[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF LJUBLJANA]

Reaction of Aryl Isothiocyanates with Ethyl 3-Aminopropionate and Synthesis of 3-Substituted 2-Thio-4-oxohexahydro-1,3-diazines

M. DERŽAJ-BIZJAK, S. OBLAK, AND M. TIŠLER

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The preparations of 3-substituted 2-thio-4-oxohexahydro-1,3-diazines from the corresponding 1-substituted 3-carboxyethylthioureas are described. Under different reaction conditions the formation of substituted 2-imino-6-oxo-1,3-thiazanes has been observed. The 1,3-diazine derivatives exist, on the basis of spectral evidence, in the thione form.

Although the reaction between an isothiocyanate and substituted 3-aminopropionic acid to form 1,3-thiazine derivatives has been known for almost thirty years,[1] it has not been fully investigated. As a part of the investigation on 1,3-thiazine derivatives[2,3] and related compounds in this laboratory, attempts were made to prepare this type of compounds through cyclization of 1-substituted 3-carboxyethylthioureas. There are known few cyclizations of this type as in the case of *N,N'*-di(β-carboxyethylthiocarbamyl)ethylenediamine,[4] 1,3-di(β-carboxyethyl)thiourea,[5] and related compounds. They were accomplished with the aid of polyphosphoric acid,[4] *p*-toluenesulfonic acid,[5] hydrochloric acid,[6,7] or acetic anhydride[1,6] as cyclizing agent. It was also observed that refluxing 1,3-di(β-carboxyethyl)thiourea with acetic anhydride caused both desulfurization and cyclization.[5]

Some 1,3-thiazine derivatives are also formed from acyl derivatives of 3-aminopropionic acid with phosphorus pentasulfide,[8] and Ghosh[1] prepared them from the corresponding substituted carboxyethylthioureas. These were prepared from 3-aminopropionic acid and *o*- or *p*-tolyl isothiocyanate. We repeated this reaction which we regarded as a general one, but we found that only in the case of *o*-tolyl isothiocyanate does the condensation with 3-aminopropionic acid take place. In all other cases a 1,3-diarylthiourea was formed. The variation of reaction conditions and use of different solvents (Methyl Cellosolve, acetone, ethylene glycol) proved to have no advantage. The formation of 1,3-diarylthioureas can be explained through the formation of an unstable intermediate thiocarbamic acid giving rise to an amine which in turn combines with the isothiocyanate forming the thiourea:

$$\mathrm{RNCS} \xrightarrow{\mathrm{H_2O}} \mathrm{RNHCSOH} \longrightarrow \mathrm{RNH_2} + \mathrm{COS}$$
$$\mathrm{RNH_2} \xrightarrow{+\ \mathrm{RNCS}} \mathrm{RNHCSNHR}$$

This reaction competes with the addition reaction involving aryl isothiocyanate and 3-aminopropionic acid. The only exception is in the case of *o*-tolyl isothiocyanate where the lower reactivity[9] and steric effects may influence the reaction course in a way that the formation of the corresponding thiourea is negligible and the condensation takes place. It is noteworthy that a similar reaction was observed in the case of phenyl isocyanate which reacts at moderate temperature with organic acids forming their anhydrides and diphenylurea.[10] Glycine reacts similarily with isothiocyanates giving in each case a mixture of the corresponding diazole and a small quantity of diarylthiourea.[11] When a more reactive isothiocyanate is involved, *e.g.*, benzoyl isothiocyanate, hydrolysis occurred before it could react with an amino acid.[12]

Initially, we tried to prepare the necessary 1-aryl-3-carboxyethylthioureas in several ways. One route to the synthesis of these compounds appeared to lie through the reaction of 1-aryl-3-carboxyethylureas (for example, 1-phenyl-3-carboxyethylurea is easily accessible from phenylurea and 3-aminopropionic acid[13]) with phosphorus pentasulfide. This reaction failed and the necessary thioureas (II) were then successfully prepared by condensing the appropriate aryl isothiocyanate with ethyl 3-aminopropionate in ethanolic solution and subsequent hydrolysis of the esters (I) with sodium ethoxide.

