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

Thiazoline, Pyrimidine and Thiazine Ring Compounds with Acid Substituents Attached to the Nitrogen

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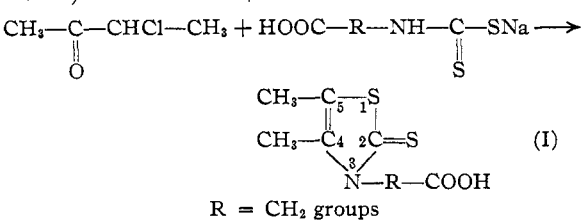
Thiazoline and thiazolidine ring structures, containing an acid group in the 3-position, have been synthesized by treating the dithiocarbamic acid derived from glycine or from *dl*-α-alanine with an α-halogenated ketone[1] or with chloroacetic acid.[2] We have had occasion to prepare some further examples of thiazoline compounds of this type; in addition, the investigation has been extended to include the preparation of previously undescribed pyrimidine and thiazine ring compounds containing acid groups in the 1- and 3-positions, respectively.

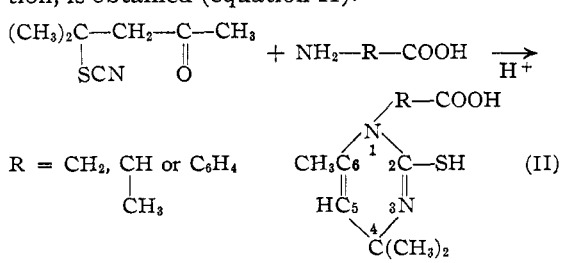
Using a technique similar to that described,[1a] 4,5-dimethyl-2-thiono-4-thiazoline-3-acetic acid, the corresponding -3-β-propionic acid and -3-γ-butyric acid were prepared. These syntheses were effected by treating 3-chloro-2-butanone with dithiocarbamic acids derived, respectively, from glycine, β-alanine and γ-aminobutyric acid (equation I).



(I)

R = CH_2 groups

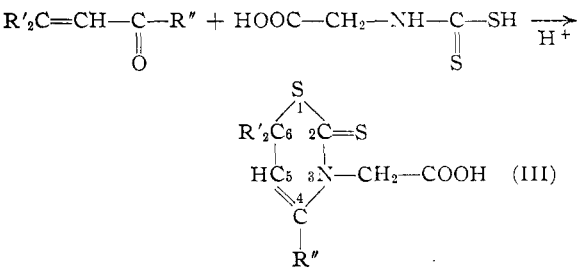
In an earlier paper,[3] the synthesis of pyrimidinethiols by the reaction of 2-methyl-2-thiocyano-4-pentanone with primary amines, was described. When the amine is replaced by an amino acid containing a primary amino group, a pyrimidinethiol, with an acid substituent in the 1-position, is obtained (equation II).



(II)

The following compounds were prepared: 1,4-dihydro-2-mercapto-4,4,6-trimethylpyrimidine-1-acetic acid (from glycine); the -1-β-propionic acid (from β-alanine); the -1-α-propionic acid (from *dl*-α-alanine); the -1-*o*-benzoic acid (from anthranilic acid); -1-*p*-benzoic acid (from *p*-aminobenzoic acid).

Jansen[4] has described the preparation of 2-thiazinethiols by treating an α,β-unsaturated ketone or aldehyde with dithiocarbamic acid. This general method has been extended to include the preparation of 2-thiono-3-acid substituted thiazines by using a dithiocarbamic acid derived from an amino acid having a primary amino group (equation III).



(III)

Using mesityl oxide: R′ and R″ = CH_3 groups
Using cinnamaldehyde: R′ = C_6H_5 and H
R″ = H

Two representative compounds were prepared by this method: 3-hydro-2-thiono-4,6,6-trimethyl-1,3,6-thiazine-3-acetic acid (from mesityl oxide); 3-hydro-6-phenyl-2-thiono-1,3,6-thiazine-3-acetic acid (from cinnamaldehyde).

