[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY]

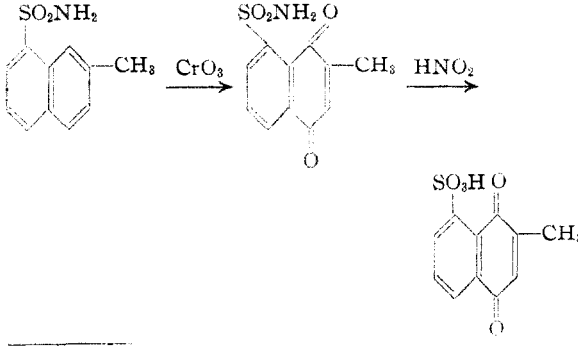
Synthesis of 2-Methyl-1,4-naphthoquinone-8-sulfonic Acid[1]

BY AARON BENDICH AND ERWIN CHARGAFF

In the course of work on the coagulation of fibrinogen by quinones, to be presented elsewhere,[2] it appeared of interest to examine **2-methyl-1,4-naphthoquinone-8-sulfonic acid.** There exist no general methods for the introduction of a sulfonic acid radical into the benzenoid portion of 1,4-naphthoquinone. The literature, in fact, contains only two examples of compounds of this type, 1,4-naphthoquinone-6-sulfonic acid[3] and its 2,3-dichloro derivative,[4] both of which were obtained by methods of very limited applicability.

Attempts to prepare the desired substance by direct sulfonation of 2-methyl-1,4-naphthoquinone with chlorosulfonic acid or by the oxidation of 2-methylnaphthalene-8-sulfonic acid[5] in acetic acid with hydrogen peroxide or chromic acid were unsuccessful. In the latter case small amounts of 2-methyl-1,4-naphthoquinone were isolated, which indicated that partial hydrolysis of the sulfonic acid had taken place during the reaction. The oxidation of 2-methylnaphthalene-8-sulfonyl chloride with chromic acid likewise failed to yield products of sufficient purity.

The method that was finally found to give satisfactory results consisted in the oxidation with chromic acid of 2-methylnaphthalene-8-sulfonamide to the corresponding naphthoquinonesulfonamide, followed by the conversion of the latter to the sulfonic acid with nitrous acid.



The oxidation of a naphthalenesulfonamide to the corresponding α-naphthoquinonesulfonamide, as briefly presented here, is perhaps of more general importance since it may lead to compounds of chemotherapeutic interest. A study of the vitamin K activity of 2-methyl-1,4-naphthoquinone-8-sulfonic acid will be presented at a later date.[5a]

Experimental

2-Methylnaphthalene-8-sulfonic Acid.—The procedure used, a modification of that of Veselý and Páč,[5] yields a mixture of 2-methylnaphthalene-1- and 8-sulfonic acids which are separated by fractional crystallization of the barium salts. To 200 g. of 2-methylnaphthalene in 270 cc. of carbon tetrachloride at −10°, 93 cc. of chlorosulfonic acid was added dropwise with mechanical stirring in the course of forty minutes. The mixture was kept at −10° for three hours and at room temperature for fifteen hours, and then poured onto 1400 g. of crushed ice. To the aqueous phase, following two extractions with 300-cc. portions of carbon tetrachloride, 165 g. of barium carbonate was added at the boiling point and the hot mixture rapidly filtered through diatomaceous earth on a hot suction funnel. After cooling of the filtrate in the refrigerator overnight, the crude barium salt that had separated was recrystallized from 700 cc. of water in the presence of Norite, when 200 g. of pure barium 2-methylnaphthalene-8-sulfonate (dried at 120°) was obtained (49% of the theoretical yield). The treatment of the solution of the barium salt with the required amount of potassium sulfate followed by the evaporation of the filtrate and drying at 120° gave the potassium salt in a yield of 97%.

2-Methylnaphthalene-8-sulfonyl Chloride.—The chlorination was carried out according to the procedure of Steiger.[6] An intimate mixture of 174 g. of finely powdered potassium 2-methylnaphthalene-8-sulfonate and 348 g. of phosphorus pentachloride was, after liquefaction had occurred, heated on the steam-bath for one-half hour. After addition of 1300 g. of crushed ice, the cooled mixture was kept at 0° for twenty hours and the sulfonyl chloride[5] filtered off and dried. It weighed 145 g. (90% of the theoretical yield) and melted at 94–95° after crystallization from 80% acetic acid.

2-Methylnaphthalene-8-sulfonamide.—The treatment of 74 g. of the finely powdered sulfonyl chloride with 600 cc. of concentrated ammonia on the steam-bath for forty minutes, followed by dilution with 1 liter of water, resulted in the separation of the sulfonamide[5] weighing 66 g. (97%

(1) This work has been supported by a grant from the John and Mary R. Markle Foundation.

(2) E. Chargaff and A. Bendich, *J. Biol. Chem.*, in press.

(3) F. Fabrowicz and W. Leśniański, *Roczniki Chem.*, 11, 636 (1931); *Chem. Abs.*, **26**, 3791 (1932).

(4) A. Claus and S. van der Cloet, *J. prakt. Chem.*, **37**, 181 (1888).

(5) V. Veselý and J. Páč, *Coll. Czech. Chem. Commun.*, **2**, 471 (1930).

(5a) According to a private communication from Dr. H. Dam of the School of Medicine, University of Rochester, this compound exhibited an extremely low vitamin K activity (less than 1/1000 of that of menadione), when assayed in chicks.

