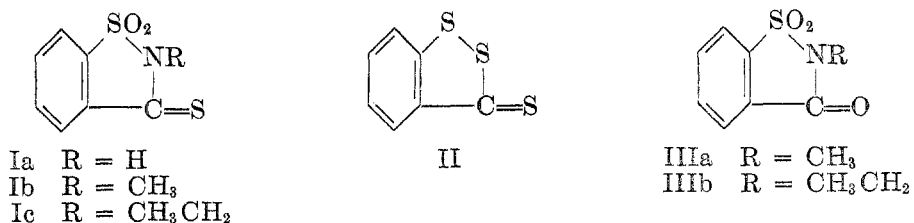


ISOMERIC ALKYL DERIVATIVES OF THIOSACCHARIN
(2,3-DIHYDRO-3-THIOBENZISOSULFONAZOLE)

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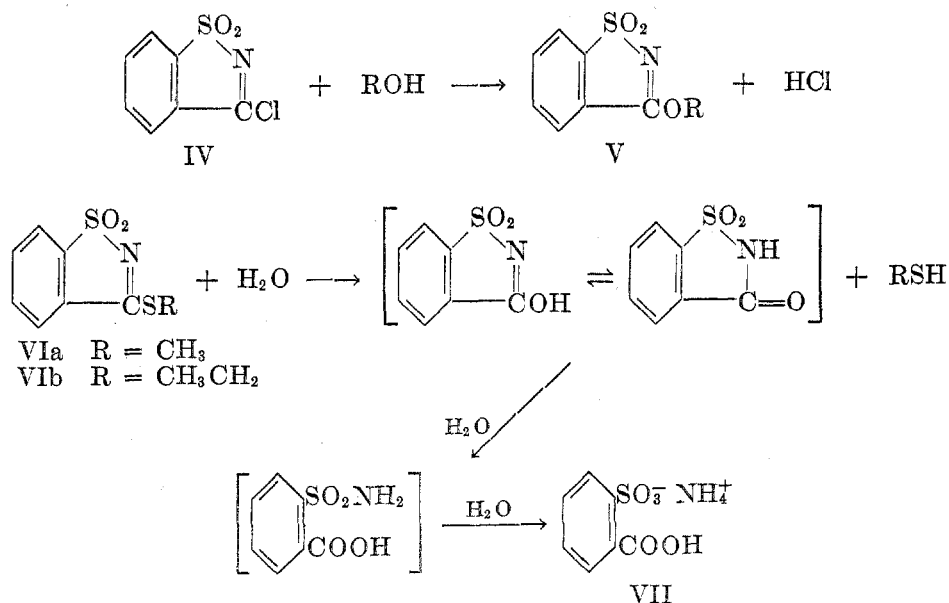
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The preparation of thiosaccharin (Ia), from saccharin and phosphorus pentasulfide, has been reported by Mannessier (1, 2), and some of its reactions have been described later by Mannessier and Mameli (3-8). Formation of a by-product, 1,2,3-benzodithiole-3-thione (II) in considerable quantity is indicated when the temperature of the saccharin-phosphorus pentasulfide mixture is allowed to reach 225-230° (1, 2). A methyl derivative of thiosaccharin is listed



as one of the products obtained in poor yield in a reaction between methyl sulfate and thiosaccharin (1). The structure of the methyl derivative as given by Mannessier is shown in (Ib).

In the course of some previous work by Meadow and Reid (9), the reaction



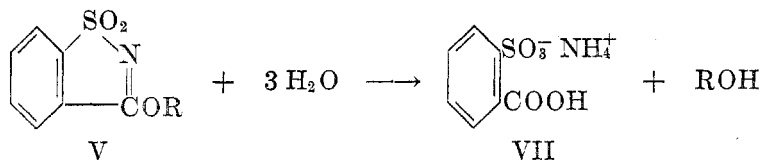
between pseudosaccharin chloride (3-chlorobenzisulfonazole, IV) and various alcohols and phenols was studied, and O-alkyl derivatives of saccharin (V) were characterized. These O-alkyl compounds, which behave chemically very much like esters, are isomeric with the N-alkyl derivatives of saccharin (III), previously reported by Remsen, McClelland, Merritt, and others (10-15).

