C_{11}H_{13}N_3O_3S$	16,0	11,8	15.7	12.0	A	Same	0.60	252 345	4,27 3,75	88
IIe	180	$C_{10}H_{11}N_3O_3S$	14,7	11,0	14,2	10,9	A	Benzene–acetonitrile, 4:1	0,23	255 338	4,41 3,68	86
IId	160	$C_{13}H_{17}N_3O_3S$	16,3	12,8	16.6	12,7	A	Chloroform–methanol, 5:1	0.57	260 339	4,36 3,63	90

TABLE 2. 1,2,4-Triazines III and 1,2,4-Triazolines IV from Thiosemicarbazides II

Compound	mp, °C (crystallization solvent)	Empirical formula	Found, %		Calc., %		TLC data			UV spectra in ethanol		Yield, % (synthetic method)
			N	S	N	S	adsorbent	eluent	R_f	λ_{max}, nm	lg ε	
IIIa	296 (DMF)	$C_9H_7N_3O_2S$	19,3	14,7	19,0	14,5	A	Benzene–acetic acid 7,5:1	0,42	248 302 393	3,92 3,90 3.77	23 (a) 27 (b) 76 (c)
IIIb	237 (ethanol)	$C_{10}H_9N_3O_2S$	17,9	13,4	17.9	13,6	A	Benzene–acetonitrile, 1:1	0.46	290 381	4.40 3.82	50 (a)
IIId	212 (n-butanol)	$C_{10}H_9N_3O_2S$	18,2	14,0	17,9	13,6	A	"	0.95	247 303 405	3,97 4.02 3,93	49 (a)
IIIe	127 (ethanol)	$C_{13}H_{15}N_3O_2S$	15,6	11,9	15,2	11,6	A	"	0.84	247 304 408	3,94 4,00 3.91	50 (a) 70 (c)
IVa	262 (n-butanol)	$C_9H_7N_3O_2S$	19.3	14,5	19.0	14,5	B	Benzene–acetic acid, 10:1	0.67	257 374	4.25 3,85	88 (a) 64 (b)
IVe	64*	$C_{13}H_{15}N_3O_2S$	15,4	11,7	15,1	11,5	A	Benzene–acetonitrile, 4:1	0.26	277 367	4,20 3,68	84 (a) 72 (b)
V	228 (methanol)	$C_{15}H_{17}N_7O_5S$	24,6	8,1	24,4	8.0	A	Benzene–acetic acid, 7,5:1		247 393	4,57 4,31	49

* This compound was converted to IIIe on recrystallization.

III and triazoles IV. The correlated comparison of the spectral characteristics seems of interest in connection with the fact that the action of thiosemicarbazides Ia, b on coumarindione in aqueous media does not give thiosemicarbazides IIa, b but rather TSC VIIa, b, the subsequent cyclization of which gives isomeric thiazines XIIIa, b instead of cyclic products IIIa, b or IV a, b.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The UV spectra of $5 \cdot 10^{-5}$ M alcohol solutions of the compounds were recorded with an SF-8 spectrophotometer. The PMR spectra of 10% solutions of the compounds in dimethyl sulfoxide (DMSO), which served as the standard, were measured with a Tesla BS-487 spectrometer (80 MHz). The homogeneity of the substances was monitored by thin-layer chromatography (TLC) on Silufol UV-254 (adsorbent A) and Al_2O_3 (adsorbent B) plates.

