Synthesis of 2-Mercaptocymene-3-carboxylic Acid

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The synthesis of 2-mercaptocymene-3-carboxylic acid is reported. Also prepared in the course of this investigation were the new compounds: 1-*S*-5-isopropyl-8-methylthianaphthalene-4-one, 1-*S*-2,3-dihydro-2,3-dibromo-5-isopropyl-8-methylthianaphthalene-4-one, and 1-*S*-2,3-dihydro-2,3-dihydroxy-5-isopropyl-8-methylthianaphthalene-4-one. These compounds are of interest because they bear structural relationships to several pharmacologically active derivatives of salicylic acid.

RELATIVELY few modifications of the salicylate structure produce an increase in either analgesic or antipyretic activity. Those modifications which produce an increase in these activities are, therefore, particularly interesting. Structural changes which have been shown to produce desirable alterations in salicylate activity include introduction of a second hydroxyl group, alkylation of the amido nitrogen of salicylamide, and nuclear substitution with weak electron donors.

Reid *et al.* (1) have shown that, while 2,6-dihydroxybenzoic acid is approximately 10 times as effective as salicylic acid in the treatment of rheumatic fever, increase in effectiveness is paralleled by an equivalent increase in toxicity.

Because the introduction of a 6-hydroxyl augments activity and a 5-hydroxyl decreases toxicity, Smith (2) suggested that 2,3,6-trihydroxybenzoic acid might prove a useful drug, but this compound has not yet been investigated.

The demonstrated stability of salicylamide to hydrolysis *in vivo* (3) may be assumed for the more potent (4) *N*-substituted salicylamides, but such compounds have not found active use as medicinal agents.

The weak electron-donating methyl substituent of cresotic acid (2-hydroxy-3-methylbenzoic acid) does not increase the effectiveness of this agent relative to acetylsalicylic acid (5), but 5-bromacetylsalicylic acid shows slightly increased potency and duration of action (6) compared to aspirin. However, simultaneous introduction of both methyl and isopropyl groups as in *p*-thymotic acid (2-hydroxy-3-isopropyl-6-methylbenzoic acid) produces a compound with 15 times the analgesic activity of sodium salicylate (5).

Recognizing that the enhancement of salicylate properties produced by the methyl-*p*-isopropyl modification might be usefully employed to increase the activity of other compounds exerting salicylate-like effects, it was of interest to prepare other derivatives of salicylic acid which might similarly manifest useful properties.

Because the pharmacology of thiosalicylic acid (2-mercaptobenzoic acid) is little known and because the behavior of thiophenolic and phenolic functions is often parallel, the synthesis of a thiosalicylate bearing methyl and isopropyl functions analogous to those in *p*-thymotic acid was considered. Two such acids are possible, and the markedly greater ease of preparing the intermediate 2-mercaptocymene suggested that attempts at synthesis of 2-mercaptocymene-3-carboxylic acid might prove more fruitful than the alternative efforts directed to the production of 3-mercaptocymene-2-carboxylic acid.

In preliminary efforts, 2-mercaptocymene was substituted for the corresponding phenol, carvacrol, in the application of the Kolbe synthesis, the Duff reaction, the Fries rearrangement, and the Reimer-Tieman reaction. None of these procedures yielded the desired product or useful intermediates.

The report that alkaline hydrolysis of thiachromone (1-*S*-thianaphthalene-4-one) produced thiosalicylic acid suggested that this might serve as a route to the synthesis of the desired alkyl-substituted thiosalicylic acid (7). Recognition of the variety of products available from the alkaline hydrolysis, however, made this direct procedure less attractive than the careful stepwise conversion of the thiachromone to the desired acid.

Accordingly, the appropriate thiachromone was prepared and the ethylenic linkage joining the thioether and carbonyl functions was brominated. The resulting dibromo derivative was converted to the corresponding dihydroxythiachromone. Subsequent treatment of this keto-diol with periodic acid resulted in the successful preparation of 2-mercaptocymene-3-carboxylic acid. The sequence of reactions is shown in Scheme I.

