was distilled at 1 mm., bath temperature 350–400°. The residue was burned to recover radioactive carbon. The yellow distillate was dissolved in hot benzene and was crystallized to give 0.330 g. of yellow dibenzanthracene, m. p. 231–243°. The purification was accomplished by boiling for one hour a mixture of 0.330 g. of yellow dibenzanthracene and 0.07 g. of lead tetraacetate in 16 cc. of benzene and 16 cc. of acetic acid. The reaction mixture was concentrated to a volume of 12 cc. The colorless dibenzanthracene was removed by filtration and washed with cold acetic acid: yield 0.230 g.; m. p. 249–253°. The product was recrystallized from benzene to give pure colorless plates of dibenzanthracene: yield 0.207 g.; m. p. 259–262°. Thus the over-all yield of pure dibenzanthracene, based on barium carbonate, is 11%.

Anal. Calcd. for $C_{22}H_{14}$: C, 94.93; H, 5.07. Found: C, 94.55; H, 5.48. Specific activity × 22, 94,000 counts/min./mg. barium carbonate. Activity of compound: 67,000 cts./min./mg. D. B. A.

Practice Elbs Reactions.—**A.** Pyrolysis time, 45 minutes; wt. ketone, 2.20 g.; wt. crude yellow compound, 0.78 g., m. p. 231–246°. Remained yellow after two treatments with 0.15 g. of lead tetraacetate.

B. Pyrolysis time, one and one-half hours; wt. ketone, 2.20 g.; wt. crude yellow compound, 0.65 g., m. p. 221–231°. Required two treatments, 0.26 g. of lead tetraacetate; wt. colorless compound, 0.36 g., m. p. 245–255°.

C. Pyrolysis time, three and one-half hours; wt. ketone, 2.20 g.; wt. crude yellow compound, 0.60 g., m. p. 246–261°. Required only one treatment with lead tetraacetate 0.12 g. Wt. colorless compound 0.46 g., m. p. 259–261°.

Determination of Specific Activities.—A typical determination was carried out as follows: A sample of 1.184 mg. of radioactive β-naphthoic acid was weighed into one boat, and 31.608 mg. of inactive benzoic acid was placed in another. The boats were inserted in a micro combustion furnace connected to a sodium hydroxide bubbler. The naphthoic acid was burned first, and then the benzoic acid. The carbon dioxide was precipitated as barium carbonate, and 378.2 mg. was obtained from which plates were made, with specific activities of 336, 336 and 338 cts./min./mg. barium carbonate.

Specific activity × 11 =

$$\frac{337 \times 378.2 \times 11}{1.184 \times 16.4 \times .77} = 93{,}800 \text{ cts./min./mg.}$$

barium carbonate, where 16.4 is the molecular weight ratio of barium carbonate/carbon and 0.77 is the fraction of carbon in naphthoic acid.

Combustion of Residues.—From the combustion of the combined residues, 22.9 g. of barium carbonate was recovered. For the determination of specific activity a 19.004-mg. sample was diluted with inactive carbonate to a weight of 332.9 mg. of barium carbonate from which three plates were obtained with specific activities of 130, 134 and 137 cts./min./mg. barium carbonate. Specific activity of sample from combustion = 134 × 332.9/19.004 = 2345 cts./min./mg. barium carbonate.

Summary

1. 1,2,5,6-Dibenzanthracene, labeled with carbon fourteen in the 9-position has been synthesized in 11% over-all yield based on carbon dioxide.

2. A study of the Elbs reaction of 1-(2-naphthoyl)-2-methylnaphthalene has shown that the volatile by-products largely result from the carbonyl carbon and that optimum yields are obtained when the reaction is heated for three hours or more.

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[CONTRIBUTION FROM RESEARCH LABORATORIES OF THE J. T. BAKER CHEMICAL COMPANY]

Tartaric, *o*-Sulfobenzoic and β-Sulfopropionic Acid Derivatives of Some Sulfonamides

BY V. B. FISH, J. R. STEVENS AND R. G. D. MOORE

A number of polycarboxylic acid derivatives of some of the sulfonamides has been reported by Moore and Miller.[1] These compounds were prepared by one or more of three general methods. These general methods include the condensation of the desired sulfonamide with an acid anhydride, ester or the free acid. In a patent, Moore,[2] mentioned 2-N^4-tartarylsulfanilamidothiazole, but did not describe the properties of the compound or specific conditions for its preparation.