The proof of structure of 3-chlorobenzisulfonazole (IV) has been carried out by Jesurun and others (16). During a recent investigation by the present authors, this compound was allowed to react with sodium methanethiol in dry benzene, yielding a crystalline derivative. It was presumed that this compound was S-methylthiosaccharin (3-methylmercaptobenzisulfonazole, VIa) containing the —SCH_3 group in the position shown. Since the melting point of this compound was very close to that reported (1) for N-methylthiosaccharin (2,3-dihydro-2-methyl-3-thiobenzisulfonazole, Ib) it was logical to assume that the reaction between thiosaccharin and methyl sulfate produced the S-methyl rather than the N-methyl derivative.

This supposition was verified by carrying out reactions between thiosaccharin and methyl sulfate in dry benzene, using conditions similar to those mentioned in the literature (1). The product obtained from this reaction was identical in every respect to that obtained from saccharin chloride and sodium methanethiol. The latter product is concluded to be S-methylthiosaccharin (VIa).

Additional support in favor of the S-methyl structure is furnished by a study of the hydrolysis of these derivatives. The compound produced either from thiosaccharin and methyl sulfate, or from saccharin chloride and sodium methanethiol (VIa) was hydrolyzed easily by refluxing in sulfuric acid solution. A good yield of methanethiol, one of the hydrolysis products, was collected in alcoholic sodium hydroxide solution and identified by the Bost method (17), using 2,4-dinitrochlorobenzene. The other hydrolysis product was more readily obtained as ammonium acid *o*-sulfobenzoate (VII) when aqueous hydrochloric acid was used instead of sulfuric acid and the resulting solution evaporated to dryness.

Hydrolysis of the O-alkyl derivatives of saccharin (V) with hydrochloric acid solution proceeds in a similar way. The O-cetyl derivative (3-hexadecylbenzisulfonazole) from saccharin chloride and cetyl alcohol (9) gave a good



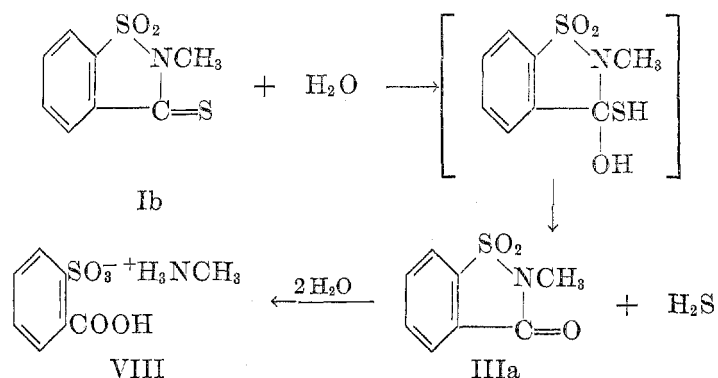
yield of cetyl alcohol and ammonium acid *o*-sulfobenzoate (VII).

The preparation of S-ethylthiosaccharin (VIb) was carried out by both methods used in the preparation of the S-methyl derivative, which also yielded a yellow compound whose properties were quite different from the N-ethyl derivative.

Inasmuch as none of the N-alkyl derivatives of thiosaccharin are known, a

method of preparation was devised which is analogous to that for the preparation of thiosaccharin from saccharin (1), *i.e.*, the action of phosphorus pentasulfide on N-methylsaccharin. The latter derivative, although reported to have been made by several methods (10-14), is most conveniently prepared by treating saccharin with methyl sulfate. Curiously, this same reagent with thiosaccharin gave mainly the S-methyl derivative. The N-methylsaccharin was then converted to the bright orange-colored N-methylthiosaccharin (Ib) with phosphorus pentasulfide. In a similar way, N-ethylthiosaccharin (Ic), also orange, was obtained from N-ethylsaccharin and phosphorus pentasulfide.

The structure of N-methylthiosaccharin was established by identifying its hydrolysis products from strongly acid solutions. It was much more resistant to acid hydrolysis than its isomer, the S-methyl derivative. The former compound was unaffected by 30% hydrochloric acid after refluxing for 10 hours. However, by using 90% sulfuric acid, it could be hydrolyzed stepwise to give, first, N-methylsaccharin (IIIa) with loss of hydrogen sulfide, then the very soluble methylammonium acid *o*-sulfobenzoate (VIII):



In order to isolate the intermediate (IIIa), the N-methylthiosaccharin was heated with 90% sulfuric acid for 10 minutes at 175-180°. After isolation, the N-methylsaccharin was hydrolyzed by refluxing for 10 hours in 30% hydrochloric acid, yielding methylammonium acid *o*-sulfobenzoate. Treatment of this salt with dilute sodium hydroxide liberated methylamine, which was absorbed in hydrochloric acid solution and identified as the crystalline hydrochloride. Methylamine was also obtained when the hydrolysis of N-methylthiosaccharin in 90% sulfuric acid was carried to completion, followed by alkalization with sodium hydroxide.

