Method (2). One gram of 3-methyl-7-methylthio-v-triazolo(d)pyrimidine was placed in 75 ml. of ammonium hydroxide, and the solution was refluxed for 2 hr. The mixture was then cooled to yield 0.8 g. of product which was found to be identical to that produced by method (1) as judged by mixed melting point behavior.

Preparation of 7-alkylthio-5-amino-v-triazolo(d)pyrimidines. (See Table III). Example A. *5-Amino-7-methylthio-v-triazolo(d)pyrimidine* (XXII). Ten grams of 6-methyl-2,4,5-triaminopyrimidine[14] was added to 30 ml. of acetic acid and 100 ml. of water. The solution was stirred, and 6 g. of sodium nitrite, in 24 ml. of water, was added dropwise over a period of approximately 20 min. The mixture was then allowed to stir an additional 30 min., and the precipitate was filtered and washed with water to give 3.4 g. of product. A small portion was recrystallized from a water-methanol solution to give a melting point of 282–284° dec.

Anal. Calcd. for $C_5H_6N_6S$: C, 33.0; H, 3.3; N, 46.2. Found: C, 33.3; H 3.5; N, 46.5.

Example B. 5-Amino-7-(p-chlorobenzylthio)-v-triazolo(d)-pyrimidine. Ten grams of 6-*p*-chlorobenzylthio-2,4,5-triaminopyrimidine[14] was added to 50 ml. of acetic acid and 150 ml. of water. Ten grams of sodium nitrite, in 40 ml. of water, was then added dropwise over a period of approximately 20 min. The mixture was then allowed to stir an additional hour. The crude product was collected and reprecipitated from dilute potassium hydroxide by glacial acetic acid to give 3.5 g. of product. A small portion was recrystallized from a water-ethanol solution for analysis, m.p. 242–244° dec.

Anal. Calcd. for $C_{11}H_9N_6S$: C, 45.2; H, 3.1; N, 28.7. Found: C, 45.7; H, 2.8; N, 29.0.

5-Amino-7-methoxy-v-triazolo(d)pyrimidine (XXIII). *Method (1).* Five grams of 5-amino-7-methylthio-v-triazolo-(d) pyrimidine was added to 50 ml. of methanol, and chlorine gas was allowed to bubble through the solution for approximately 20 min. with no external cooling. The product was filtered and washed with water. Recrystallization from water yielded a white crystalline substance, m.p. >300°.

Anal. Calcd. for $C_5H_6N_6O$: C, 36.2; H, 3.6; N, 50.6. Found: C, 36.5; H, 4.1; N, 50.2.

Method (2). To 1 g. of 6-methoxy-2,4,5-triaminopyrimidine sulfate,[15] in 40 ml. of water, was added, with stirring, 0.75 g. of sodium nitrite. The product was filtered and washed with a small amount of cold water to yield 0.7 g., m.p. >300°. An analytical sample was prepared by recrystallization from water. This product was identical with that prepared by method (1), as judged by identical ultraviolet and infrared absorption spectra. At *p*H 11, 5-amino-7-methoxy-v-triazolo(d)pyrimidine exhibits absorption maxima λ max. 291, mμ, ε 7,300; at *p*H 1, λ max. 283 mμ, ε 12,800, and λ max. 236 mμ, ε 8,800.

Anal. Calcd. for $C_5H_6N_6O$: C, 36.2; H, 3.6; N, 50.6. Found: C, 35.8; H, 3.5; N, 50.2.

TEMPE, ARIZ.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF LJUBLJANA]

Reaction of 4-Arylthiosemicarbazides with Some α-Keto Acids and Synthesis of Some Substituted 3-Thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazines[1a]

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4-Arylthiosemicarbazides were treated with glyoxylic, pyruvic, and benzoylformic acids to form derivatives of 3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazines *via* the corresponding intermediate thiosemicarbazones. The thione-thiol tautomerism of these substances is discussed.