Experimental[5,6]

4,5-Dimethyl-2-thiono-4-thiazoline-3-acetic Acid. General Procedure.—A water solution of the sodium dithiocarbamate was first prepared by treating 22.5 g. (0.3 mole) of glycine, 24 g. (0.6 mole) of sodium hydroxide and 22.8 g. (0.3 mole) of carbon bisulfide in 150 ml. of water. The reaction was performed at 20° and required about two hours to reach completion as evidenced by the disappearance of the carbon bisulfide layer. Thirty-two grams (0.3 mole) of 3-chloro-2-butanone was added rapidly, the temperature rising to 50°. The temperature was held at 70–80° for one hour, and after cooling to room temperature, 10% hydrochloric acid was added to neutralize the sodium salt of the product. The buff-colored solid that precipitated was recovered by filtration to give 46 g. (81% yield) of crude product melting at 208–210°. On recrystallizing from water, then from alcohol, the melting point was 213°.

Anal. Calcd. for $C_7H_9NO_2S_2$: C, 41.36; H, 4.46; N, 6.90; S, 31.54; mol. wt., 203. Found: C, 41.39; H, 4.49; N, 6.93; S, 31.44; mol. wt., 207.

4,5-Dimethyl-2-thiono-4-thiazoline-3-β-propionic Acid.—By replacing glycine used in the general procedure with β-alanine, there was obtained from a 0.25-mole reaction 22.7 g. (42% yield) of crude product melting at 157–159°.

(1) (a) Groth and Holmberg, *Ber.*, **56**, 289 (1923); (b) Groth, *Arkiv Kemi. Mineral. Geol.*, **9**, No. 1 (1924); (c) Holmberg, *Compt. rend. trav. lab. Carlsberg., Ser. chim.*, **22**, 211 (1938).

(2) Körner, *Ber.*, **41**, 1901 (1908); Andreasch, *Monatsh.*, **29**, 399 (1908); Holmberg, *J. prakt. Chem.*, [2] **81**, 451 (1910); Andreasch, *Monatsh.*, **31**, 785 (1911).

(3) Mathes, Stewart and Swedish, THIS JOURNAL, **70**, 1452 (1948).

(4) Jansen, U. S. Patent 2,440,095.

(5) The melting points given are uncorrected.

(6) The yields represent only the product recovered by filtration without attempting to determine the optimum yield.

After recrystallizing first from water, then from carbon tetrachloride, the melting point was 162–163°.

Anal. Calcd. for $C_8H_{11}NO_2S_2$: C, 44.20; H, 5.10; N, 6.44; S, 29.49; mol. wt., 217. Found: C, 44.18; H, 5.09; N, 6.43; S, 29.52; mol. wt., 219.

4,5-Dimethyl-2-thiono-4-thiazoline-3-γ-butyric Acid.—By replacing glycine used in the general procedure with γ-aminobutyric acid, there was obtained from a 0.2-mole reaction 18 g. (39% yield) of crude product which after recrystallization from water melted at 129–130°.

Anal. Calcd. for $C_9H_{13}NO_2S_2$: C, 46.73; H, 5.66; N, 6.06; S, 27.72; mol. wt., 231. Found: C, 46.69; H, 5.66; N, 6.16; S, 27.80; mol. wt., 233.

1,4-Dihydro-2-mercapto-4,4,6-trimethylpyrimidine-1-acetic Acid. General Procedure.—A mixture consisting of 18.7 g. (0.25 mole) of glycine, 39.3 g. (0.25 mole) of 2-methyl-2-thiocyano-4-pentanone[7] and 125 ml. of water was heated for six hours at 85–90°. After cooling to room temperature, the crystalline solid which precipitated was recovered by filtration to give 31 g. (58% yield) of crude product melting at 168–170°. After recrystallizing from alcohol the melting point was 175–176°.

Anal. Calcd. for $C_9H_{14}N_2O_2S$: C, 50.47; H, 6.55; N, 13.08; S, 14.95; mol. wt., 214. Found: C, 50.47; H, 6.59; N, 13.06; S, 15.03; mol. wt., 210.

1,4-Dihydro-2-mercapto-4,4,6-trimethylpyrimidine-1-β-propionic Acid.—By replacing glycine used in the general procedure with β-alanine, there was obtained from a 0.25-mole reaction 29.5 g. (52% yield) of crude product melting at 133–135°. After recrystallizing from benzene the melting point was 142–143°.

