[CONTRIBUTION FROM THE B. F. GOODRICH RESEARCH CENTER]

SOME MERCAPTOTHIADIAZINES AND THEIR INTERMEDIATE COMPOUNDS

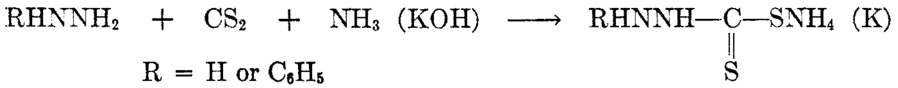
ROGER A. MATHES

Received February 28, 1952

Mercaptothiadiazines were first reported by Busch (1) who reacted potassium phenyldithiocarbazate with ethylene bromide to form a compound designated as "phenylpentahydrothio-1,3,4-diazthin"; in a continuation of this work, Busch and Best (2) prepared a number of homologous compounds from other potassium aryldithiocarbazates. Andreasch (3, 4) synthesized what he believed to be N-amino and N-anilino rhodanines by reacting ethyl chloroacetate with the hydrazine salt of dithiocarbazic acid and with ammonium phenyldithiocarbazate, respectively. In later work, Bose (5) described a number of alkyl thiol derivatives of thiadiazines which were prepared by reacting phenacyl bromides with alkyl phenyldithiocarbazates. The author has had occasion to prepare further examples of mercaptothiadiazines particularly those with variations in the groups attached to the 5 and 6 carbon atoms of the ring.

Ammonium dithiocarbazate[1] (I) was prepared according to the method of Losanitch (6) and potassium phenyldithiocarbazate (II) was synthesized following Busch's directions (1), as shown in equation A.

Equation A.

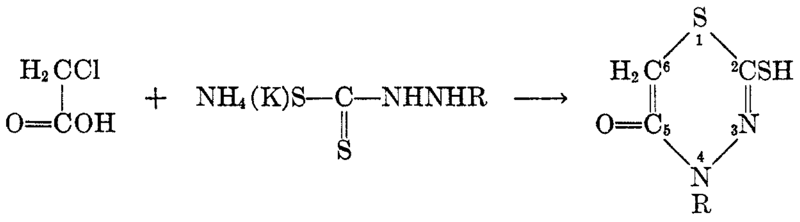


$$\mathrm{RHNNH_2} + \mathrm{CS_2} + \mathrm{NH_3\ (KOH)} \longrightarrow \mathrm{RHNNH{-}\underset{\underset{\displaystyle S}{\|}}{C}{-}SNH_4\ (K)}$$

$$\mathrm{R = H\ or\ C_6H_5}$$

2-Mercapto-1,3,4,4*H*-thiadiazine-5(6*H*)-one (III) and 2-mercapto-4-phenyl-1,3,4,4*H*-thiadiazine-5(6*H*)-one (IV), shown in equation B, previously synthesized by Andreasch (3, 4) from ethyl chloroacetate, were readily obtained from chloroacetic acid. Intermediate compounds, before ring closure, were unstable although the intermediate for IV, (2-phenylthiocarbazyl)mercaptoacetic acid (V), was identified.

Equation B.



Using α-chloro ketones, etc., (equation C), the following compounds and intermediates were synthesized: (from 3-chloro-2-butanone) — 5,6-dimethyl-2-mer-

---

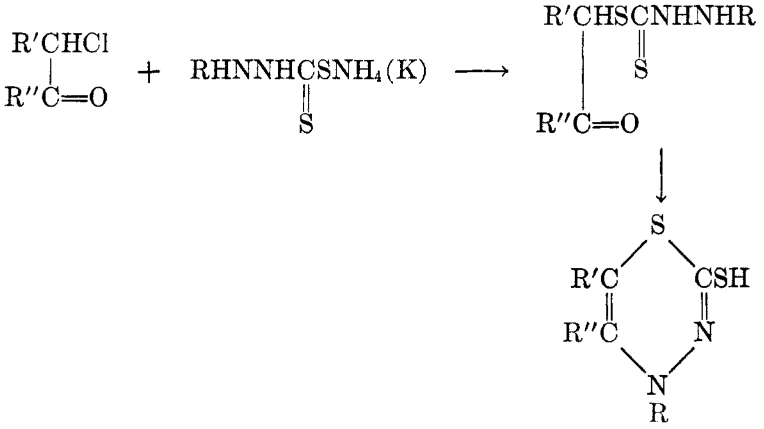
[1] Ammonium dithiocarbazate, as a water solution, can be preserved with little decomposition for periods of 2–3 months by refrigeration (about 0°).