It is well known that with thiosemicarbazones of α-keto acids ring closure can occur with the formation of derivatives of 3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine (II) and these were reviewed recently.[1b] Besides the above-mentioned method of preparation they were prepared also from thiosemicarbazide and oximes of α-keto esters.[2,3] All these derivatives represent mainly 6-substituted derivatives. Known are also 2-substituted derivatives, formulated as 2-alkyl-3-mercapto-5-oxo-2,5-dihydro-1,2,4-triazines, which can be in turn prepared from 2-alkylthiosemicarbazides and α-keto acids.[4–7] Of 4-substituted derivatives only some alkyl derivatives are known[3,8,9] and the cyclization failed in the case of the benzyl derivative.[9] It was therefore desirable to study the cyclization of products, obtained from condensation of 4-substituted thiosemicarbazides with α-keto acids, and the tautomerism associated with these compounds.

The cyclization of thiosemicarbazones could be achieved by refluxing an ethanolic solution, except in the case of 4-arylthiosemicarbazones of glyoxylic acid. The use of an alkaline solution was therefore attempted as it is known that the cyclization of 2-alkylthiosemicarbazones of phenylpyruvic acid proceeds with great facility in dilute sodium hydroxide solution.[7] Such cyclization failed with 4-arylthiosemicarbazones of pyruvic acid and the compounds could be recovered unchanged, but in the case of some 4-arylthiosemicarbazones of glyoxylic acid the molecules were split into the corresponding *N*-arylthioureas (III).

(1a) Part VI of this series, *Arch. Pharm.*, **292/64**, 90 (1959).

(1b) J. G. Erickson, P. F. Wiley, and V. P. Wystrach, *The 1,2,3- and 1,2,4-Triazines, Tetrazines and Pentazines*, Interscience Publishers, New York, 1956, p. 78.

(2) A. Godfrin, *J. pharm. chim.*, **30**, 321 (1939).

(3) R. E. Hagenbach, E. Hodel, and H. Gysin, *Angew. Chem.*, **66**, 359 (1954).

(4) E. Cattelain, *Bull. soc. chim. France*, **11**, 249 (1944).

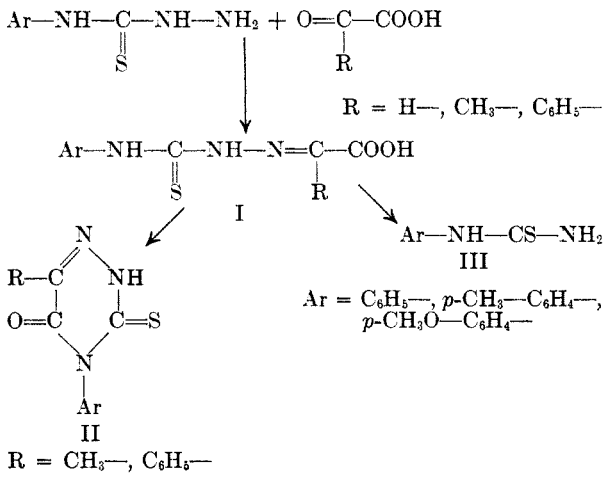
(5) E. Cattelain, *Bull. soc. chim. France*, **12**, 39 (1945).

(6) E. Cattelain, *Compt. rend.*, **208**, 1656 (1939).

(7) E. Cattelain, *Compt. rend.*, **210**, 301 (1940).

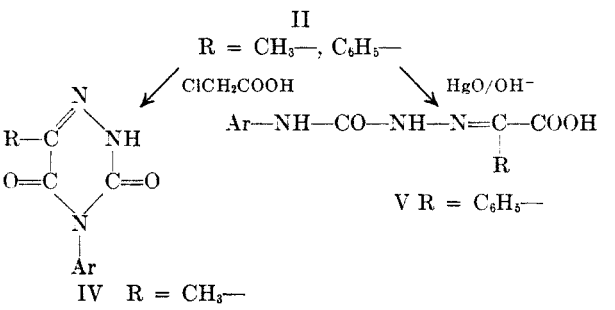
(8) E. Cattelain, *Bull. soc. chim. France*, **11**, 273 (1944).

(9) E. Cattelain, *Compt. rend.*, **210**, 763 (1940).