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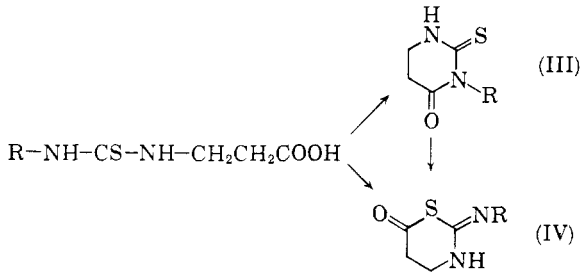
$$R{-}NCS + H_2N{-}CH_2CH_2COOC_2H_5 \longrightarrow R{-}NH{-}CS{-}NH{-}CH_2CH_2COOC_2H_5 \longrightarrow$$

I

$$R{-}NH{-}CS{-}NH{-}CH_2CH_2COOH$$

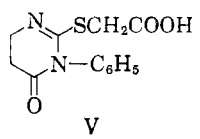
II

These acids were cyclized with acetic anhydride, preferentially with short and gentle heating, into 3-aryl-2-thio-4-oxo-hexahydro-1,3-diazines (III). In some cases, if these conditions were not held and the cyclization was performed with heating the reaction mixture above 70° and for longer periods, 2-arylimino-6-oxo-1,3-thiazanes (IV)[1,14] were obtained in low yields. In the case of the phenyl



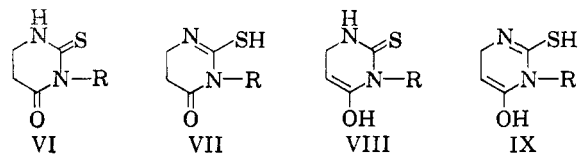
compound (IV. R = C_6H_5) we could establish that it was formed also from the 1,3-diazine (III. R = C_6H_5) when this was heated in an acetic anhydride solution. Another route for preparing our compounds (III) seemed possible *e.g.*, the introduction of sulfur into the 2,4-dioxo compounds, but the reaction left the starting material unchanged.

3 - Aryl - 2 - thio - 4 - oxohexahydro - 1,3 - diazines are colorless substances which are transformed back into the acids when treated with 5% aqueous sodium hydroxide or hydrochloric acid. They gave a positive iodine–azide reaction, indicating thus the presence of a thio group.[15] This reacted also with monochloroacetic acid and the *S*-carboxymethyl compound (V) was obtained. This and the 1,3-thiazine derivatives gave a negative iodine-azide reaction.



V

In order to establish the structure of the cyclized compounds III, the ultraviolet and infrared spectra were recorded and correlated. There are possible different tautomeric forms, for example



VI VII VIII IX

The infrared spectra showed no absorption bands in the 2600–2550-cm.$^{-1}$ region, assignable to the mercapto group,[16] but typical carbonyl frequencies could be found, excluding thus structures VIII and IX. Moreover, further evidence was obtained from the ultraviolet spectra as in the case of different thio group containing heterocycles we have examined recently.[3,17,18] Comparison of the ultraviolet spectrum of 3-phenyl-2-thio-4-oxo-hexahydro-1,3-diazine (III. R = C_6H_5) in ethanolic and alkaline solution clearly indicates the presence of the thione form in neutral solutions. The absorption spectrum of an alcoholic solution of this compound (λ_{max} 2800 Å, ϵ 10,800) differs markedly from that of an alkaline solution (λ_{max} 2300 Å, ϵ 14,300) and a similar difference was observed also with the *p*-methoxyphenyl compound (III. R = *p*-CH_3O—C_6H_4). On the basis of all this spectral evidence, the structure (VI) should be the correct one for 3-aryl-2-thio-4-oxohexahydro-1,3-diazines.

EXPERIMENTAL[19]

Ethyl 3-aminopropionate hydrochloride was prepared from the acid according to the procedure of Abderhalden and Fodor.[20]

Aryl isothiocyanates were prepared by the usual procedure[21] and were purified by distillation before use.

