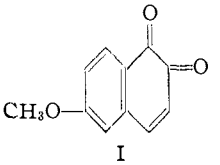
6-Methoxy-1,2-naphthoquinone[1]

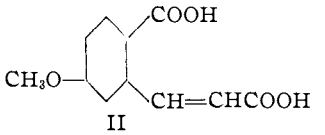
BY H. E. FRENCH AND KERN SEARS[2]

6-Methoxy-1,2-naphthoquinone (I), required as an intermediate for a series of compounds, was prepared by the usual coupling process from 6-methoxy-2-naphthol.[3] The route to this intermediate by methylation of 2,6-dihydroxynaphthalene derived from 2-naphthol-6-sulfonic acid appeared unsatisfactory as a preparative method.[4] The claimed preparation by the hydrolysis of 6-bromo-2-naphthol with aqueous base under pressure[5] gave a tar from which a small amount of β-naphthol was isolated. Similar treatment of 6-bromo-2-methoxynaphthalene gave only traces of the desired 6-methoxy-2-naphthol. These poor results may be attributed to the positive character of the halogen.

6-Methoxy-2-naphthol was obtained in fairly good yield from 6-methoxy-2-bromonaphthalene by oxidation of the corresponding Grignard reagent according to the procedure of Kharasch.[6] Oxidation of the naphthoquinone (I) with peracetic or monoperphthalic acid gave 2-carboxy-5-methoxycinnamic acid (II). The oxidation was



I



II

much less vigorous in this case than with the unsubstituted naphthoquinone.[7] When 6-methoxy-2-naphthol was oxidized with peracetic acid prepared from a mixture of acetic acid and acetic anhydride it gave a 7.4% yield of the cinnamic acid (II), whereas none of this product was obtained with peracetic acid prepared from pure acetic anhydride. On the basis of these results the oxidation may be due to unreacted hydrogen peroxide in acetic acid solution, although Böeseken obtained 2-carboxycinnamic acid from 2-naphthol by the action of peracetic acid.[8]

Experimental

6-Bromo-2-methoxynaphthalene.—6-Bromo-2-naphthol (1 mole)[9] dissolved in a solution of 80 g. of sodium hydroxide in 3000 ml. of water was methylated by heating with two portions of methyl sulfate (126 g. and 63 g.) to 70°. The mixture was thoroughly cooled after the addition of each portion. The product was filtered with suction and distilled under reduced pressure. The material boiling at 189–199° (20 mm.) weighed 170 g. (71.7%) and melted at 102–104° after crystallization from alcohol. Most of the unchanged naphthol was recovered from the aqueous solution.

6-Methoxy-2-naphthol.—A solution of 500 ml. of dry ether, 118.5 g. of 6-bromo-2-methoxynaphthalene, 123 g. of isopropyl bromide, and 300–400 ml. of dry benzene was added with stirring to a mixture of magnesium turnings (36.5 g.), 50 ml. of dry ether, and a trace of iodine. After completed reaction the mixture was stirred two hours at room temperature and one hour at reflux temperature. Dry oxygen was passed through this mixture until the visible chemiluminescence disappeared and ten minutes longer. The reaction mixture gave a negative test with Michler ketone at this point. A solution of 45 ml. of concentrated sulfuric acid in 200 ml. of water was added to the mixture with cooling, and the resulting liquid layers were separated. The naphthol was extracted from the organic layer with 1000 ml. of 10% aqueous potassium hydroxide containing some sodium hydrosulfite. It was precipitated with acid, filtered off and dried. The yield of dark yellow product was 35–37 g. (40–42%). Crystallization from water or from benzene–petroleum ether gave a white product melting at 150–151°. The m. p. has been reported as 136–137[4a] and 140.[4b]

2,6-Dimethoxynaphthalene.—Methylation of the above material with methyl sulfate in aqueous potassium hydroxide gave the known dimethyl ether which melted at 149–150.5[5] after crystallization from petroleum ether. The mixed melting point with 6-methoxy-2-naphthol (150–151°) was 118–140°.

1-Amino-6-methoxy-2-naphthol Hydrochloride.—Sulfanilic acid (42 g.) diazotized in the usual way,[3a] was added to a cold solution of 34.8 g. of 6-methoxy-2-naphthol and 61.6 g. of potassium hydroxide in 500 ml. of water. The red reaction mixture was allowed to stand for several hours and was heated to 45°. Sodium hydrosulfite (92 g.) was added, and the light yellow reaction mixture was heated to boiling, cooled to 20° in an ice-bath, and filtered. The product was crystallized and decolorized with Norite in portions from the same solution of 200 ml. of concentrated hydrochloric acid and 2 g. of stannous chloride in 800 ml. of water. The hydrochloride formed colorless needles which gradually turned purple. The yield was 30.5 g. (67.2%).