These findings are completely contrary to those of semicarbazones of α-keto acids where the cyclization in alkaline solution took place in the case of glyoxylic acid,[10] but failed with pyruvic acid.[11,12]

The replacement of the sulfur atom in the 3-thioxo compounds (II) with oxygen leads to substituted 6-azauracils. 6-Azauracil (IV. Ar = R = H; 3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine), the simplest member of the series, evoked particular interest after the discovery of its bacteriostatic[13–15] and antitumor[13,16,17] activity, particularly as ribofuranoside.[18] For the purpose of metabolic studies also labeled 6-azauracil was synthesized[19–22] and recently new 5-alkyl-6-azauracils were prepared.[23] The replacement of the sulfur atom was best accomplished with a boiling 20% aqueous solution of monochloroacetic acid, however only when one aromatic substituent was in the ring. In the case of the 4,6-diphenyl compound (II. Ar = R = C_6H_5—) and other similar compounds this reagent proved to be ineffective and an alkaline suspension of yellow mercuric oxide was used. Instead of the expected reaction the splitting of the molecule occurred and thus the 4,6-diphenyl compound (II. Ar = R = C_6H_5—) afforded the 4-phenylsemicarbazone of benzoylformic acid (V. Ar = R = C_6H_5—).



All known derivatives of 3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine, *e.g.*, the 2- and 6-substituted compounds are formulated as existing in the thiol form,[1,3,24] as 3-mercapto-5-oxo-2,5-dihydro-1,2,4-triazines. The presence of the thiol form was postulated on the basis of the observed acidity and the conversion of these compounds with aqueous iodine or cupric sulfate into the corresponding disulfides. It was not taken into account that the disulfides are also acidic and form colored complexes with cuprous and cupric ions.

The cyclization products we obtained did not react in an ethanolic solution with aqueous iodine solution and the infrared spectra showed no absorption bands in the 2600–2550 cm.$^{-1}$ region, characteristic for the mercapto group.[25] The spectra were determined as mulls in hexachlorobutadiene and Nujol and some as solutions in carbon disulfide. Moreover, further evidence could be obtained from the ultraviolet spectra as in the case of 2-mercaptobenzothiazoles[26–28] where the thione-thiol tautomerism was thus extensively studied. The only recorded ultraviolet spectrum was that of the 2-phenyl-4,6-dimethyl compound.[29] The comparison of the ultraviolet spectra of some of our compounds in ethanolic solution and in alkaline solution also clearly support the presence of the thione form in the solid state and neutral solutions, and excludes their formulation as VI which is to be favored in alkaline solution. In alcoholic solution the compounds show absorption maxima at 2740–2880 Å and the compounds with two aromatic substituents in the ring show, in ethanol an additional absorption band in the 3210–3340 Å region compared with those triazines bearing only one aromatic substituent. The absorption spectra of alcoholic solutions of II (Ar = R = C_6H_5—, λ_{max} 2840 and 3500 Å and Ar = p-CH_3-C_6H_4—, R = CH_3—, λ_{max} 2740 Å) differ markedly from those of alkaline solutions with only one maximum at 3200 Å (II.

(10) W. Seibert, *Ber.*, **80**, 494 (1957).
(11) J. Bougalt, *Ann. chim. (Paris)*, **5**, 317 (1916).
(12) J. Bougalt, *Compt. rend.*, **159**, 83 (1914).
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(14) R. E. Handschumacher and A. D. Welch, *Federation Proc.*, **15**, 267 (1956).
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(16) M. T. Hakala, L. W. Law, and A. D. Welch, *Proc. Am. Assoc. Cancer Research*, **2**, 113 (1956).
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(22) P. K. Chang, T. L. V. Ulbricht, *J. Am. Chem. Soc.*, **80**, 976 (1958).
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(25) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, New York, 1954, p. 288.
(26) H. P. Koch, *J. Chem. Soc.*, 401 (1949).
(27) R. A. Morton and A. L. Stubbs, *J. Chem. Soc.*, 1321 (1939).
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(29) J. A. Elvidge and F. S. Spring, *J. Chem. Soc.*, S 135 (1949).