Reaction of aryl isothiocyanates with ethyl 3-aminopropionate. General procedure. A mixture of 0.76 g. (0.005 mole) of ethyl 3-aminopropionate hydrochloride, an ethanolic sodium ethoxide solution (prepared from 0.115 g. of sodium and 5 ml. of absolute ethanol) and aryl isothiocyanate (0.005 mole, was refluxed for 10 min., filtered from inorganic material, and the solvent removed *in vacuo*. The residual oil triturated with 10 ml. water yielded the crystalline product which was recrystallized from ethanol or aqueous ethanol. Physical constants, yields and analytical figures for 1-aryl-3-carbethoxyethylthioureas (I) are compiled in Table I.

The infrared spectrum of the phenyl compound (I. R = C_6H_5) in potassium bromide showed bands at 2.98 and 3.12 μ (assignable to NH groups) and at 5.80 μ (assignable to the ester group).

Preparation of 1-aryl-3-carboxyethylthioureas (II). The prepared ester (0.005 mole) was refluxed with an ethanolic sodium ethoxide solution (prepared from 0.23 g. of sodium

(14) The imino form, although not proved, is postulated on the basis of similarity with derivatives of 2-imino-3,4,5,6-tetrahydro-1,3-thiazine, where it was shown that the imino form is the most probable.[2] Further work dealing with the structure of these compounds is in progress in our laboratory.

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TABLE I

1-SUBSTITUTED 3-CARBETHOXYETHYLTHIOUREAS

R—NH—CS—NH—$CH_2CH_2COOC_2H_5$

Compound No.	R	Yield, %	M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	Phenyl	76	71	$C_{12}H_{16}N_2O_2S$	57.13	57.30	6.39	5.57	11.11	11.00
2	*o*-Tolyl	47.5	80	$C_{13}H_{18}N_2O_2S$	58.63	58.56	6.81	6.89	10.52	10.43
3	*m*-Tolyl	83	78	$C_{13}H_{18}N_2O_2S$	58.63	58.52	6.81	6.91	10.52	10.48
4	*p*-Tolyl	51	80	$C_{13}H_{18}N_2O_2S$	58.63	58.74	6.81	6.81	10.52	10.60
5	*o*-Methoxyphenyl	75.5	116	$C_{13}H_{18}N_2O_3S$	55.31	55.26	6.43	6.60	9.92	9.94
6	*p*-Methoxyphenyl	98.5	96	$C_{13}H_{18}N_2O_3S$	55.31	55.45	6.43	6.52	9.92	10.06
7	*m*-Chlorophenyl	95.5	78	$C_{12}H_{15}ClN_2O_2S$	50.25	50.05	5.27	5.11	9.77	9.75
8	*p*-Chlorophenyl	69.5	95	$C_{12}H_{15}ClN_2O_2S$	50.25	50.27	5.27	5.33	9.77	9.51

TABLE II

1-SUBSTITUTED 3-CARBOXYETHYLTHIOUREAS

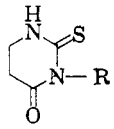
R—NH—CS—NH—CH_2CH_2COOH

Compound No.	R	Yield, %	M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
9	Phenyl	55.5	110	$C_{10}H_{12}N_2O_2S$	53.57	53.61	5.39	5.48	12.50	12.56
10	*o*-Tolyl	70	144[a]	$C_{11}H_{14}N_2O_2S$	55.45	55.56	5.92	6.06	11.76	11.67
11	*m*-Tolyl	65	139	$C_{11}H_{14}N_2O_2S$	55.45	55.47	5.92	5.78	11.76	11.76
12	*p*-Tolyl	63	135[b]	$C_{11}H_{14}N_2O_2S$	55.45	55.56	5.92	5.85	11.76	11.68
13	*o*-Methoxyphenyl	44.5	147	$C_{11}H_{14}N_2O_3S$	51.96	52.06	5.55	5.61	11.02	11.15
14	*p*-Methoxyphenyl	59	127	$C_{11}H_{14}N_2O_3S$	51.96	51.92	5.55	5.57	11.02	10.97
15	*m*-Chlorophenyl	80	138	$C_{10}H_{11}ClN_2O_2S$	46.42	46.28	4.28	4.40	10.83	10.73

[a] Lit.,[1] m.p. 144–145°. [b] Lit.,[1] m.p. 151–152°, but this substance is erroneously formulated as 1-(*p*-tolyl)-3-carbethoxythiourea.

