

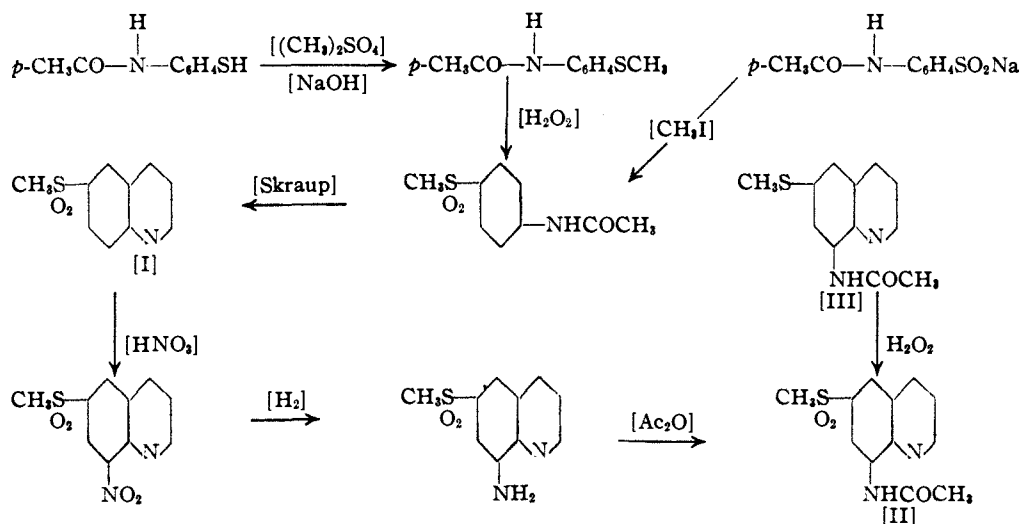
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

8-Amino-6-quinolyl Methyl Sulfone

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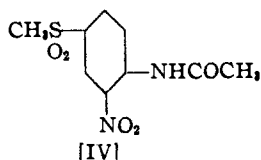
In connection with studies on experimental avian malaria and antitubercular agents an examination has been made of the synthesis of some sulfur-substituted heterocycles. We are now reporting the preparation of 8-amino-6-quinolyl methyl sulfone by the following sequence of reactions starting with a Skraup synthesis of 6-quinolyl methyl sulfone.

was reduced by aluminum powder and hydrochloric acid to *p*-acetaminothiophenol.² Third, to a cooled mixture of 41 g. (0.245 mole) of *p*-acetaminothiophenol in 162 cc. of water containing 18 g. (0.45 mole) of sodium hydroxide was added 39.8 g. (0.315 mole) of methyl sulfate in five portions over a ten-minute period.³ The mixture heated as a consequence of the exothermic reaction, and the product precipitated promptly. After stirring to room temperature, the sulfide^{2,3} was filtered, washed with water, and dried at 60–70°. The yield of crude product melting at 124.5–



The nitration of 6-quinolyl methyl sulfone [I] occurred in the 8-position as might have been predicted. This was established by comparison of the 8-acetamino-6-quinolyl methyl sulfone [II] obtained from [I] with the oxidation product of an authentic specimen of 8-acetamino-6-quinolyl methyl sulfide [III].

A more direct approach to the 8-acetamino-6-quinolyl methyl sulfone (or the corresponding 8-amino compound) might be a Skraup reaction on 3-nitro-4-acetaminophenyl methyl sulfone [IV].



However, in some orienting experiments it was observed that nitration of *p*-acetaminophenyl methyl sulfone gave a dinitro compound which may be 3,5-dinitro-6-aminophenyl methyl sulfone.

Experimental

***p*-Acetaminophenyl Methyl Sulfone. [A] By Oxidation of *p*-Acetaminophenyl Methyl Sulfide.**—First, di-*p*-acetaminophenyl disulfide was prepared by reduction of *p*-acetaminobenzenesulfonyl chloride.¹ Second, the disulfide

127° was 41 g. (92.3%). Fourth, to a suspension of 20 g. (0.11 mole) of *p*-acetaminophenyl methyl sulfide in 125 cc. of glacial acetic acid was added 30 cc. of 30% hydrogen peroxide over a ten-minute period. During this time the remaining solid dissolved and a clear solution resulted. The warm solution was then refluxed for two and one-half hours; the acetic acid was removed under reduced pressure; and the sulfone was recrystallized from methanol, using some Norite A for decolorization. The yield of *p*-acetaminophenyl methyl sulfone melting at 182–184° was 17 g. (72.6%).