EXPERIMENTAL¹

Thiosaccharin (Ia). A mixture of saccharin (18.3 g., 0.1 mole) and phosphorus pentasulfide (Eastman, 25.0 g., 0.11 mole) was heated in a small round-bottom flask immersed in an oil-bath. The bath temperature was allowed to rise slowly from 50° to 155° over a 45-minute period. Heating was continued 15 minutes longer while the temperature rose from 155° to 170°. The reaction mixture was extracted with benzene yielding 80-85% of yellow crude

¹ All melting points are uncorrected. Semimicroanalyses were carried out in this laboratory. Molecular weights were determined by the Rast method.

thiosaccharin, m.p. 177–179°. With alternate procedures numerous side reactions reduced the yield considerably. Recrystallization from benzene-heptane mixtures sharpened the melting point to 178–178.5° (Lit. 180°).

S-Methylthiosaccharin (VIa) from methyl sulfate and thiosaccharin. A mixture of thiosaccharin (4.9 g., 0.025 mole), redistilled methyl sulfate (9.71 g., 0.077 mole), and 15 ml. of dry benzene was refluxed three hours, cooled, and the crystals allowed to separate. The impure product was washed with dilute ammonium hydroxide to remove unchanged thiosaccharin or saccharin. Weight of crude S-methylthiosaccharin, 2.55 g. (51%). Recrystallization from alcohol using Norit to remove traces of a yellow color gave colorless crystals, m.p. 217.5–218.5°.

Anal. Calc'd for $C_5H_7NO_2S_2$: S, 30.07; M.W., 213.

Found: S, 30.10; M.W., 204.

S-Methylthiosaccharin from methanethiol and saccharin chloride. Freshly cut sodium (0.8 g., 0.035 mole) was suspended in 80 ml. of dry benzene and a large excess of methanethiol (12–15 g., 0.25–0.30 mole) was added slowly over a period of one hour to form sodium methanethiol. After standing three hours the temperature was raised to about 50° to bring the last traces of sodium into solution. To the suspension of light-yellow salt was added 8.0 g. (0.039 mole) of saccharin chloride (9), m.p. 145–147°, over a period of one-half hour, raising the temperature from 25° to about 60°. After cooling, the solid mass of crystals was washed with warm water and the residue recrystallized from a large volume of alcohol; yield, 5.8 g. (77%) of S-methylthiosaccharin, m.p. 216.5–218.5°. A second recrystallization from hot alcohol gave colorless crystals, m.p. 218–219°. A mixture m.p. with the product obtained from methyl sulfate and thiosaccharin was undepressed.

Anal. Calc'd for $C_5H_7NO_2S_2$: S, 30.07; N, 6.57.

Found: S, 30.27; N, 6.60.

S-Ethylthiosaccharin (VIb), from ethyl sulfate and thiosaccharin. Following the procedure outlined for VIa, the crude S-ethyl derivative was obtained in 33% yield. Purification of the product with Norit in alcohol produced colorless crystals, m.p. 182.5–183.5°.

Anal. Calc'd for $C_7H_9NO_2S_2$: S, 28.21. Found: S, 28.11.

S-Ethylthiosaccharin from ethanethiol and saccharin chloride. A 70% yield of the crude S-ethyl derivative (1.6 g.) was obtained from a mixture of sodium (0.23 g., 0.01 mole), a large excess of ethanethiol (10 g., 0.16 mole), and 80 ml. of dry benzene. The saccharin chloride (2.0 g., 0.01 mole) was added slowly, using conditions similar to those for the S-methyl derivative, yielding colorless crystals from alcohol, m.p. 182.5–184.0°. A second recrystallization from alcohol gave m.p. 183–184°. A mixture m.p. with the ethyl derivative prepared from ethyl sulfate and thiosaccharin was 182.5–184°.