(6) R. E. Steiger, *Helv. Chim. Acta*, **13**, 173 (1930).

yield). The product, crystallized from 70% ethyl alcohol, melted at 197°.

2-Methyl-1,4-naphthoquinone-8-sulfonamide.—To a solution of 30 g. of pure 2-methylnaphthalene-8-sulfonamide in 300 cc. of glacial acetic acid at 80°, 60 g. of chromic acid in 120 cc. of 50% acetic acid was added dropwise within ten minutes with constant stirring. The deep green solution was refluxed for five minutes and then immediately cooled to room temperature, 1.5 liters of water was added and the mixture kept at 0° for four hours. The naphthoquinonesulfonamide which had precipitated weighed 12.4 g. after thorough washing and drying. The filtrate was evaporated to dryness *in vacuo*, the residue taken up in 400 cc. of water and subjected to a continuous ether extraction, which yielded an additional 1.9 g. of the naphthoquinonesulfonamide. The total yield corresponded to 42% of the theoretical amount. The substance crystallized in yellow plates from ethyl alcohol containing 15% of acetic acid and melted with decomposition at 231–232°.

Anal. Calcd. for $C_{11}H_9O_4NS$: C, 52.58; H, 3.61; N, 5.58; S, 12.76. Found: C, 52.44; H, 3.48; N, 5.46; S, 12.76.

This compound, and all naphthoquinone derivatives described in the following section, gave the Craven color test.[7]

2-Methyl-1,4-naphthoquinone-8-sulfonic Acid.—To 10 g. of the methylnaphthoquinonesulfonamide, suspended in a mixture of 100 cc. of glacial acetic acid, 40 cc. of water and 26 cc. of concentrated sulfuric acid, 66 cc. of a 37% aqueous sodium nitrite solution was added with constant stirring in the course of thirty minutes at 25°.[8] To the clear solution, 150 g. of barium acetate in 450 cc. of boiling water was added and the hot mixture was filtered through diatomaceous earth. One portion of the barium salt crystallized from the filtrate on cooling as yellow needles weighing 1.8 g. A larger amount (2.3 g.) was obtained when the mother liquor was concentrated *in vacuo* to 175 cc. and chilled. The total yield of 4.1 g. of barium 2-methyl-1,4-naphthoquinone-8-sulfonate corresponded to 33% of the theoretical amount.

Anal. (Dried at 100° *in vacuo.*) Calcd. for $C_{22}H_{14}O_{10}S_2Ba$: Ba, 21.47; volatile S, 5.01. Found: Ba, 21.32; volatile S, 5.05.

For the conversion into the potassium salt, 400 mg. of potassium sulfate was added to a solution of 1.30 g. of the barium salt in 50 cc. of hot water. The filtrate was concentrated *in vacuo* to 25 cc., saturated with potassium chloride and cooled, when 1.11 g. of potassium 2-methyl-1,4-naphthoquinone-8-sulfonate crystallized as glistening yellow plates (94% of the theoretical yield). The salt was recrystallized from saturated potassium chloride solution.

Anal. (Dried at 100° *in vacuo.*) Calcd. for $C_{11}H_7O_5SK$: C, 45.50; H, 2.43; S, 11.04; K, 13.47. Found: C, 45.20; H, 2.53; S, 10.96; K, 13.33.

For further characterization, thallous 2-methyl-1,4-naphthoquinone-8-sulfonate was prepared according to Gilman and Abbott.[9] The compound, several times recrystallized from water, formed yellow hexagonal plates melting with decomposition at 263–264°.

Anal. (Dried at 100° *in vacuo.*) Calcd. for $C_{11}H_7O_5STl$: Tl, 44.86. Found[10]: Tl, 44.75.

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Summary

2-Methyl-1,4-naphthoquinone-8-sulfonic acid was synthesized by way of 2-methylnaphthalene-8-sulfonamide and 2-methyl-1,4-naphthoquinone-8-sulfonamide.

(7) R. Craven, *J. Chem. Soc.*, 1605 (1931).

(8) Method based on unpublished experiments of Drs. H. T. Clarke and H. B. Gillespie on the action of nitrous acid on benzenesulfonamide.

(9) H. Gilman and R. K. Abbott, Jr., THIS JOURNAL, **65**, 123 (1943).

(10) R. J. Meyer and A. Bertheim, *Ber.*, **37**, 2051 (1904).

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[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Condensation of Ethyl α-Acetylpropionate with Ethyl Chlorofumarate

BY R. B. WOODWARD AND W. A. REED

By condensation of the sodium derivative of ethyl α-acetylpropionate with ethyl chlorofumarate, Ruhemann and Wolf[1] obtained a *compound*, m. p. 132°, to which the formula $C_{11}H_{14}O_5$ was assigned. On hydrolysis with strong acid or base, this substance was transformed, with elimination of carbon dioxide, into a new *substance*, m. p. 244° (dec.), for which analytical data indicated the formulation $C_6H_6O_3$. In the first and a later paper,[2] these substances were variously formulated as furan (I, II), allene (III, IV) and α-pyrone (V) derivatives, it being assumed in all cases that the initial condensation product had been formed from the reactants through loss of sodium chloride and *ethyl acetate*, the carbethoxyl of the latter arising from ethyl chlorofumarate, and the methyl from ethyl α-acetylpropionate. The improbability of the reaction

(1) Ruhemann and Wolf, *J. Chem. Soc.*, **69**, 1386 (1896).

(2) Ruhemann, *ibid.*, **71**, 325 (1897).