No mention has been found in the literature of the preparation of N^4-sulfocarboxylic acid derivatives of the sulfonamides. It seemed desirable to prepare such compounds for pharmacological evaluation.

The 2-N^4-tartaryl and diacetyltartaryl derivatives (I) were prepared by the action of diacetyltartaric anhydride[3] on a solution or suspension of the sulfonamide in glacial acetic acid or anhydrous pyridine. In general, the reaction mixtures were heated to about 80° for two hours. The crude products either crystallized on cooling or were precipitated by pouring the reaction mixture into benzene when acetic acid was used as a reaction medium. When the reaction was made in pyridine the subsequent treatment was varied to suit the particular case. The crude products were recrystallized from a suitable solvent until a satisfactory product was obtained. The tartaryl derivatives were prepared from the corresponding diacetyl compounds by a mild alkaline hydrolysis.

$$HO_2CCH(OAc)CH(OAc)CONHC_6H_4SO_2NHY \quad (I)$$

The derivatives of *o*-sulfobenzoic acid (II) were prepared by the action of *o*-sulfobenzoic anhydride on the sulfonamide in anhydrous pyridine. The pyridine salts were isolated and purified by recrystallization from water or aqueous alcohol. The pyridine salts were converted to the corresponding sodium salts by treatment with a

(1) Moore and Miller, THIS JOURNAL, **64**, 1572 (1942).
(2) Moore, U. S. Patent 2,324,013 (1943).
(3) Wohl and Oesterlin, *Ber.*, **34**, 1144 (1901).

slight excess of sodium hydroxide. The pyridine and excess water were removed under reduced pressure.

$$NaO_3SC_6H_4CONHC_6H_4SO_2NHY \quad (II)$$

The β-sulfopropionic acid derivatives (III) were prepared by the reaction of β-sulfopropionic anhydride[4] on the sulfonamide in dry pyridine. The reaction products were isolated as the pyridine salts and then converted to the sodium salt as described above.

$$NaO_3SCH_2CH_2CONHC_6H_4SO_2NHY \quad (III)$$

The type formulas II and III represent the structure of these compounds and are supported by data obtained in their preparation. Aqueous solutions of the corresponding pyridine salts are quite acidic. A solution of 0.1 g. of the pyridine salt of *o*-sulfobenzoylsulfathiazole in 100 ml. of water was found to give a *p*H of 2.95. It was also found that the pyridine salt of *o*-sulfobenzoylsulfanilamide could be recrystallized unchanged from 10% aqueous hydrochloric acid.

Experimental

N⁴-Tartarylsulfanilamide.—To a solution of 34.4 g. (0.20 mole) of sulfanilamide in 100 ml. of dry pyridine, 40 g. (0.184 mole) of diacetyltartaric anhydride was added in about four equal portions, and the mixture evaporated to a thick sirup. An additional 200-ml. portion of water was added and the solution made just alkaline to phenolphthalein with sodium hydroxide. The solution was again evaporated nearly to dryness and was maintained just alkaline during the evaporation. The crystalline mass was dissolved in water and strongly acidified with hydrochloric acid. The product was recrystallized twice from water and once from 30% acetic acid; yield was 29.5 g. (52.7%), m. p. 210° dec.

Anal. Calcd. for $C_{10}H_{12}O_7N_2S$: C, 39.50; H, 3.95; N, 9.22. Found: C, 39.50; H, 3.85; N, 9.23.