EXPERIMENTAL

1 - S - 5 - Isopropyl - 8 - methylthianaphthalene-4-one.—Following the method of Simonis and Elias (7) a mixture of 2-mercaptocymene (16.62 Gm., 0.10 mole) and ethyl 3-ketobutyrate (13.01 Gm., 0.10 mole) was added dropwise to approximately 30 Gm. of phosphorus pentoxide maintained at −5° to −10° at such a rate that the stirred mixture neither clumped nor formed a slurry. This addition usually took from 20 to 30 min. The mixture, protected from atmospheric moisture, was kept at this temperature for 1 more hr. and then heated on a steam bath for a minimum of 2 hr., during which time the mixture changed from yellow to red to dark brown and became plastic. The cooled mixture was poured upon 100 Gm. of ice, and the resulting dark brown solution was steam distilled. The distillate was exhaustively extracted with ether, and the combined ethereal extracts were washed and dried. The solvent was removed by distillation and a portion of the residual yellow oil crystallized on standing overnight in the cold. The crystals were separated by filtration and recrystallized from 95% ethanol. Yield 3.74 Gm. (17.18%), m.p. 101° (corrected).

Anal.—Calcd. for $C_{13}H_{14}OS$: S, 14.68. Found: S, 14.69.

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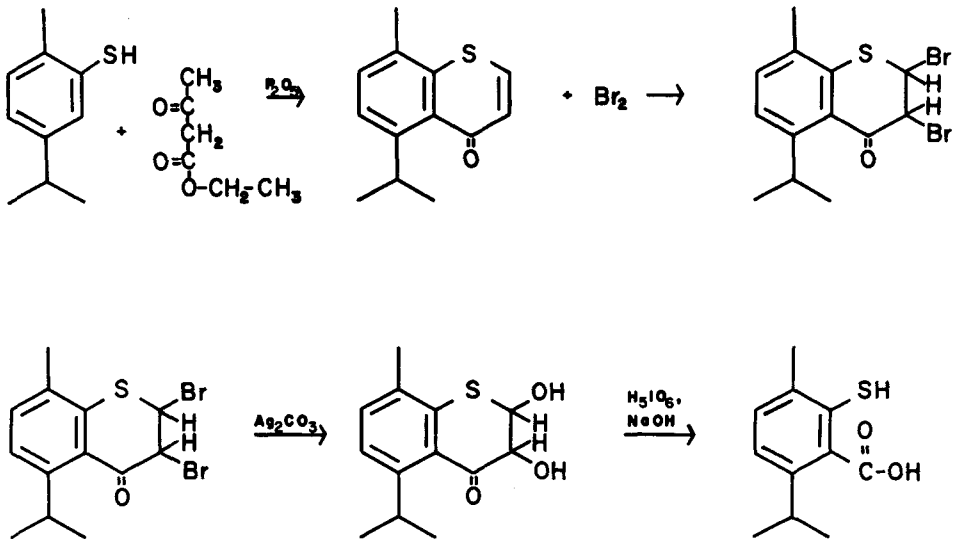

Scheme I

1 - S - 2,3 - Dihydro - 2,3 - dibromo - 5 - isopropyl-8 - methylthianaphthalene - 4 - one.—An approximately 1% solution of bromine in glacial acetic acid was added dropwise to a stirred solution of 218 mg. (0.001 mole) of 1-*S*-5-isopropyl-8-methylthianaphthalene-4-one in 5 ml. of glacial acetic acid until the red color imparted by the bromine persisted for at least 5 min. The mixture was stirred for an additional 15 min. after the last addition of bromine, and solid sodium bisulfite was added to dispel the color of the excess halogen. The yellow solid which separated during the addition of the bromine was separated by filtration and recrystallized from methanol. Yield, 352 mg. (93.12%), m.p. 147° (corrected).

Anal.—Calcd. for $C_{13}H_{14}Br_2OS$: S, 8.48. Found: S, 8.49.