capto-1,3,4,4*H*-thiadiazine (VI), 5,6-dimethyl-2-mercapto-4-phenyl-1,3,4,4*H*-thiadiazine (VII), and its intermediate, 3-(2-phenyldithiocarbazyl)-2-butanone (VIII); (from phenacyl chloride) 2-mercapto-5-phenyl-1,3,4,4*H*-thiadiazine (IX).

2-Mercapto-4-phenyl-1,3,4,4*H*-thiadiazine (X) and its intermediate, (2-phenyldithiocarbazyl)acetaldehyde (XI), were obtained from chloroacetaldehyde. Several attempts were made to prepare 2-mercapto-1,3,4,4*H*-thiadiazine. The product obtained in high yield from ammonium dithiocarbazate appeared to be polymeric and was insoluble in all ordinary solvents.

An α-chloro-β-keto ester, ethyl α-chloroacetoacetate, yielded 2-mercapto-6-carbethoxy-5-methyl-1,3,4,4*H*-thiadiazine (XII).

Equation C.



REACTANT	R	R′	R″	PRODUCT
3-Chloro-2-butanone	H	CH_3	CH_3	VI
	C_6H_5	CH_3	CH_3	VII
Phenacyl chloride	H	H	C_6H_5	IX
Chloroacetaldehyde	C_6H_5	H	H	X
Ethyl α-chloroacetoacetate	H	C_2H_5OOC	CH_3	XII

When XII was heated with a solution of sodium hydroxide in an attempt to prepare the 5-methyl-6-carboxythiadiazine, the carbethoxy group was split off. The resulting compound, 2-mercapto-5-methyl-1,3,4,4*H*-thiadiazine (XIII) was purified and characterized.

EXPERIMENTAL[2]

2-Mercapto-1,3,4,4H-thiadiazine-5(6H)-one (III). A solution of 18.9 g. (0.2 mole) of chloroacetic acid and 50 cc. of water was agitated vigorously while slowly adding 26.3 g. (0.21 mole) of ammonium dithiocarbazate (I) (6) as a 40% aqueous solution. The reaction temperature was maintained at 2–3° during the 50-minute period of addition. A white solid, presumably the intermediate, precipitated during the reaction; with continued stirring,

---

[2] All melting points are uncorrected.

the precipitate dissolved when the reaction mixture reached room temperature. The solution was heated to 50° whereupon a voluminous, yellow solid precipitated. After cooling to 0°, the product was recovered by filtration to give 12.3 g. (41%). Purification was effected by recrystallization from benzene; the analytical sample had m.p. 90–91°.[3]

Anal. Calc'd for $C_3H_4N_2OS_2$: C, 24.30; H, 2.77; S, 43.27.

Found: C, 24.35; H, 2.66; S, 43.36.

2-Mercapto-4-phenyl-1,3,4,4H-thiadiazine-5(6H)-one (IV). With rapid agitation, 22 g. (0.1 mole) of potassium phenyldithiocarbazate (II) (1), dissolved in 90 cc. of water, was added slowly to 9.5 g. (0.1 mole) of chloroacetic acid as a 20% water solution. The temperature of the reaction mixture was held at 5° during the 30-minute addition time. The greenish colored precipitate which formed was recovered by filtration to give 21 g. (87%), based on the intermediate. Upon purification by recrystallization from benzene, the white, crystalline intermediate, *(2-phenylthiocarbazyl)mercaptoacetic acid* (V), melted at 117–118°.

Anal. Calc'd for $C_9H_{10}N_2S_2O_2$: N, 11.56. Found: N, 11.73.

