THE REACTION OF SOME COMPOUNDS CONTAINING THIOAMIDE GROUPS WITH 2,4,6-TRICHLORO-1,3,5-TRIAZINE

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Received November 23, 1965

ABSTRACT

The reaction between some compounds containing thioamide groups and cyanuric chloride was investigated. Evidence is presented that the reaction proceeds on the thioamide sulfur and not on the nitrogen as postulated earlier. The reaction with thiourea was used for the preparation of trithiocyanuric acid, as well as for the preparation of 3-chloro-6(1*H*)-pyridazinethione or 3-mercapto-6(1*H*)-pyridazinethione, and presents a new and convenient method for the synthesis of these compounds.

In connection with our investigations of the reactivity of heterocyclic compounds containing thioamide groups as a part of the ring system (1–4), it seemed of interest to investigate the reaction between compounds with thioamide groups and compounds with reactive halogens, particularly cyanuric chloride. An examination of the literature (5) revealed that the reaction of cyanuric chloride (2,4,6-trichloro-1,3,5-triazine) with different thiosemicarbazones was interpreted as proceeding on the N_2-nitrogen of the thiosemicarbazones. N-(4,6-Dichloro-1,3,5-triazinyl-2)-thioureas are also known, but they were prepared in a different manner (6).

A substantial amount of work on alkylations and acylations of different compounds with thioamide groups has been reported (7). Several recent publications have enlarged the earlier reports on the alkylation or acylation of thioureas (8), thioamides (9), thiosemicarbazides and thiosemicarbazones (10, 11), and heterocyclic compounds containing thioamide groups as a part of the ring system (12–15). In all cases the reaction proceeds with the attack on the thioamide sulfur, except in the reaction between 2-thiobenzothiazoline and diethylaminomethylchloride, in which case a N-substituted product was isolated; this is explained by the predisposition of these compounds to undergo unimolecular substitution (12).

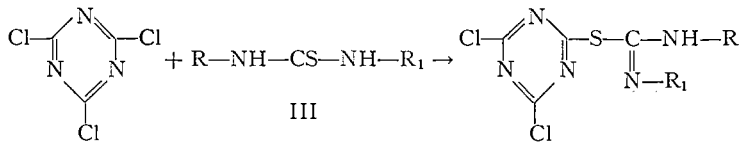
Compounds containing thioamide groups were formerly postulated as reacting in their normal form (I) or in their tautomeric iminothiol form (II). This must certainly not be a

I II

condition, as in recent years the dipolar character of the thioamide group has been established (1, 2, 16–22). Thioamides are protonated on the sulfur atom and not on the nitrogen (23, 24), and the evidence, obtained from measurements of bond distances (25), provides additional support for the dipolar character. Furthermore, alkylations of ambident anions have been discussed (26) and evidence has been presented that the reaction course depends on the character of the transition state.

Finally, one must take into account the possibility of the migration of the initially bound alkyl group. So far, only the spontaneous O → S alkyl migration is known in the case of solid thioisobiuret hydrohalides at room temperature (27), and it seems very unlikely that, under the relatively mild reaction conditions used, a migration from the sulfur of the initially bound triazine would occur to give a N-substituted derivative.

Thus, the reaction between cyanuric chloride and compounds with thioamide groups (III) should proceed preferentially in the direction of the formation of isothiuronium salts or their derivatives; the present findings give a satisfactory basis for such an interpretation of the reaction course.



III IV

Regardless of which compound containing a thioamide group was employed for the reaction with cyanuric chloride, all reaction products gave a negative iodine–azide reaction (28), characteristic of the presence of a mercapto or thiocarbonyl group. This test was positive with all starting compounds containing thioamide groups. An assignment of the thiocarbonyl stretching frequency, which was used for the indication that such a reaction does proceed as N-substitution (5), seems to be very delicate, as this frequency is dependent on the structural environment and falls within a wide range, 1 400 – 1 000 cm^{-1} (29, 30).

Further evidence for the alkylation site could be obtained from the hydrolysis of the alkylation products that were obtained, as this is one of the possible methods of introducing a thiol (thione) group in many heterocyclic systems. The method involving the action of aqueous alkali on isothiuronium salts has superseded most of the others used for the laboratory-scale syntheses (31).