TABLE 3. Phenylglyoxylic Acid Thiosemicarbazones VI-XI

Compound	mp, °C (crystallization solvent)	Empirical formula	Found, %		Calc., %		UV spectra in ethanol		Yield, %
			N	S	N	S	λ_{max}, nm	log ε	
VIa	188[8, 19] (water)	$C_9H_9N_3O_2S$	18,4	14,3	18,8	14,4	237 315	4,20 4,53	80
VIb	165[20] (ether)	$C_{10}H_{11}N_3O_2S$	17,6	13,8	17,7	13,8	255 313	4,40 4,35	90
VIc	134 (ethanol)	$C_{11}H_{13}N_3O_2S$	17,0	12,7	16,7	12,8	282 308	4,38 4,40	85
VIIa	206[6] (aqueous methanol)	$C_9H_9N_3O_3S$	17,7	13,2	17,6	13,4	213 309	4,14 4,25	73
VIIb	189 (methanol)	$C_{10}H_{11}N_3O_3S$	16,6	12,6	16,6	12,7	209 270 322	4,36 4,10 3,75	70
IXa	219[7] (aqueous ethanol)	$C_9H_8BrN_3O_2S$	13,9	10,9	13,9	10,6	252 305	4,05 4,44	94
IXb	156[7] (acetone – petroleum ether)	$C_{10}H_{10}BrN_3O_2S$	13,5	10,4	13,3	10,1	—	—	89
Xa	190[5] (water)	$C_9H_8N_4O_4S$	21,2	12,1	20,9	12,0	240 303	4,41 4,16	58
Xb	145[7] (acetone – petroleum ether)	$C_{10}H_{10}N_4O_4S$	19,7	11,3	19,8	11,4	245 300	4,28 4,16	47
Xc	147 (ethanol)	$C_{11}H_{12}N_4O_4S$	19,2	10,7	18,9	10,8	275 305	4,42 4,26	74
XIa	188 (ethanol)	$C_{10}H_9N_3O_4S$	15,9	12,3	15,7	12,0	232 307	4,40 4,51	63
XIb	190 (ether)	$C_{11}H_{11}N_3O_4S$	14,9	11,2	14,9	11,4	270	4,57	68
XIc	142 (aqueous ethanol)	$C_{12}H_{13}N_3O_4S$	14,5	10,9	14,2	10,8	277 302	4,30 4,26	58

TABLE 4. 1,2,4-Triazines XII-XVII

Compound	mp, °C (crystallization solvent)	Empirical formula	Found, %		Calc., %		TLC data			UV spectra in ethanol		Yield, %
			N	S	N	S	adsorbent	eluent	R_f	λ_{max}, nm	lg ε	
XIIa	257[18, 19] (ethanol)	$C_9H_7N_3OS$	20,5	15,8	20,5	15,6	A	Benzene – acetonitrile, 2:1	0,67	283 336	4,78 4,27	98
XIIb	199[20] (ethanol)	$C_{10}H_9N_3OS$	19,3	14,5	19,2	14,6	A	Same	0,76	284 320	4,38 4,13	97
XIIIa	266[6] (n-propanol)	$C_9H_7N_3O_2S$	19,0	14,4	19,0	14,5	B	Benzene – acetic acid, 10:1	0,67	282 343	4,36 3,88	79
XIIIb	197 (ethanol)	$C_{10}H_9N_3O_2S$	18,1	13,2	17,9	13,6	A	Chloroform–methanol, 10:1	0,56	280 344	4,45 4,20	86
XIVa	330[6] (ethanol)	$C_9H_8N_4OS$	25,7	14,5	25,4	14,5	A	Benzene – acetonitrile, 2:1	0,56	278 390	4,52 4,32	72
XV	235[7] (n-propanol)	$C_{10}H_8BrN_3OS$	14,3	10,9	14,1	10,8	A	Same	0,73	277 334	4,57 3,93	83
XVIa	217[5] (ethanol)	$C_9H_6N_4O_3S$	22,6	12,8	22,4	12,8	A	„ „	0,60	272 324	4,66 4,02	94
XVIb	247[7] (acetic acid)	$C_{10}H_8N_4O_3S$	20,9	11,9	21,2	12,1	A	Ethyl acetate heptane 3:2	0,50	274 338	4,37 3,75	55
XVIIa	262[4] (ethanol)	$C_{10}H_7N_3O_3S$	16,8	12,7	16,8	12,9	A	Benzene – acetonirile, 2:1	0	278 320	4,51 3,99	93
XVIIb	228 (ethanol)	$C_{10}H_9N_3O_3S$	15,6	12,0	16,0	12,2	A	Same	0	258 292	4,15 3,99	54

Phenylglyoxylic [9], 2-bromo- [7, 10] and 2-nitrophenylglyoxylic [11], and phthalonic [12] acids and thiosemicarbazides Ib [13, 14], Ic [15, 16], Id [15, 17], and Ie [15] were obtained by known methods.