A sample of the intermediate was heated in an excess of hydrochloric acid for 10 minutes at 75°. The product recovered melted at 133–134°[4] after recrystallization from benzene and ether.

Anal. Calc'd for $C_9H_8N_2S_2O$: C, 48.20; H, 3.59; N, 12.49; S, 28.59.

Found: C, 48.26; H, 3.57; N, 12.49; S, 28.67.

5,6-Dimethyl-2-mercapto-1,3,4,4H-thiadiazine (VI). While vigorously agitating 65.5 g. (0.5 mole) of I as a 17% aqueous solution, 53.5 g. (0.5 mole) of 3-chloro-2-butanone was added slowly at 5–10°. After adding 5 cc. of hydrochloric acid to the resulting solution, the reaction mixture was heated at 90° for 10 minutes. The oil which formed solidified upon cooling to room temperature. Several extractions with 1% hydrochloric acid removed the residual oiliness, and gave 35 g. (44%) of the crude product. Recrystallization from water gave white, needle crystals melting at 77–78.5°.

Anal. Calc'd for $C_5H_8N_2S_2$: C, 37.47; H, 5.03; N, 17.50; S, 40.00; Mol. wt., 160.

Found: C, 37.47; H, 5.05; N, 17.46; S, 40.01; Mol. wt., 161.

5,6-Dimethyl-2-mercapto-4-phenyl-1,3,4,4H-thiadiazine (VII). While vigorously stirring a mixture of 10.7 g. (0.1 mole) of 3-chloro-2-butanone and 100 cc. of 50% ethanol, there was added 22 g. (0.1 mole) of II as a 20% aqueous solution. The temperature was maintained at 5–9° during the addition time of 30 minutes. The granular precipitate which formed was removed to yield 21.7 g. (92%) of the crude intermediate, *3-(2-phenyldithiocarbazyl)-2-butanone* (VIII). After recrystallization from carbon tetrachloride, the white, crystalline intermediate melted at 117–118°.

Anal. Calc'd for $C_{11}H_{14}N_2S_2O$: C, 51.94; H, 5.55; N, 11.01.

Found: C, 51.89; H, 5.40; N, 10.94.

The intermediate (5 g., 0.02 mole) was added to 25 cc. of hydrochloric acid, and while stirring, the mixture was heated to 70° to effect ring closure. There was obtained 4 g. (86%) of crude thiadiazine which yielded a white, crystalline product melting at 107.5–109°, after recrystallization from carbon tetrachloride.

Anal. Calc'd for $C_{11}H_{12}N_2S_2$: C, 55.87; H, 5.11; N, 11.90; S, 27.12.

Found: C, 55.57; H, 5.12; N, 11.66; S, 27.11.

2-Mercapto-5-phenyl-1,3,4,4H-thiadiazine (IX). A solution of 45 g. (0.36 mole) of I in 250 cc. of water was rapidly agitated while slowly adding 43.4 g. (0.3 mole) of phenacyl chloride suspended in 200 cc. of ethanol. During the addition time of 30 minutes, the temperature of the reaction mixture was maintained at 5–15°. The temperature rapidly rose to 35°, 10 cc. of hydrochloric acid was added, and the reaction mixture was heated to 65°. An oil, which formed on continued agitation, solidified to a yellow, crystalline solid which was recovered to give 55 g. (88%) of the crude thiadiazine. After purification by recrystallization from ether, the analytical sample melted at 133–134°.

Anal. Calc'd for $C_9H_8N_2S_2$: C, 51.89; H, 3.90; N, 13.44; S, 30.77.

Found: C, 52.07; H, 3.88; N, 13.44; S, 30.81.

---

[3] Andreasch (4) and Holmberg (7) reported m.p. 92°.

[4] Andreasch (3) reported m.p. 125° while Holmberg gave m.p. 133.5–134°.

2-Mercapto-4-phenyl-1,3,4,4H-thiadiazine (X). While vigorously stirring a solution of 17.5 g. (0.22 mole) of chloroacetaldehyde in 100 cc. of water, there was added 22.2 g. (0.1 mole) of II as a 20% aqueous solution. The temperature was maintained at 10–14° during the addition time of 30 minutes. The voluminous, white solid which precipitated was recovered to give 33.6 g. (75%) of the crude intermediate, (2-phenyldithiocarbazyl)acetaldehyde (XI). After recrystallization from benzene, the cream-colored, crystalline intermediate melted at 155–156°.