N⁴-Tartarylsulfathiazole: Method A.—To a suspension of 25.5 g. (0.1 mole) of sulfathiazole in 130 ml. of pyridine, was added 20 g. (0.093 mole) of diacetyltartaric anhydride. The reaction was carried out as described for N¹-tartarylsulfanilamide. The reaction mixture was diluted with 200 ml. of water and allowed to evaporate at room temperature to remove most of the pyridine. Water was added, and the solution made alkaline to phenolphthalein with sodium hydroxide. The solution was allowed to stand at room temperature and sodium hydroxide added as necessary to maintain alkalinity. When the solution remained alkaline for an hour without additional sodium hydroxide, it was acidified with acetic acid and concentrated on the steam-bath. Water was added, and the solution filtered to remove undesirable by-products. The filtrate was strongly acidified with hydrochloric acid resulting in the separation of an oil which crystallized on standing. The mixture was cooled in ice and filtered. Crystallization twice from water, using carbon, and once from 30% acetic acid gave a light yellow product, m. p. 170° dec.

Anal. Calcd. for $C_{13}H_{13}O_7N_3S_2H_2O$: C, 38.50; H, 3.70. Found: C, 38.70; H, 3.69.

The material was redried at 100° under reduced pressure yielding an anhydrous product which was quite hygroscopic.

Anal. Calcd. for $C_{13}H_{13}O_7N_3S_2$: C, 40.30; H, 3.38; N, 10.85. Found: C, 40.30; H, 3.50; N, 10.90.

Method B.—N⁴-Tartarylsulfathiazole was prepared by the deacetylation of diacetyltartarylsulfathiazole with sodium hydroxide.

An aqueous solution of 100 g. (0.21 mole) of diacetyltartarylsulfathiazole, prepared as described below, was treated with 10% sodium hydroxide solution to a *p*H of about 9, 300 ml. being required. The solution was boiled for two hours, and the *p*H was then re-adjusted to about 9 with 6 ml. more of 10% sodium hydroxide solution. The filtered solution was acidified with 20% hydrochloric acid and the product collected on a filter. The product was recrystallized from water to yield 54 g. (83%), m. p. 170° dec.

Anal. Calcd. for $C_{13}H_{13}O_7N_3S_2$: C, 40.30; H, 3.38; N, 10.85. Found: C, 40.15; H, 3.45; N, 10.80.

N⁴-Diacetyltartarylsulfathiazole.—A suspension of 225 g. (1.0 mole) of sulfathiazole in 700 ml. of glacial acetic acid was treated with 200 g. (0.93 mole) of diacetyltartaric anhydride. The mixture was warmed to 80° and stirred at that temperature for two hours. Solid material separated during the reaction, and the material was dissolved by adding water and heating to 90°. The solution was decolorized once with carbon and allowed to crystallize. The crude product was filtered, washed with water, recrystallized from 30% acetic acid and dried; yield was 268.6 g. (57%), m. p. 155° dec.

Anal. Calcd. for $C_{17}H_{17}O_9N_3S_2$: C, 43.30; H, 3.63; N, 8.92. Found: C, 43.15; H, 3.64; N, 8.90.

N⁴-Diacetyltartarylsulfadiazine.—A suspension of 25.1 g. (0.1 mole) of sulfadiazine in 100 ml. of glacial acetic acid was treated with 20 g. (0.093 mole) of diacetyltartaric anhydride. The crude material was precipitated by adding the reaction mixture to 500 ml. of benzene, filtered and recrystallized twice from a mixture of equal volumes of benzene and isopropyl alcohol. The yield of vacuum dried material was 20.4 g. (47%), m. p. 160° dec.

Anal. Calcd. for $C_{18}H_{18}O_9N_4S$: C, 46.40; H, 3.86; N, 12.00; acetyl, 18.4. Found: C, 46.45; H, 3.77; N, 11.80; acetyl, 18.4.

N⁴-Sodium-*o*-sulfobenzoylsulfanilamide.—A solution of 133 g. (0.772 mole) of sulfanilamide in 300 ml. of pyridine was treated with 180 g. (0.977 mole) of powdered *o*-sulfobenzoic anhydride. The pyridine salt was isolated by adding the reaction mixture to excess acetone. The crude salt was recrystallized twice from water and dried; yield was 300 g. (89.5%), m. p. 239°.

Anal. Calcd. for $C_{18}H_{17}O_6N_3S_2$: C, 49.70; H, 3.90. Found: C, 49.80; H, 3.74.

The pyridine salt was treated with an excess of sodium hydroxide solution and evaporated to dryness on the steam-bath. The crude sodium salt was recrystallized twice from water slightly acidified with hydrochloric acid. The product was dried first under reduced pressure at 40° and finally at 110°; yield was 216.7 g. (74%).