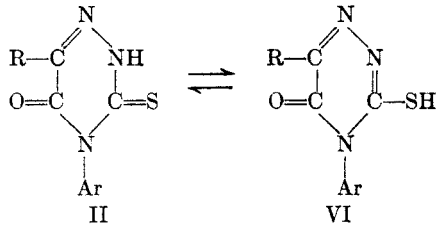
TABLE I

4-ARYLTHIOSEMICARBAZONES OF α-KETO ACIDS

Ar—NH—CS—NH—N=C(R)COOH

Compound No.	Ar	R	M.P., °	Formula	Analyses Calcd. % C	% H	% N	Found % C	% H	% N	UV spectrum (C_2H_5OH) $\lambda_{max.}$ Å	ϵ
1	Phenyl-	H	138	$C_9H_9O_2N_3S$	48.43	4.06	18.83	48.35	4.18	18.80	2940	29780
2	*p*-Tolyl-	H	147	$C_{10}H_{11}O_2N_3S$	50.63	4.67	17.72	50.75	4.85	17.68	2960	23240
3	*p*-Methoxyphenyl-	H	141	$C_{10}H_{11}O_3N_3S$	47.43	4.38	16.60	47.61	4.56	16.75	2940	24800
4	Phenyl-	Methyl-	186	$C_{10}H_{11}O_2N_3S$	50.63	4.67	17.72	50.60	4.72	17.59	2940	24000
											2980	23580
											3040	23580
5	*o*-Ethoxyphenyl-	Methyl-	174	$C_{12}H_{15}O_3N_3S$	51.24	5.38	14.94	51.22	5.38	15.15	3020	24220
6	*m*-Tolyl-	Methyl-	184	$C_{11}H_{13}O_2N_3S$	52.58	5.22	16.73	52.47	5.36	16.81		
7	*o*-Methoxyphenyl-	Methyl-	178	$C_{11}H_{13}O_3N_3S$	49.43	4.90	15.73	49.58	5.07	15.75		
8	*p*-Methoxyphenyl-	Methyl-	205	$C_{11}H_{13}O_3N_3S$	49.43	4.90	15.73	49.41	4.98	15.52		
9	*p*-Chlorophenyl-	Methyl-	195	$C_{10}H_{10}O_2N_3SCl$	44.20	3.71	15.47	44.26	3.93	15.58		

Ar = R = C_6H_5—) and 2800–2810 Å (II. Ar = *p*-CH_3-C_6H_4, R = CH_3—), respectively. On the basis of all above-mentioned indications these compounds are best represented as substituted 3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazines (II).



II VI

On the basis of the infrared spectra where typical carbonyl frequencies can be found (for example IV. Ar = C_6H_5—, R = CH_3—, at 1704 cm.$^{-1}$), the desulfurized compounds are represented most likely as derivatives of 3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine, while the dihydroxy form was not excluded by Bougalt[11,12] with similar compounds. Furthermore, the dioxo compounds show absorption maxima in the ultraviolet spectrum at about 2640–2660 Å and the spectra closely resemble those of 6-methyluracils.[30]

EXPERIMENTAL[31]

Condensation of 4-substituted thiosemicarbazides with α-keto acids. The condensation could be effected in acid or alkaline solution:

(a) To a solution of 4-arylthiosemicarbazide in hydrochloric acid (1:8) an equimolar quantity of an aqueous solution of α-keto acid (0.01 mole) was added and after a few minutes a precipitate of the thiosemicarbazone could be collected.

(b) To a cold alkaline solution of the α-keto acid (0.01 mole) was added an equimolar amount of solid 4-arylthiosemicarbazide. After standing for 15 min. the unchanged thiosemicarbazide was filtered off and after acidification of the filtrate the condensation product was obtained.

(30) R. N. Lacey and W. R. Ward, *J. Chem. Soc.*, 2134 (1958).

(31) All melting points were determined with Kofler's heating microscope.

For the preparation of compounds listed in Table I the following example is illustrative.

4-p-Tolylthiosemicarbazone of pyruvic acid. To a stirred solution of 4-*p*-tolylthiosemicarbazide (1.81 g.) in dilute hydrochloric acid (1:8, 40 ml.) was added an aqueous solution of pyruvic acid (0.88 g. in 20 ml. water). The precipitate was filtered, washed with dilute hydrochloric acid (1:8, 40 ml.), and finally with water until acid-free. After recrystallization from 20% ethanol the product melted at 192°. Yield: 90%.

Anal. Calcd. for $C_{11}H_{13}O_2N_3S$: C, 52.58; H, 5.22; N, 16.73. Found: C, 52.67; H, 5.01; N, 17.00.