Thiourea, which appears to have the required combination of a considerable nucleophilic power and a weak basic strength ($pK_a = -1.19$) (32), reacted readily with cyanuric chloride or with 3,6-dichloropyridazine; the initially formed isothiuronium salts were then hydrolyzed to the corresponding trithiocyanuric acid (2,4,6-trimercapto-1,3,5-triazine), 3-chloro-6(1*H*)-pyridazinethione, or 3-mercapto-6(1*H*)-pyridazinethione. It is well known that the reactivity of the 1,3,5-triazine system is very great and exceeds the reactivity of different 3-substituted pyridazines (33). This was also observed in the case of the above reaction where, regardless of the amount of the thiourea used in the reaction, the trithiocyanuric acid was always obtained, in a smaller yield of course.

Some evidence of the reaction course may also be obtained from the ultraviolet spectra. Only a few publications have dealt with the ultraviolet spectra of 1,3,5-triazines; a useful compilation of some spectral data was presented by Koopman (34). He reported that 2,4-dichloro-6-amino- or substituted amino-1,3,5-triazines possess two absorption bands, one in the 2 250 – 2 440 Å region (high intensity) and the other in the 2 600 – 2 800 Å region (low intensity), whereas the 2,4-dichloro-6-alkylthio- or arylthio-1,3,5-triazines exhibit only one absorption band, that in the 2 600 – 2 670 Å region (high intensity). The ultraviolet spectra of some of our products all show a high-intensity band in the 2 960 – 3 180 Å region; these findings present additional evidence for the proposed S-alkylated products.

EXPERIMENTAL

Melting points were determined on a Kofler heating microscope. Ultraviolet spectra were measured on a Beckman model DU spectrophotometer.

S-(4,6-Dichloro-1,3,5-triazinyl-2)-acetone Thiosemicarbazone (IV, R = H, R_1 = N=C(CH_3)$_2$)

A solution of acetone thiosemicarbazone (2.6 g, 0.02 mole) (35) in acetone (100 ml) was added slowly to a stirred solution of cyanuric chloride (3.7 g, 0.02 mole) in acetone (300 ml). The reaction mixture was stirred at room temperature for 20 min and a saturated aqueous solution of sodium bicarbonate added until the

pH reached 7. The solvent was evaporated *in vacuo*, the residue treated with cold water (50 ml), and the precipitate collected by filtration and dried. The product was crystallized from a mixture of cyclohexane and ethyl acetate, yield 56%, m.p. >340 °C. The compound gave a negative iodine–azide reaction. Ultraviolet spectrum (in methanol): λ_{max} 3 020 Å, ϵ = 12 850.

Anal. Calcd. for $C_7H_8Cl_2N_6S$: C, 30.11; H, 2.89; N, 30.11; S, 11.48. Found: C, 29.92; H, 3.15; N, 30.32; S, 11.73.

In the same way as described above the following compounds were prepared, and in all cases the iodine–azide reaction was negative.

S-(4,6-Dichloro-1,3,5-triazinyl-2)-acetone 4'-phenylthiosemicarbazone (IV, R = C_6H_5, R_1 = N=CH$(CH_3)_2$) was obtained from acetone 4-phenylthiosemicarbazone (36). The product was crystallized from benzene, yield 47%, m.p. 193 °C. Ultraviolet spectrum (in dioxane): λ_{max} 2 540 and 3 180 Å, ϵ = 10 520 and 23 050.

Anal. Calcd. for $C_{13}H_{12}Cl_2N_6S$: C, 43.94; H, 3.38; N, 23.66; S, 9.02. Found: C, 44.14; H, 3.67; N, 23.55; S, 9.48.

S-(4,6-Dichloro-1,3,5-triazinyl-2)-phenylthiourea (IV, R = C_6H_5, R_1 = H) was obtained from phenylthiourea. The crude product was dissolved in ethyl acetate and poured into water. The precipitate was separated by filtration, washed with water, and air-dried, yield 12%, m.p. 198 °C.

Anal. Calcd. for $C_{10}H_7Cl_2N_5S$: C, 40.01; H, 2.35; N, 23.33; S, 10.67. Found: C, 40.18; H, 2.56; N, 23.64; S, 10.45.

S-(4,6-Dichloro-1,3,5-triazinyl-2)-1'-phenyl-3'-methylthiourea (IV, R = C_6H_5, R_1 = CH_3) was obtained from 1-phenyl-3-methylthiourea (37). The product was purified from ethanol, yield 10%, m.p. 136 °C.