Anal. Calc'd for $C_7H_9NO_2S_2$: S, 28.21; N, 6.16; M.W., 227.

Found: S, 28.23; N, 6.23, M.W., 233.

N-Methylsaccharin (IIIa). Saccharin (18.3 g., 0.1 mole) was converted into the sodium salt by adding it to 20 g. of 20% sodium hydroxide. Methyl sulfate (26.6 g., 0.21 mole) was added dropwise over a 15-minute period with constant stirring. The temperature was allowed to rise to about 60–70° with the formation of two separate layers. Sodium hydroxide pellets (1.5 g., 0.038 mole) were then added; the mixture solidified on cooling. The product was washed with cold water, filtered, and dried, yielding 15.9 g., (81%) of crude product, m.p. 125–127°. Recrystallization from either alcohol or a large volume of hot water produced long needles, m.p. 130–131°.

Anal. Calc'd for $C_8H_7NO_3S$: N, 7.10; M.W., 197.

Found: N, 7.24; M.W., 199.

N-Ethylsaccharin (IIIb). Yields of 50–60% were obtained when the dry sodium salt of saccharin (6.2 g., 0.03 mole) was heated with ethyl sulfate (9.4 g., 0.06 mole) and very little water (0.7 g., 0.04 mole) was added. After refluxing the mixture gently for about one hour, the contents solidified on cooling. The product was recrystallized from hot water, and 3.4 g. (54%) of small, needle-like, colorless crystals, m.p. 93–94° were obtained.

Anal. Calc'd for $C_9H_9NO_3S$: N, 6.63; M.W., 211.

Found: N, 6.47; M.W., 213.

N-Methylthiosaccharin (Ib). This derivative was prepared by heating a mixture of *N*-methylsaccharin (6.0 g., 0.03 mole) and phosphorus pentasulfide (10.0 g., 0.045 mole) in a flask immersed in an oil-bath. The temperature was allowed to rise gradually from 20° to 150° over a 30-minute period, with evidence of a definite reaction at 135–140°. Heating was continued for another 30 minutes during which time the temperature rose from 150° to 175°. After cooling, the product was extracted with benzene, dried, then washed with about 600 ml. of boiling water to remove traces of unreacted IIIa, to yield 5.0 g. (78%) of crude yellow compound. This material was insoluble in aqueous ammonia and hot water, moderately soluble in benzene or hot alcohol, less soluble in *n*-heptane, and easily recrystallized from either a benzene-heptane mixture or alcohol, producing brilliant orange-yellow needles from the latter solvent, m.p. 171.5–173°. A mixture melting point of this compound with thiosaccharin, m.p. 178–178.5°, was depressed to 138–144°.

Anal. Calc'd for $C_8H_7NO_2S_2$: N, 6.57; M.W. 213.

Found: N, 6.60; M.W., 204.

N-Ethylthiosaccharin (Ic). A mixture of *N*-ethylsaccharin (6.0 g., 0.028 mole) and phosphorus pentasulfide (10.0 g., 0.045 mole) was heated in a flask, using conditions like those for Ib. After extraction with benzene and washing with hot water, a crude yellow product (5.4 g., 85%), m.p. 107–110.5° was obtained. Distinctly yellow, feather-like crystals, m.p. 109.5–110.5°, resulted after one recrystallization from hot alcohol. Solubility characteristics were similar to Ib.

Anal. Calc'd for $C_9H_9NO_2S_2$: S, 28.21. Found: S, 28.23.

Hydrolysis of S-methylthiosaccharin (VIa). A mixture of VIa (2.13 g., 0.01 mole) and 90 ml. of 30% sulfuric acid was refluxed 2.5 hours, during which time a slow stream of nitrogen gas conducted the evolved methanethiol into a cold solution of 0.4 g. (0.01 mole) of sodium hydroxide and 3 ml. of water in 40 ml. of absolute alcohol. Adding this solution of the sodium salt to 2.02 g. (0.01 mole) of 2,4-dinitrochlorobenzene in 10 ml. of absolute alcohol and warming gently gave a yellow precipitate which was washed with water and dried, yielding 1.8 g. of crude product (81% recovery of methanethiol). Recrystallization from 95% ethanol gave a yellow crystalline compound, m.p. 127–127.5° (Lit. 128°), which was identical with a similar derivative made from known methanethiol. Oxidation of the derivative with potassium permanganate produced the colorless sulfone, m.p. 183–184°, which was also identical to the known sulfone.