TABLE III

3-ARYL-2-THIO-4-OXO-HEXAHYDRO-1,3-DIAZINES



Compound No.	R	Yield, %	M.P.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
16	*m*-Tolyl	28	210	$C_{11}H_{12}N_2OS$	59.99	59.88	5.49	5.61	12.72	12.88
17	*p*-Tolyl	10	232	$C_{11}H_{12}N_2OS$	59.99	59.92	5.49	5.44	12.72	12.91
18	*p*-Methoxyphenyl[a]	8	236	$C_{11}H_{12}N_2O_2S$	55.93	55.88	5.12	5.13	11.86	11.61
19	*m*-Chlorophenyl	23	231	$C_{10}H_9ClN_2OS$	49.83	49.92	3.76	4.00	11.63	11.69

[a] Ultraviolet spectrum: in ethanol λ_{max} 2800 Å, ϵ 14,800; in 0.1*N* sodium hydroxide λ_{max} 2350 Å, ϵ 9120.

and 5 ml. of absolute ethanol) for 10–15 min. The solvent was evaporated *in vacuo*, some water was added and acidified with hydrochloric acid (1:1). The precipitated acid was collected and recrystallized from ethanol or aqueous ethanol. Physical constants, yields and analytical figures for 1-aryl-3-carboxyethylthioureas (II) are summarized in Table II. The infrared spectrum of 1-phenyl-3-carboxyethylthiourea in potassium bromide showed bands at 2.93 and 3.13 μ (assignable to NH groups) and at 5.91 μ (assignable to the carboxyl group).

3-Phenyl-2-thio-4-oxo-hexahydro-1,3-diazine (III. R = C_6H_5). A mixture of 1-phenyl-3-carboxyethylthiourea (0.3 g.), acetanhydride (5 ml.) and concd. sulfuric acid (1–2 drops) was heated to 60° on a water bath for 5 min. and after cooling to room temperature was introduced with stirring into 20 ml. of water. The colorless crystals (yield, 40%) were separated and recrystallized from ethanol, m.p. 228°.

Anal. Calcd. for $C_{10}H_{10}N_2OS$: C, 58.25; H, 4.89; N, 13.58. Found: C, 58.40; H, 4.98; N, 13.59. In ethanol λ_{max} 2800 Å, ϵ 10,800; in 0.1*N* sodium hydroxide λ_{max} 2300 Å, ϵ 14,300.

Similar results were obtained with compounds 11, 12, 14, and 15 (Table II) and the cyclized products are listed in Table III.

Reaction of aryl isothiocyanates with 3-aminopropionic acid. Formation of 1,3-diarylthioureas. A mixture of the corresponding isothiocyanate (0.01 mole) and 3-aminopropionic acid (0.89 g., 0.01 mole) in ethanol (5 ml.) and water (5 ml.) was refluxed about 3 hr. The product, which crystallized from the reaction mixture on cooling was recrystallized from ethanol. No products obtained depressed the m.p

when admixed with authentic specimens of diarylthioureas, and their infrared spectra were identical. Thus the following 1,3-diarylthioureas were obtained (aryl and yields are given): phenyl- (39%), *m*-tolyl- (28%), *p*-tolyl- (56%) and *p*-chlorophenyl- (67%).

1-(o-Tolyl)-3-carboxyethylthiourea from 3-aminopropionic acid. The same procedure as described above for the formation of 1,3-diarylthioureas was applied. The acid, obtained in 46% yield, was recrystallized from ethanol, m.p. 144°. Mixed m.p. with the compound 10 was undepressed and their infrared spectra were identical.

2-Phenylimino-3,4,5,6-tetrahydro-1,3-thiazin-6-one (IV. R = C_6H_5). If 1-phenyl-3-carboxyethylthiourea was cyclized with acetic anhydride and heated on a water bath at 90° the solution turned yellow and after 1 hr. the mixture was cooled and poured slowly in water. On standing crystals separated (yield, 32%) and upon recrystallization from ethanol the yellow crystals melted at 142°.