2-Hydroxylphenylglyoxyclic Acid Thiosemicarbazides (IIa-e). A 0.01-mole sample of thiosemicarbazide Ib, c and 12 ml of acetic acid were added at room temperature to a mixture of 0.01 mole of coumarindione, and the mixture was shaken. In the preparation of IIa, the coumarindione was added to a solution of the thiosemicarbazide, whereas in the case of IId, e the thiosemicarbazide was added to a solution of coumarindione in acetic acid. The reaction time was 15 min for IIb, as compared with 30 min for the remaining compounds. After several hours, the mixture was filtered, and the solid material was washed with acetic acid (two 2-ml portions) and repeatedly with ether, after which it was dried over P_2O_5. Thiosemicarbazides IIa, b, d, e undergo partial cyclization to IIIa, b, d, e under the recrystallization conditions.

5-(2-Hydroxyphenyl)-6-oxo-1,3,4-triazine-3-thiones (IIIa, b, d, e). A) A 0.01-mole sample of thiosemicarbazide IIa was refluxed in 8 ml of acetic acid for 10 min. In the case of IIb, d, e, the amount of acid was increased to 15 ml, and the heating time was increased to 2 h. The mixture was allowed to stand at room temperature for 4 h, after which it was filtered and the solid material was washed with acetic acid (3 ml) and ether (three 3-ml portions) and dried at 110°.

B) A solution of 0.01 mole of thiosemicarbazide II a in 50 ml of alcohol was refluxed for 3 h, and the hot suspension was filtered. The solid material was washed with hot alcohol (two 10-ml portions) of ether and dried.

C) A 0.01-mole sample of IVa or IVe was dissolved in 60 ml of DMSO, and the solution was heated at 100° for 30 min. It was then diluted with water, and the resulting precipitate was filtered, washed with DMSO (two 5-ml portions) and water (five 2-ml portions), and dried to give IIIa and IIIe.

3-(2-Hydroxybenzoyl)-Δ^2-1,2,4-triazoline-5-thiones (IVa and IVe). A 0.01-mole sample of thiosemicarbazide IIa in 14 ml of 1 M NaOH or of IIe in 30 ml of 1 M NaOH was refluxed for 4 h, after which it was allowed to stand at room temperature for several hours. The solid material was removed by filtration and recrystallized.

2,4-Dinitrophenylhydrazone V. A 1-g sample of triazolinethione IVa was refluxed in 10 ml of DMSO with 1 g of 2,4-dinitrophenylhydrazine, previously dissolved in 2 ml of concentrated H_2SO_4 and 15 ml of alcohol, for 3 h. The mixture was cooled and diluted with 50 ml of water, and the resulting precipitate was removed by filtration and recrystallized.

2-Substituted Phenylglyoxylic Acid Thiosemicarbazones (VI-XI) and 2-Nitrophenylglyoxylic Acid Thiosemicarbazone (Xa). Boiling solutions of 3.8 g of 2-nitrophenylglyoxylic acid in 6 ml of water and 1.75 g of thiosemicarbazide in 10 ml of water were mixed, and the mixture was refluxed for 2 min and allowed to stand at room temperature for 1 h. The solid material was removed by filtration, washed with water, and dried over P_2O_5. Thiosemicarbazones VI and IX-XIa, b, c, were similarly obtained (Table 3).

2-Hydroxyphenylglyoxylic Acid Thiosemicarbazones (VIIa, b). These compounds were obtained from thiosemicarbazide and coumarindione in water.

2-Aminophenylglyoxylic Acid Thiosemicarbazone (VIIIa). This compound could not be isolated, since it is unstable and immediately forms triazine XIVa in alkaline media.

5-Oxo-1,2,4-triazine-3-thiones (XII-XVII). A 0.01-mole sample of thiosemicarbazone VIa was dissolved in 15-20 ml of 1 M NaOH, and the solution was refluxed for 5 h. It was then cooled and acidified to pH 3-4 with concentrated HCl, and the resulting precipitate was removed by filtration and recrystallized (Table 4). The remaining derivatives were similarly synthesized.

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