Anal. Calc'd for $C_9H_{10}N_2OS_2$: C, 47.77; H, 4.45; N, 12.38; S, 28.33; Mol. wt. 226.
Found: C, 47.83; H, 4.32; N, 12.28; S, 28.34; Mol. wt., 218.

Ring closure was effected by warming a sample of the intermediate in a large excess of hydrochloric acid. After recrystallization from chloroform and alcohol, the cream-colored, crystalline thiadiazine melted at 105–106°.

Anal. Calc'd for $C_9H_8N_2S_2$: C, 51.85; H, 3.90; N, 13.44; S, 30.77; Mol. wt., 208.
Found: C, 52.04; H, 3.85; N, 13.33; S, 30.73; Mol. wt., 203.

2-Mercapto-6-carbethoxy-5-methyl-1,3,4,4H-thiadiazine (XII). While stirring a solution of 32.9 g. (0.2 mole) of ethyl α-chloroacetoacetate in 150 cc. of 50% ethanol, 27.5 g. (0.22 mole) of ammonium dithiocarbazate as a 40% aqueous solution was added. The addition time was 40 minutes at a temperature of 6–8°. The product precipitated as an oily, doughy mass which was removed by filtration and dissolved in 200 cc. of methanol. The methanol solution was added, with stirring, to 1 liter of cold water whereupon a yellow, crystalline solid precipitated. The crude product weighed 19 g. (43.5%) and after purification by recrystallization from benzene-hexane melted at 97–98°.

Anal. Calc'd for $C_7H_{10}N_2O_2S_2$: C, 38.52; H, 4.61; N, 12.84; S, 29.37; Mol. wt., 218.
Found: C, 38.54; H, 4.69; N, 12.79; S, 29.32; Mol. wt., 215.

2-Mercapto-5-methyl-1,3,4,4H-thiadiazine (XIII). A solution of 3.3 g. (0.015 mole) of XII was dissolved in 0.8 g. (0.02 mole) of sodium hydroxide as a 3% aqueous solution. The resulting red-brown solution was boiled for 3 minutes, cooled to room temperature, and neutralized with 10% hydrochloric acid. The precipitate was filtered and gave 1.8 g. (82%) of crude product. Purification, which was effected by recrystallizing twice from methanol and once from water, gave pale yellow needles melting at 124.5–125.5°.

When the experiment described was repeated without heating the sodium hydroxide solution, XII was recovered unchanged.

Anal. Calc'd for $C_4H_6N_2S_2$: C, 32.86; H, 4.13; N, 19.16; S, 43.85; Mol. wt., 146.
Found: C, 32.89; H, 4.11; N, 19.19; S, 43.89; Mol. wt., 147.

Acknowledgment. Analyses were performed by J. R. Kubik and A. K. Kuder.

SUMMARY

The synthesis of 2-mercapto-1,3,4,4*H*-thiadiazines has been extended by reacting α-chloroketones, chloroacetaldehyde, and an α-chloro-β-ketoester with salts of dithiocarbazic acids. Intermediate compounds, before splitting off water to effect ring closure, have been characterized where they were sufficiently stable to permit isolation.

BRECKSVILLE, OHIO

REFERENCES

(1) BUSCH, *Ber.*, **27**, 2507 (1894).
(2) BUSCH AND BEST, *J. prakt. Chem.*, [2] **60**, 187 (1899).
(3) ANDREASCH, *Monatsh.*, **27**, 1211 (1906).
(4) ANDREASCH, *Monatsh.*, **29**, 399 (1908).
(5) BOSE, *Quart. J. Indian Chem. Soc.*, **3**, 197 (1926); *Chem. Abstr.*, **21**, 391 (1927).
(6) LOSANITCH, *J. Chem. Soc.*, **119**, 763 (1921).
(7) HOLMBERG, *J. prakt. Chem.*, [2] **81**, 451 (1910).