Anal. Calcd. for $C_{13}H_{11}O_6N_3S_2Na$: C, 41.30; H, 2.91; N, 7.41; Na, 6.09. Found: C, 41.40; H, 2.85; N, 7.38; Na, 6.02.

N⁴-Sodium-*o*-sulfobenzoylsulfathiazole.—A suspension of 290 g. (1.14 mole) of sulfathiazole in dry pyridine was treated with 184 g. (1.0 mole) of *o*-sulfobenzoic anhydride. The mixture was warmed until all the solid materials were dissolved. The reaction mixture was poured into 1.5 liters of acetone and stirred until the crystalline pyridine salt was precipitated. The salt was crystallized from water twice; yield was 373 g. (72%), m. p. 243° dec.

The pyridine salt was treated with two equivalents of sodium hydroxide, and the solution evaporated to dryness. The crude di-sodium salt was dissolved in warm water, and the *p*H adjusted to 4 with hydrochloric acid. The mono-sodium salt crystallized on cooling the solution and was recrystallized twice from water with one decolorization; yield was 258 g. (56%).

Anal. Calcd. for $C_{16}H_{12}O_6N_3S_3Na$: C, 41.65; H, 2.62; N, 9.10; Na, 4.98. Found: C, 41.60; H, 2.54; N, 9.03; Na, 4.96.

N⁴-Sodium-*o*-sulfobenzoylsulfadiazine.—To a suspension of 22.6 g. (0.09 mole) of sulfadiazine in 100 ml. of

(4) Kharasch, Chao and Brown, THIS JOURNAL, **62**, 2393 (1940).

dry pyridine there was added 14.4 g. (0.08 mole) of *o*-sulfobenzoic anhydride. The solution was poured into 600 ml. of acetone and the precipitated pyridine salt was filtered. The crude salt was recrystallized twice from water with one decolorization with carbon, m. p. 243°.

Anal. Calcd. for $C_{22}H_{19}O_6N_5S_2$: C, 51.50; H, 3.71. Found: C, 51.70; H, 3.70.

The pyridine salt was suspended in water and sodium hydroxide was added to *p*H 7.2. The pyridine was removed, and the solution concentrated to a sirup under reduced pressure. Absolute alcohol was added, and the mixture again concentrated under reduced pressure. The precipitated salt was filtered and washed with 95% alcohol and dried. Analysis showed the product to be a mixture of the mono- and di-sodium salts.

Anal. Calcd. for $C_{17}H_{12}O_6N_4S_2Na_2 \cdot H_2O$: C, 41.40; H, 2.82; Na, 9.28. Found: C, 40.70; H, 2.97; Na, 8.54.

The mono-sodium salt was prepared by treating the pyridine salt with two equivalents of sodium hydroxide and evaporating the resulting solution to dryness. The solid material was dissolved in a small volume of water and acidified to *p*H 3.8 with hydrochloric acid. The material which crystallized was recrystallized twice from aqueous alcohol. The product proved to be the monohydrate even after being dried at 110°. The theoretical amount of water was removed by drying at 110° and 3 mm. pressure, yield 76%.

Anal. Calcd. for $C_{17}H_{13}O_6N_4S_2Na \cdot H_2O$: C, 43.10; H, 3.18; N, 11.81; Na, 4.85; H_2O, 3.80. Found: C, 43.27; H, 3.12; N, 11.65; Na, 4.83; H_2O, 3.87.

N⁴-Sodium-β-sulfopropionylsulfanilamide.—A suspension of 35 g. (0.2 mole) of sulfanilamide in 50 ml. of dry pyridine was treated with 25 g. (0.18 mole) of β-sulfopropionic anhydride. A reaction occurred with the liberation of considerable heat. The reaction mixture was poured slowly into 600 ml. of acetone with constant stirring. The pyridine salt separated and was recrystallized from 95% ethanol; yield was 23.6 g. (33.8%), m. p. 185–186°.

Anal. Calcd. for $C_{14}H_{17}O_6N_3S_2$: C, 43.40; H, 4.39; S, 16.52. Found: C, 43.20; H, 4.22; S, 16.40.