Hydrolysis of 1.46 g. (0.007 mole) of VIa for 2.5 hours in 50 ml. of 30% hydrochloric acid, followed by evaporation to dryness, produced a crude salt (1.38 g., 90%) which, after recrystallization from 25 ml. of absolute alcohol, was shown to be ammonium acid *o*-sulfobenzoate (VII).

Anal. Calc'd for $C_7H_5NO_3S$: N, 6.39. Found: N, 6.39.

Hydrolysis of O-hexadecylsaccharin (V, R = $C_{16}H_{33}$). This derivative (2.25 g., 0.0055 mole) prepared by Meadow and Reid (9), was completely hydrolyzed after refluxing for four hours with 60 ml. of 30% hydrochloric acid. *n*-Hexadecyl alcohol (1.3 g., 95%) crystallized on cooling and was filtered off, then recrystallized from alcohol, m.p. 48.5–49° (Lit. 48–49°). The *n*-hexadecyl alcohol was further identified by converting it back to *O-n*-hexadecylsaccharin, m.p. 68–69°, with saccharin chloride (9). The filtrate obtained after hydrolysis was evaporated to dryness, and the ammonium acid *o*-sulfobenzoate (VII) was identified by analysis after recrystallization from absolute alcohol. The salt evolved ammonia readily when warmed with sodium hydroxide solution.

Anal. Calc'd for $C_{77}H_{151}NO_3S$: C, 38.35; H, 4.14.

Found: C, 38.40; H, 4.17.

Hydrolysis of N-methylsaccharin (IIIa). A mixture of IIIa (2.5 g., 0.013 mole) and 50 ml. of 30% hydrochloric acid was refluxed for 5 hours, 50 ml. of concentrated hydrochloric acid was added, and refluxing was continued for an additional 5 hours. Only 0.05 g. of unchanged IIIa remained suspended in the solution, which was filtered and the filtrate evaporated to dryness. A crystalline salt (2.8 g., 90%) was obtained, which was very soluble in water, ethyl alcohol, and butanol; insoluble in chloroform and *n*-heptane. Recrystallization from a

butanol-*n*-heptane mixture gave a product melting at 137–138° that produced methylamine when warmed with sodium hydroxide solution. An analysis confirmed the structure as methylammonium acid *o*-sulfobenzoate (VIII).

Anal. Calc'd for $C_8H_{11}NO_3S$: S, 13.75. Found: S, 13.94.

Identification of methylamine. Sodium hydroxide (0.4 g. in 3 ml. water) was added to 1 g. of methylammonium acid *o*-sulfobenzoate obtained from the hydrolysis of IIIa. The methylamine evolved was conducted by a stream of nitrogen into 4 ml. of 18% hydrochloric acid. The solution was evaporated to dryness and the crude salt (0.24 g., 80%) was recrystallized from absolute ethanol yielding plates, m.p. 226–227.5°. (Lit. 226–228°)

Hydrolysis of N-methylthiosaccharin (Ib). A mixture of Ib (0.5 g., 0.0022 mole) and 2 ml. of 90% sulfuric acid was warmed for 10 minutes at 175–180°, cooled, and then poured into 10 ml. of cold water. The white precipitate, (0.3 g., 70%), m.p. 130–131°, proved to be N-methylsaccharin, since a mixture melting point with an authentic sample (IIIa) was unchanged.

Complete hydrolysis of Ib was effected by heating it at 175–180° with 90% sulfuric acid as above for at least 30 minutes. The sulfuric acid hydrolysate was neutralized cautiously with dilute sodium hydroxide solution, a slight excess was added, and the methylamine evolved was identified as the crystalline hydrochloride, m.p. 226–227°, as previously described.

SUMMARY

Two sets of methyl and ethyl derivatives of thiosaccharin have been described. Those compounds prepared for the first time are: N-methylthiosaccharin, N-ethylthiosaccharin, and S-ethylthiosaccharin. One of the derivatives, although reported in the literature previously as *N-methylthiosaccharin* has been shown to be, in reality, the *S-methyl* derivative.

The action of alkyl sulfates on saccharin and thiosaccharin produces a different type of derivative in each case. The position of the alkyl group in each type of isomer was proven by degradation and synthesis.

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