In ethanol λ_{max} 2980 Å, ϵ 22,960.

Cyclization of 4-arylthiosemicarbazones of pyruvic and benzoylformic acid. The following example is illustrative for the preparation of triazines from 4-arylthiosemicarbazones of pyruvic acid.

4-p-Tolyl-6-methyl-3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine. 4-*p*-Tolylthiosemicarbazone of pyruvic acid (2.0 g.) was refluxed in 20% ethanol (30 ml.) for 5 hr. Most of the ethanol and water were then distilled and the residue recrystallized from dilute ethanol (1:4) to give the pure triazine (yield: 51%), m.p. 208°.

Anal. Calcd. for $C_{11}H_{11}ON_3S$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.87; H, 4.80; N, 18.26.

In ethanol λ_{max} 2740 Å, ϵ 16,400; in 0.1*N* sodium hydroxide λ_{max} 2800–2810 Å, ϵ 11,840. Other compounds are listed in Table II. 4-Arylthiosemicarbazones of benzoylformic acid were not isolated and in this case the following procedure, used also for the preparation of other compounds listed in Table II, was applied.

4,6-Diphenyl-3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine. 4-Phenylthiosemicarbazide (2.2 g.) was dissolved in boiling ethanol (30 ml.), benzoylformic acid (2.0 g.) added, and the mixture refluxed for 8 hr. The precipitate, collected after cooling, was recrystallized from ethanol and melted at 285–286°. Yield: 2.05 g. (55%).

Anal. Calcd. for $C_{15}H_{11}ON_3S$: C, 64.05; H, 3.94; N, 14.94. Found: C, 63.93; H, 4.02; N, 14.94. In ethanol λ_{max} 2840 Å, ϵ 23,800 and λ_{max} 3500 Å, ϵ 11,120; in 0.1*N* sodium hydroxide λ_{max} 3200 Å, ϵ 15,940.

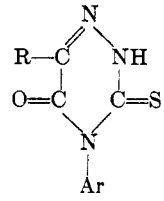
The diphenyl compound, when treated with an ethereal solution of diazomethane, afforded the *N*-methyl derivative which after two recrystallizations from ethanol melted at 211°.

Anal. Calcd. for $C_{16}H_{13}ON_3S$: C, 65.08; H, 4.44; N, 14.23. Found: C, 65.01; H, 4.56; N, 14.38. In ethanol λ_{max} 2840 Å, ϵ 26,260 and λ_{max} 3500 Å, ϵ 14,750.

Conversion of 4-arylthiosemicarbazones of glyoxylic acid into the corresponding N-arylthioureas. The attempted cyclization of 4-arylthiosemicarbazones of glyoxylic acid in ethano-

TABLE II

SUBSTITUTED 3-THIOXO-5-OXO-2,3,4,5-TETRAHYDRO-1,2,4-TRIAZINES



Compound No.	Ar	R	M.P.,°	Formula	Analyses						UV spectrum (C_2H_5OH)	
					Calcd.			Found			λ_{max}, Å	ϵ
					% C	% H	% N	% C	% H	% N		
1	Phenyl-	Methyl-	218.5	$C_{10}H_9ON_3S$	54.79	4.14	19.17	54.75	4.23	19.04	2740	16320
2	*m*-Tolyl-	Methyl-	230–231	$C_{11}H_{11}ON_3S$	56.65	4.75	18.02	56.72	4.83	18.27	2810	17810
3	*o*-Methoxyphenyl-	Methyl-	226	$C_{11}H_{11}O_2N_3S$	53.01	4.45	16.86	52.90	4.41	16.73	2750	16870
4	*p*-Methoxyphenyl-	Methyl-	184–185	$C_{11}H_{11}O_2N_3S$	53.01	4.45	16.86	53.08	4.55	16.64	2790	19630
5	*o*-Ethoxyphenyl-	Methyl-	150	$C_{12}H_{13}O_2N_3S$	54.75	4.98	15.96	54.62	4.92	15.82	2740	19850
6	*p*-Chlorophenyl-	Methyl-	224–225	$C_{10}H_8ON_3SCl$	47.34	3.18	16.56	47.36	3.25	16.57	2885	23540
7	*o*-Tolyl	Phenyl-	235–236	$C_{16}H_{13}ON_3S$	65.08	4.44	14.23	65.16	4.61	14.16	2850	19130
											3340	10240
8	*m*-Tolyl-	Phenyl-	263–264	$C_{16}H_{13}ON_3S$	65.08	4.44	14.23	64.99	4.43	14.07	2855	18980
											3280	13430
9	*p*-Tolyl-	Phenyl-	307–308	$C_{16}H_{13}ON_3S$	65.08	4.44	14.23	65.12	4.48	14.36	2855	18540
											3280	16090
10	*p*-Methoxyphenyl-	Phenyl-	290	$C_{16}H_{13}O_2N_3S$	61.73	4.21	13.50	61.76	4.38	13.55	2850	19390
											3285	15890
11	*m*-Chlorophenyl-	Phenyl-	250–251	$C_{15}H_{10}ON_3SCl$	57.05	3.19	13.31	56.92	3.08	13.48	2880	16040
											3230	17610
12	*p*-Chlorophenyl-	Phenyl-	318–320	$C_{15}H_{10}ON_3SCl$	57.05	3.19	13.31	57.01	3.27	13.35	2880	16660
											3210	17130