A solution of 16 g. of the pyridine salt in water was adjusted to *p*H 7.0 with sodium hydroxide. The solution was evaporated nearly to dryness under reduced pressure. A portion of 95% ethanol was added, and the evaporation repeated. The solid material was crystallized twice from 95% alcohol. Yield was 12 g. (88%).

Anal. Calcd. for $C_9H_{11}O_6N_2S_2Na$: C, 32.72; H, 3.36; N, 8.47; Na, 6.96. Found: C, 32.75; H, 3.29; N, 8.46; Na, 7.02.

N⁴-Sodium-β-sulfopropionylsulfathiazole.—A suspension of 225 g. (1 mole) of sulfathiazole in 500 ml. of dry pyridine was treated with an equivalent amount (136 g.) of β-sulfopropionic anhydride. When the addition was complete, the hot solution was kept at 80° for two hours and then added to 2 liters of benzene. The benzene extract was decanted from the sirup, which was air dried and extracted with hot water. Considerable unreacted sulfathiazole did not dissolve and was removed by filtration after the solution had cooled. The filtrate was decolorized with carbon and evaporated to dryness under reduced pressure. The sirup was recrystallized from twice its volume of alcohol, m. p. 210–215° dec.

Anal. Calcd. for $C_{17}H_{18}O_6N_4S_3$: C, 43.40; H, 3.83. Found: C, 43.30; H, 3.71.

The pyridine salt was converted to the sodium salt by treating the aqueous solution with sodium hydroxide to *p*H 7.2. One mole of pyridine salt required 1.25 mole of sodium hydroxide. The product crystallized out in part, and the remainder was obtained from the mother liquors by evaporation to dryness. The residue thus obtained was recrystallized from water.

Anal. Calcd. for $C_{12}H_{12}O_6N_3S_3Na$: C, 34.90; H, 2.93; N, 10.16; Na, 5.56. Found: C, 34.85; H, 2.88; N, 10.08; Na, 5.56.

Summary

1. The preparation of some N⁴-tartaryl and diacetyltartarylsulfonamides by the action of diacetyltartaric anhydride on the sulfonamide in pyridine or glacial acetic acid has been described.

2. The *o*-sulfobenzoyl derivatives of sulfanilamide, sulfathiazole and sulfadiazine have been prepared.

3. A method has been described for the preparation of the β-sulfopropionic acid derivatives of sulfanilamide and sulfathiazole.

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[CONTRIBUTION FROM THE CHEMOTHERAPY DIVISION, STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

Studies in Chemotherapy. XV. Amides of Pantoyltaurine[1]

BY R. WINTERBOTTOM, J. W. CLAPP, W. H. MILLER, J. P. ENGLISH AND R. O. ROBLIN, JR.

Since the demonstration by McIlwain and Hawking[2] that pantoyltaurine[3] acted as a therapeutic agent in rats infected with a lethal strain of hemolytic streptococcus, numerous papers[4] have appeared describing the preparation and antibacterial activity of other pantothenic acid analogs. None of these appears to show consistently greater bacteriostatic action *in vitro* than pantoyltaurine. Only one, 2-(pantoylamino)-ethyl-4-aminophenyl sulfone,[5] has been found to be active *in vivo*. In this case, as with pantoyltaurine, administration of the compound by repeated subcutaneous injection was necessary to attain a therapeutic effect. Although pantoyltaurine was shown to be inactive against *Plasmodium relictum* infection in the canary,[2] the work of Trager[6] suggested that pantothenic acid might be a growth

(1) Presented in part before the Division of Medicinal Chemistry, Atlantic City Meeting of the American Chemical Society, April 10, 1946.

(2) McIlwain and Hawking, *Lancet*, **244**, 449 (1943).

(3) The abbreviated term "pantoyl" is used for the radical "α,γ-dihydroxy-β,β-dimethylbutyryl."

(4) *Cf.* Roblin, *Chem. Rev.*, **38**, 255 (1946).

(5) Madinaveitia, Martin, Rose and Swain, *Biochem. J.*, **39**, 85 (1945).

(6) Trager, *J. Expil. Med.*, **77**, 411 (1943).