Anal. Calcd. for $C_{10}H_{16}N_2O_2S$: C, 52.61; H, 7.06; N, 12.27. Found: C, 52.71; H, 7.00; N, 12.15.

1,4-Dihydro-2-mercapto-4,4,6-trimethylpyrimidine-1-α-propionic Acid.—By replacing glycine used in the general procedure with *dl*-α-alanine, there was obtained from a 0.25-mole reaction 21.5 g. (38% yield) of crude product melting at 187–190°. After recrystallizing from benzene the melting point was 191–192°.

Anal. Calcd. for $C_{10}H_{16}N_2O_2S$: C, 52.61; H, 7.06; N, 12.27. Found: C, 52.60; H, 7.09; N, 12.24.

1,4-Dihydro-2-mercapto-4,4,6-trimethylpyrimidine-1-*o*-benzoic Acid.—By replacing glycine used in the general procedure with anthranilic acid there was obtained from a 0.25-mole reaction 41 g. (59% yield) of crude product melting at 208–209°. After recrystallizing from chloroform the melting point was 210°.

Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.86; H, 5.84; N, 10.12; S, 11.60. Found: C, 60.84; H, 5.86; N, 10.08; S, 11.60.

1,4-Dihydro-2-mercapto-4,4,6-trimethylpyrimidine-1-*p*-benzoic Acid.—By replacing glycine used in the general procedure with *p*-aminobenzoic acid, there was obtained from a 0.19-mole reaction 46.2 g. (90% yield) of crude product melting at 207–208°. After recrystallizing from chloroform the melting point was 209–210°.

Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.86; H, 5.84; N, 10.12. Found: C, 60.59; H, 5.80; N, 10.02.

3-Hydro-2-thiono-4,6,6-trimethyl-1,3,6-thiazine-3-acetic Acid. General Procedure.—A water solution of the sodium dithiocarbamate was first prepared by the reaction of 37.5 g. (0.5 mole) of glycine, 40 g. (1.0 mole) of sodium hydroxide and 38 g. (0.5 mole) of carbon bisulfide in 200 ml. of water. This dithiocarbamate solution was added slowly, with vigorous stirring, to a solution of 49 g. (0.5 mole) of mesityl oxide in 98 g. (1.0 mole) of 37% hydrochloric acid diluted with 100 ml. of ice-water. The reaction mixture was then heated at 60° for one hour. After cooling to room temperature the crude product was recovered by filtration to give 28 g. (24% yield). After recrystallizing from ethanol the melting point was 157–159°.

Anal. Calcd. for $C_9H_{13}NO_2S_2$: C, 46.73; H, 5.66; N, 6.06; S, 27.72; mol. wt., 231. Found: C, 46.74; H, 5.68; N, 6.05; S, 27.76; mol. wt., 232.

3-Hydro-6-phenyl-2-thiono-1,3,6-thiazine-3-acetic Acid.—There was obtained from a 0.5-mole reaction in which mesityl oxide used in the general procedure was replaced with cinnamaldehyde, 110 g. (82% yield) of crude, quite impure product. After extracting with ethanol and recrystallizing from chloroform the melting point was 178–179°.

Anal. Calcd. for $C_{12}H_{12}NO_2S_2$: C, 54.11; H, 4.54; N, 5.26. Found: C, 54.29; H, 4.46; N, 5.23.

Acknowledgment.—The analyses of all compounds were made by James R. Kubik and Arthur K. Kuder.

Summary

Syntheses have been developed for previously undescribed 1-acid-substituted 2-pyrimidinethiols and 3-acid-substituted 2-thionothiazines. Five examples of the former type were prepared by reaction of 2-methyl-2-thiocyano-4-pentanone with various amino acids. Of the latter type, two representative compounds were synthesized by treating the dithiocarbamic acid derived from glycine with mesityl oxide and with cinnamaldehyde, respectively.

Employing the method described in the literature, three new 3-acid-substituted 2-thionothiazolines were prepared by treating 3-chloro-2-butanone with dithiocarbamic acids derived from glycine, β-alanine and γ-aminobutyric acid.

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(7) The crude compound (before water washing) is sufficiently acidic that the addition of free acid as catalyst to the reaction mixture is not necessary.