1 - S - 2,3 - Dihydro - 2,3 - dihydroxy - 5 - isopropyl - 8 - methylthianaphthalene - 4 - one.—Freshly prepared, acetone-dried silver carbonate (1.103 Gm., 0.004 mole) was suspended in a solution of 378 mg. (0.001 mole) of 1-*S*-2,3-dihydro-2,3-dibromo-5-isopropyl-8-methylthianaphthalene-4-one in 20 ml. of acetone, and the mixture was allowed to stand 8 hr. protected from light. The insoluble silver compounds were collected on a sintered-glass funnel and washed twice with small portions of acetone. The combined filtrate and washings were gently warmed to dissipate solvent and the residual red oil solidified on standing. When twice recrystallized from 95% ethanol, the product yielded pale pink needles. Yield, 217 mg. (86.11%), m.p. 142° (corrected).

Anal.—Calcd. for $C_{13}H_{16}O_3S$: S, 12.71. Found: S, 12.71.

2-Mercaptocymene-3-carboxylic Acid.—A solution of 253 mg. (0.001 mole) of 1-*S*-2,3-dihydro-2,3-dihydroxy - 5 - isopropyl - 8 - methylthianaphthalene-4-one and 227 mg. (0.001 mole) of periodic acid (H_5IO_6) in 5 ml. of 95% ethanol was refluxed for 24 hr. After cooling, the light brown solution was diluted with 20 ml. of water and neutralized with solid sodium bicarbonate. Unreacted material and a trace of iodine were removed by ether extraction. The hydroalcoholic solution was acidified and extracted with three 10-ml. portions of ether. The three ether extracts were combined, water washed, and the solvent was removed by distillation.

To the residual oil was added 10 ml. of 10% aqueous sodium hydroxide solution, and the mixture was warmed on a water bath for 2 hr. The resulting solution was acidified with hydrochloric acid and extracted with three 10-ml. portions of ether. The combined ether extracts were water washed, dried over anhydrous sodium sulfate, and the ether was removed by distillation.

The residual yellow material was twice recrystallized from aqueous ethanol and gave white needles. Yield, 164 mg. (78.09%), m.p. 81.5–82.0° (corrected).

Anal.—Calcd. for $C_{11}H_{14}O_2S$: S, 15.25. Found: S, 15.28.

SUMMARY

The synthesis of 2-mercaptocymene-3-carboxylic acid was accomplished by bromination of 1-*S*-5-isopropyl-8-methylthianaphthalene-4-one to yield 1 - *S* - 2,3 - dihydro - 2,3 - dibromo - 5 - isopropyl - 8-methylthianaphthalene-4-one and conversion of this dibromo derivative to 1-*S*-2,3-dihydro-2,3-dihydroxy - 5 - isopropyl - 8 - methylthianaphthalene-4-one by treatment with silver carbonate. Periodate oxidation of this keto-diol and treatment with dilute alkali then yielded 2-mercaptocymene-3-carboxylic acid. These compounds are of interest because of their structural and electronic relationship to the analgesic and antipyretic, salicylic acid, and to certain of its derivatives.

REFERENCES

(1) Reid, J., *et al.*, *Brit. Med. J.*, **2**, 321(1951).
(2) Smith, P. K., *Postgrad. Med. J.*, **28**, 179(1952).
(3) Mandel, H. G., Rodwell, V. M., and Smith, P. K., *J. Pharmacol. Exptl. Therap.*, **106**, 433(1952).
(4) Carron, M., Tabart, J., and Julien, Mrs., *Therapie*, **7**, (No. 1), 27(1952).
(5) O'Brien, J. E., Ph.D. Thesis, University of Connecticut, Storrs, Conn., 1957.
(6) Goodman, L. S., and Gilman, A., "The Pharmacological Basis of Therapeutics," 2nd ed., The Macmillan Co., New York, N. Y., 1955, p. 282.
(7) Simonis, H., and Elias, A., *Ber.*, **49**, 768(1916).