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Preparation of Carboxymethylthiophenazines

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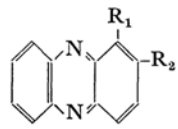
In previous papers,[1,2] the reactions of halogenophenazine derivatives with piperidine and morpholine were reported. In this paper, the reactions of various halogenophenazine derivatives with mercaptoacetic acid will be reported.

Landquist has reported that the reaction of 2-chlorophenazine-5,10-dioxide (I) with sodium mercaptoacetate gave 2-carboxymethylthiophenazine (II).[3] By a modification of this method, we could obtain II from 2-chlorophenazine (III), 2-bromophenazine (IV), 2-chlorophenazine-5-oxide (V), 3-chlorophenazine-5-oxide (VI), and 3-bromophenazine-5-oxide (VII). The reaction of either 1-chlorophenazine (VIII) or 1-chlorophenazine-5-oxide (IX) with sodium mercaptoacetate gave 1-carboxymethylthiophenazine (X). In this case, 1-chlorophenazine was shown to be less reactive toward the reagent than 2-chloro compounds.



II: R_1=H; R_2=SCH_2CO_2H
X: R_1=SCH_2CO_2H; R_2=H

The enhancement of the reactivity of halogen by the oxide groups in halogenophenazine oxides was also observed in the present experiments.

The growth-inhibitory activity of II and X against Crocker Sarcoma 180 has also been investigated and will be reported on elsewhere.[4]

Experimental[5]

2-Carboxymethyl thiophenazine (II). *a) From III.* To a solution of III (1.7 g) in ethanol (40 m*l*), a sodium mercaptoacetate solution prepared from mercaptoacetic acid (1.5 g) and a 10% sodium hydroxide aqueous solution (14 m*l*) was added. The mixture was refluxed for 17 hr and then poured into water (0.5 *l*). The aqueous solution was filtered, and the filtrate was slightly acidified with diluted hydrochloric acid. The crystals (1.9 g) thereby separated were collected, washed with water, and dried. Recrystallization from ethanol afforded fine, brownish-yellow prisms (mp 255—256°C (decomp.)), which were identified as II[3] by a comparison of their infrared spectra.

b) From IV. To a solution of IV (0.2 g) in ethanol (4 m*l*), a solution of mercaptoacetic acid (150 mg) in 10% sodium hydroxide (1.4 m*l*) was added; the mixture was then treated as in the case of a) to give II (140 mg).

c) From V. To a solution of V (1.9 g) in ethanol (40 m*l*), a solution of mercaptoacetic acid (1.5 g) in 10% sodium hydroxide (14 m*l*) was added; The mixture was then refluxed for 5.5 hr and treated as in the case of a) to give II (1.7 g).

d) From VI. To a solution of VI (1.9 g) in ethanol (40 m*l*), a solution of mercaptoacetic acid (1.5 g) in 10% sodium hydroxide (14 m*l*) was added. The mixture was then refluxed for 5 hr and treated as in the case of a) to afford II (1.8 g).

e) From VII. To a solution of VII (0.2 g) in ethanol (4 m*l*), a solution of mercaptoacetic acid (150 mg) in 10% sodium hydroxide (1.4 m*l*) was added. The mixture was then refluxed for 4.5 hr and treated as in the case of a) to give II (140 mg).

1-Carboxymethylthiophenazine (X). *a) From VIII.* To a solution of VIII (1.7 g) in ethanol (40 m*l*), a solution of mercaptoacetic acid (1.5 g) in 10% sodium hydroxide aqueous solution (14 m*l*) was added. The mixture was refluxed for 20 hr and then poured into water (0.5 *l*). The crystals which separated were filtered and recrystallized from methanol to recover VIII (1.2 g). The filtrate was slightly acidified with diluted hydrochloric acid to give crystals (530 mg). Recrystallization from ethanol afforded X (mp 240—241°C (decomp.)) as fine, brownish-yellow crystals.

Found: C, 62.19; H, 3.96; N, 10.08%. Calcd for $C_{14}H_{10}N_2O_2S$: C, 62.21; H, 3.73; N, 10.36%.

b) From IX. To a solution of IX (1.9 g) in ethanol (40 m*l*), a solution of mercaptoacetic acid (1.5 g) in 10% sodium hydroxide (14 m*l*) was added. The resultant mixture was refluxed for 10 hr and treated as in the case of a) above to yield both X (550 mg) and VIII (1.2 g).

1) H. Endo, M. Tada and K. Katagiri, This Bulletin, **42**, 502 (1969).
2) H. Endo, M. Tada and K. Katagiri, *ibid.*, **42**, 506 (1969).
3) J. K. Landquist, *J. Chem. Soc.*, **1956**, 2550.
4) H. Endo, M. Tada and K. Katagiri, *Sci. Rep. Res. Inst. Tohoku Univ. Ser. C*, to be published.
5) All melting points are uncorrected.