Anal. Calcd. for $\text{C}_9\text{H}_{11}\text{O}_3\text{NS}$: S .15.03. Found: S, 15.1 and 15.1.

[B] From Sodium *p*-Acetaminobenzenesulfinate and Methyl Iodide.—To a stirred solution of 8 g. (0.2 mole) of sodium hydroxide in 80 cc. of water was added 28 g. (0.14 mole) of *p*-acetaminobenzenesulfonic acid.^{4a} Then to this basic solution was added 20.3 g. (0.143 mole) of methyl iodide and the mixture was refluxed for two hours. The solid which separated from the cooled solution was filtered and dried. An additional small amount of product was formed when the filtrate was refluxed for two hours with 10 g. (0.07 mole) of methyl iodide. The total yield of *p*-acetaminophenyl methyl sulfone melting at 182–184° was 21.5 g. (72%).^{4b} From another preparation starting with 95 g.

(1940).], used this procedure to obtain *p*-acetaminothiophenol, but in this present work the disulfide was the product. See. Smiles and Stewart. "Organic Syntheses." Coll. Vol. I, 8 (1941), for the preparation of the sulfonyl chloride.

(2) Hinsberg, *Ber.*, **39**, 2430 (1906).

(3) Zincke and Jörg, reference (1).

(4a) Smiles and Bere. "Organic Syntheses." Coll. Vol. I, 7 (1941).

(4b) Child and Smiles, *J. Chem. Soc.*, 2696 (1926), prepared the sulfone by methylation of the sulfonic acid but reported no yield.

(1) Zincke and Jörg, *Ber.*, **42**, 3362 (1909), and Gabel and Grinberg, *J. Applied Chem. USSR*, **14**, 1481 (1939) [*C. A.*, **34**, 6244

(0.407 mole) of *p*-acetaminobenzenesulfonyl chloride, and heating the sodium sulfinate with 0.483 mole of methyl iodide for nine hours there was obtained 75 g. (88%) of sulfone melting at 182–184°.

Skraup Reaction with *p*-Acetaminophenyl Methyl Sulfone.—To a mixture of 22 g. (0.112 mole) of *p*-acetaminophenyl methyl sulfone, 19.4 g. (0.084 mole) of arsenic acid anhydride, and 40.2 g. (0.448 mole) of dried glycerol was added 24.8 g. (0.252 mole) of concentrated sulfuric acid with stirring over a five-minute period. The reaction mixture (at about 70°) was gradually heated to 130–135° and held at that temperature for one hour by heating in an oil-bath. The temperature was then raised to 140–145° and held there for three hours. The dark solution was poured into 450 cc. of water, filtered and the filtrate was neutralized in the cold with ammonium hydroxide. A solid and oil separated when the alkaline solution was allowed to stand in an ice-bath; the mixture was filtered, and the product was purified by recrystallization from water using decolorizing charcoal. The yield of 6-quinolyl methyl sulfone melting at 125–127° was 5 g. (21.6%). Two recrystallizations from water raised the melting point to 126.5–128°.

Anal. Calcd. for $C_{10}H_9O_2NS$: N, 6.76. Found: N, 6.91.

In another preparation the yield of product melting at 124–126° was 6.7 g. (28.8%) when the mixture was heated at 130–135° for one hour and then at 140–145° for five hours. However, the yield decreased in an experiment where the heating at 140–145° was for a six-hour period, and in another experiment where the heating at 140–145° was for a three-hour period.