lic solution was not successful and therefore an alkaline medium was used. When the 4-phenylthiosemicarbazone of glyoxylic acid was refluxed with a 1M aqueous solution of potassium carbonate the compound at first dissolved, but after a few minutes a precipitate formed. The mixture was refluxed for 10 min. more, the solid filtered and crystallized from alcohol. The compound was identified as *N*-phenylthiourea, m.p. 154°, undepressed with an authentic specimen.

In the same way the formation of *N*-*p*-tolylthiourea (m.p. 188°) and *N*-*p*-methoxyphenylthiourea (m.p. 210°) was observed.

Desulfurization of derivatives of 3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine. 4-Phenyl-6-methyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine. The 3-thioxo compound (1.87 g.) was heated with aqueous monochloroacetic acid (9 ml. of 20%) and from the resulting solution a precipitate soon formed. After 5 hr. of refluxing the precipitate was collected, washed with water, and recrystallized from hot water, m.p. 242.5°. Yield: 0.7 g. (35%); in ethanol λ_{max} 2640 Å, ϵ 6360.

Anal. Calcd. for $C_{10}H_9O_2N_3$: C, 59.10; H, 4.46; N, 20.68. Found: C, 58.98; H, 4.60; N, 20.65.

4-p-Tolyl-6-methyl-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine was prepared by essentially the same procedure as above, starting from 1 g. of 3-thioxo compound. After recrystallization from water (0.62 g., 67% yield) the substance melted at 248°. In ethanol λ_{max} 2660 Å, ϵ 6270.

Anal. Calcd. for $C_{11}H_{11}O_2N_3$: C, 60.82; H, 5.10; N, 19.35. Found: C, 60.85; H, 5.18; N, 19.18.

Attempted desulfurization of 4,6-diphenyl-3-thioxo-5-oxo-2,3,4,5-tetrahydro-1,2,4-triazine. When the diphenyl compound (0.1 g.) was dissolved in 1*N* sodium hydroxide (10 ml.) with gentle heating and freshly precipitated mercuric oxide (1 g.) was added, this instantly turned black. After 5 min. of thorough mixing, the mixture was filtered and the clear filtrate acidified with dilute hydrochloric acid. The precipitate was collected and recrystallized from ethanol, m.p. 184°.

Anal. Calcd. for $C_{15}H_{13}O_3N_3$: C, 63.59; H, 4.63; N, 14.83. Found: C, 63.43; H, 4.96; N, 14.77.

This compound (V, Ar = R = C_6H_5—) was identical with the synthesized one, *e.g.*, from 4-phenylsemicarbazide and benzoylformic acid, which did not depress its melting point. The diphenyl compound could not be desulfurized with 20% monochloroacetic acid and after 5 hr. of reflux the compound was recovered unchanged. Other diaryl compounds failed to be desulfurized with aqueous monochloroacetic acid.

Acknowledgment. The authors are much indebted to Prof. D. Hadži for recording and interpreting the infrared spectra and to Prof. D. Stucin for some of the ultraviolet spectra.

LJUBLJANA, YUGOSLAVIA