Anal. Calcd. for $C_{11}H_9Cl_2N_5S$: C, 42.04; H, 2.89; N, 22.29. Found: C, 42.30; H, 3.02; N, 22.46.

S-(4,6-Dichloro-1,3,5-triazinyl-2)-n-heptanal thiosemicarbazone (IV, R = H, R_1 = N=CH$(CH_2)_5CH_3$) was prepared according to the procedure of Gingras *et al.* (5), m.p. 179 °C. Ultraviolet spectrum (in methanol): λ_{max} 2 960 Å, ϵ = 19 310.

S-(6-Chloropyridazinyl-3)-acetone Thiosemicarbazone

To a solution of acetone thiosemicarbazone (1.3 g, 0.01 mole) (35) in acetone (50 ml) was added 3,6-dichloropyridazine (1.5 g, 0.01 mole), and the mixture was left overnight at room temperature. The precipitated product was collected and dissolved in water (30 ml), and a saturated solution of sodium bicarbonate added until the pH reached 7. The precipitate was separated by filtration, dried, and crystallized from ethanol with the addition of some N,N-dimethylformamide, yield 18%, m.p. 121 °C.

Anal. Calcd. for $C_8H_{10}ClN_5S$: C, 39.42; H, 4.11; N, 28.75. Found: C, 39.56; H, 3.84; N, 28.98.

S-(6-Chloropyridazinyl-3)-benzaldehyde Thiosemicarbazone

The same reaction as above was applied, and the starting compound was benzaldehyde thiosemicarbazone (35, 37). After neutralization with sodium bicarbonate solution, the solvent was evaporated *in vacuo* and a red oil separated. This oil was separated from the residual liquid and, after it was allowed to stand overnight, crystals separated. The product was washed with ether and crystallized from ethanol with the addition of some N,N-dimethylformamide, yield 29%, m.p. 159 °C. Ultraviolet spectrum (in dioxane): λ_{max} 3 020 Å, ϵ = 20 450.

Anal. Calcd. for $C_{12}H_{11}ClN_5S$: C, 49.23; H, 3.76; N 23.93. Found: C, 49.46; H, 3.79; N, 23.88.

Trithiocyanuric Acid

To a solution of thiourea (6.8 g, 0.09 mole) in acetone (130 ml) was added cyanuric chloride (5.55 g, 0.03 mole), and the mixture was heated under reflux for 2 h on a water bath. The precipitated isothiuronium compound was filtered off and transferred to a solution of sodium hydroxide (6 g in 50 ml of water). The resulting solution was filtered, acidified with concentrated hydrochloric acid until the pH reached 1, filtered, and dried. The product was purified by dissolution in a 5% aqueous solution of sodium bicarbonate (30 ml) and subsequent acidification with concentrated hydrochloric acid to a pH of 1. The product was collected by filtration and dried *in vacuo*, yield 86%, m.p. >300 °C (38, 39).

Anal. Calcd. for $C_3H_3N_3S_3$: S, 54.18. Found: S, 54.01.

The above reaction was also conducted with a different mole ratio of the starting compounds (2:1 and 1:1), but in both cases only trithiocyanuric acid was obtained; however, the yields were correspondingly lower.

3-Chloro-6(1H)-pyridazinethione

To a solution of thiourea (1.52 g, 0.02 mole) in acetone (50 ml) was added 3,6-dichloropyridazine (3.0 g, 0.02 mole), and the reaction mixture was heated under reflux on a water bath for 2 h. The cooled reaction mixture was separated by filtration and the isolated isothiuronium compound was dissolved in an aqueous solution of sodium hydroxide (1 g in 20 ml of water). The solution was acidified with concentrated hydrochloric acid to a pH of 1, and the precipitate was separated and dried. It was purified by dissolution in 5% sodium bicarbonate solution (30 ml), filtration, and acidification with concentrated hydrochloric acid to a pH of 1, yield 80%, m.p. 150 °C (lit. (40) m.p. 130–140 °C). The mixed melting point with an authentic specimen was not depressed.

3-Mercapto-6(1H)-pyridazinethione

By the above procedure, but with double the amount of thiourea, the compound was obtained in 74% yield, m.p. 246 °C (1) (lit. (40) m.p. 230–240 °C). The mixed melting point with an authentic specimen was undepressed.

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