Nitration of 6-Quinolyl Methyl Sulfone.—To a cooled (by cold-water-bath) mixture of 15 cc. of concentrated sulfuric acid and 5 cc. of fuming nitric acid was added 2 g. (0.0088 mole) of 6-quinolyl methyl sulfone. The mixture was then heated in an oil-bath at 130° (external temp.) for six hours, after which the mixture was poured into 200 cc. of ice and water. A solid separated, but the solution was made alkaline with ammonium hydroxide, and the solid which was removed by filtration was washed with water and dried. The yield of crude 8-nitro-6-quinolyl methyl sulfone melting at 197–199° was 1.4 g. (63%). After recrystallization from ethanol the melting point was 200–201°.

Anal. Calcd. for $C_{10}H_8O_4N_2S$: N, 11.11; S, 12.71. Found: N, 10.92; S, 12.50 and 12.44.

The yields of crude nitro-sulfone in two other preparations were 1.3 g. and 1.5 g. (m. p. 198–200°).

In some orienting experiments it was observed that there was no appreciable nitration when the quinoline sulfone and the nitrating mixture was heated in a boiling water bath for two hours; nor when the quinoline-sulfone was treated with concentrated sulfuric acid and potassium nitrate and the mixture allowed to stand overnight at room temperature, or heated in a boiling water-bath for four hours.

8-Amino-6-quinolyl Methyl Sulfone.—Catalytic reduction of a mixture of 1.3 g. (0.005 mole) of 8-nitro-6-quinolyl

methyl sulfone in 50 cc. of absolute ethanol by 4 g. of Raney nickel and a hydrogen pressure of 40 pounds gave 0.65 g. (57%) of product melting at 150–153°. Recrystallization from absolute ethanol raised the melting point to 152.5–154.5°.

Anal. Calcd. for $C_{10}H_{10}O_2N_2S$: N, 12.6; S, 14.42. Found: N, 12.85; S, 14.58 and 14.57.

The same yield was obtained in another reduction.

8-Acetamino-6-quinolyl Methyl Sulfone.—Acetylation of 0.3 g. of 8-amino-6-quinolyl methyl sulfone in 15 cc. of benzene by refluxing for five minutes with 1 cc. of acetic anhydride gave 0.3 g. (84.5%) of the acetamino compound which melted at 191–193° after recrystallization from absolute ethanol. A mixed melting point determination with the 8-acetamino-6-quinolyl methyl sulfone (m. p. 193–195°) obtained by the hydrogen peroxide oxidation of 8-acetamino-6-quinolyl methyl sulfide was 193–195°.

Nitration of *p*-Acetaminophenyl Methyl Sulfone.—To a solution of 8 g. (0.036 mole) of *p*-acetaminophenyl methyl sulfone in 36 cc. of concentrated sulfuric acid, at 5–10°, was added a solution of 5 g. (0.049 mole) of potassium nitrate in 16 cc. of concentrated sulfuric acid. After stirring at room temperature for four hours, the mixture was poured into 600 cc. of ice and water. There was obtained 6 g. of a solid which melted at 232.5–234° after recrystallization from 50% dioxane. The analyses indicate the compound to be a dinitro compound, probably 3,5-dinitro-4-amino-phenyl methyl sulfone.

Anal. Calcd. for $C_7H_7O_4N_2S$: N, 16.1; S, 12.27. Found: N, 16.0; S, 12.26 and 12.27.

There was no appreciable nitration when *p*-acetaminophenyl methyl sulfone in concentrated sulfuric acid was treated with concentrated nitric acid at 10–18° for twenty minutes; nor when an acetic acid solution of the sulfone was treated with fuming nitric acid for one hour at 38–40° or for two hours at 30–35° or at room temperature overnight.

Acknowledgments.—The authors are grateful to Leo Tolman for assistance and for the reference sample of 8-acetamino-6-quinolyl methyl sulfide.

Summary

8-Amino-6-quinolyl methyl sulfone has been prepared by first nitrating 6-quinolyl methyl sulfone, obtained by a Skraup reaction with *p*-acetaminophenyl methyl sulfone. The position of the nitro (or amino) group was established by reduction of the nitro group, acetylation, and then comparison with the oxidation of an authentic specimen of 8-acetamino-6-quinolyl methyl sulfide.

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