Anal. Calcd. for $C_{10}H_{10}N_2OS$: C, 58.25; H, 4.89; N, 13.58. Found: C, 58.13; H, 4.98; N, 13.69.

In ethanol λ_{max} 2460 Å, ϵ 12,160 and 2950 Å, ϵ 10,250.

The same compound was obtained with heating the corresponding 1,3-diazine derivative (III. R = C_6H_5) (0.1 g.) with acetic anhydride (5 ml.) and concd. sulfuric acid (2 drops) on a water bath at about 70° for 2 hr; yield, 8% m.p. and mixed m.p. with the above prepared sample was undepressed.

2-(o-Tolylimino)-3,4,5,6-tetrahydro-1,3-thiazin-6-one (IV. R = *o*-CH_3—C_6H_4) was similarly prepared according the above procedure from the acid in 27% yield. Yellow crystals (from ethanol), m.p. 127°.

Anal. Calcd. for $C_{11}H_{12}N_2OS$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.70; H, 5.69; N, 12.81.

Reactions of 3-phenyl-2-thio-4-oxo-hexahydro-1,3-diazine. A. *With 5% hydrochloric acid.* The compound was heated on a water bath with the acid for 20 min. and on cooling colorless crystals separated which were identified as 1-phenyl-3-carboxyethylthiourea (compound 9), m.p. 110°.

B. *With 5% sodium hydroxide.* The same reaction conditions as above were used. On cooling and acidification the solution was left overnight. The separated crystals were collected and identified as the acid (compound 9), m.p. 110°.

C. *With monochloroacetic acid.* Equivalent amounts of the compound and monochloroacetic acid as 20% aqueous solution were heated under reflux for 30 min. and left overnight. The separated *S*-carboxymethyl compound V upon recrystallization from aqueous acetic acid melted at 126°.

Anal. Calcd. for $C_{12}H_{12}N_2O_3S$: C, 54,54; H, 4,58; N, 10.60. Found: C, 54,31; H, 4,69; N, 10.68.

Acknowledgment. The authors are much indebted to Dr. S. Detoni for recording and interpreting the infrared spectra.

LJUBLJANA, YUGOSLAVIA

[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION OF SMITH KLINE AND FRENCH LABORATORIES AND THE RESEARCH INSTITUTE OF TEMPLE UNIVERSITY]

The Synthesis of Phenothiazines. VII.[1] Methyl- and Arylsulfonylation of Phenothiazine and Its 10-Substituted Derivatives

JOHN J. LAFFERTY, ELEANOR GARVEY, EDWARD A. NODIFF,[2] WALTER E. THOMPSON, AND CHARLES L. ZIRKLE

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3-Methyl-, 3-phenyl-, and 3-*p*-tolylsulfonylphenothiazine were obtained from the reactions of phenothiazine or its 10-sulfonyl derivatives with the corresponding sulfonyl chlorides in the presence of aluminum chloride. The same products also were obtained from the rearrangement of the corresponding 10-sulfonyl derivatives in the presence of aluminum chloride. 3-Methylsulfonylphenothiazine also was prepared by a Smiles rearrangement of 2'-formamido-2-nitro-4-methylsulfonyldiphenyl sulfide.

To provide sulfonylphenothiazines as intermediates for analogs of the tranquilizing agent, chlorpromazine, we studied the Friedel-Crafts reaction of phenothiazine and some of its 10-substituted derivatives with sulfonyl chlorides. No example of the sulfonylation of this ring system has been reported previously, although the corresponding acylation reactions have been studied by various investigators.[3-8]

In acylation reactions of 10-alkylphenothiazines, the entering acyl group orients *para* (3- position) to the phenothiazine nitrogen atom.[5] On the other hand, acylation of 10-acylphenothiazines occurs in the 2-position, *para* to the sulfur atom, to yield 2,10-diacyl derivatives.[4,6-8] In the case of phenothiazine itself, the position of acylation apparently has never been established conclusively.[3,4,7] The reaction, in this case, is complicated by the fact that 10-acylation may occur to a great extent prior to C-acylation.[4] Thus, according to the literature cited, the reactions of phenothiazine with sulfonyl chlorides might be expected to lead to 3-sulfonyl and/or 2,10-disulfonyl derivatives,

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