6-Methoxy-1,2-naphthoquinone.—The above aminonaphthol hydrochloride (30.3 g.) was dissolved in 2500 ml. of 0.1% aqueous hydrochloric acid by warming. The solution was filtered, cooled, and oxidized with a solution of 95 g. of ferric chloride in 75 ml. of water and 34 ml. of hydrochloric acid.[3b]

The dark orange precipitate was filtered, washed thoroughly with water and dried. The quinone, melting at 135–140°, weighed 22 g. (53.6%). Crystallization from alcohol gave red-orange needles melting at 124–127°.

Anal. Calcd. for $C_{11}H_8O_3$: C, 70.21; H, 4.23. Found: C, 69.82; H, 4.65.

3-Methoxybenzo[a]phenazine.—6-Methoxy-1,2-naphthoquinone (0.5 g.) in 20 ml. of hot glacial acetic acid was treated with a solution of 0.6 g. of *o*-phenylenediamine and 0.5 g. of sodium acetate in 20 ml. of glacial acetic acid. The crystalline phenazine was filtered off and recrystallized from aqueous acetic acid. It melted at 160–161°.

Anal. Calcd. for $C_{17}H_{12}N_2O$: C, 78.45; H, 4.66. Found: C, 78.45; H, 4.70.

2-Carboxy-5-methoxycinnamic Acid. A. Peracetic Acid Oxidation.—6-Methoxy-1,2-naphthoquinone (9.12 g.) suspended in 50 ml. of acetic acid was treated with 25 ml. of 1.4 molar peracetic acid in acetic acid.[10] A yellow

(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Missouri.

(2) From the thesis submitted by Mr. Sears in partial fulfillment of the requirements for the degree of Master of Arts at the University of Missouri.

(3) (a) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 35; (b) *ibid.*, p. 430.

(4) (a) Windaus, *Ber.*, **27**, 1738 (1924); (b) Cabal, *Rev. acad. cien. Madrid*, **32**, 423 (1935), (c) Willstätter and Parnas, *Ber.*, **40**, 1406 (1907).

(5) Britton, U. S. Patents 1,959,283 (May 15, 1934), and 1,996,744 (April 9, 1935).

(6) Kharasch and Reynolds, THIS JOURNAL, **65**, 501 (1943).

(7) Böeseken and Sloof, *Rec. trav. chim.*, **49**, 92 (1930).

(8) Böeseken, Lochman and Konigsfeldt, *ibid.*, **54**, 315 (1935).

(9) "Organic Syntheses," Vol. 20, John Wiley and Sons, Inc., New York, N. Y., 1940, p. 18.

(10) Böeseken, Cohn and Kipp, *Rec. trav. chim.*, **55**, 817 (1936).

precipitate of the acid was filtered off after standing for three days at room temperature. It was purified through its sodium salt, and recrystallized from aqueous alcohol. The yield was 2.3 g. (23%).

Monoperphthalic Acid Oxidation.—The quinone (4.74 g.) was added to an excess of monoperphthalic acid in ether solution and the mixture was allowed to stand at room temperature for thirty hours. The precipitate of acid was filtered and the acid purified as before. The yield was 2.08 g. (31.2%).

The pure dicarboxylic acid melted at 186–190° (dec.) when the temperature of the block was raised 4° per minute.

Anal. Calcd. for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54; neut. equiv., 111.3. Found: C, 59.32; H, 4.80; neut. equiv., 111.1.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MISSOURI
COLUMBIA, MISSOURI RECEIVED NOVEMBER 14, 1947

A Peptide Derivative Related to Gramicidin

BY JOSEPH S. FRUTON

The studies of Hotchkiss[1] and of Gordon, *et al.*,[2] have shown that gramicidin is a cyclopeptide which is characterized by an unusually high content in D-leucine and L-tryptophan, these two components accounting for approximately one half of the total amino acids found after complete hydrolysis of gramicidin. In the course of our studies on the effect of peptides and peptide derivatives on bacterial growth, the substance D-leucyl-L-tryptophan diketopiperazine was synthesized. The synthesis involved the reaction of carbobenzoxy-D-leucyl azide with L-tryptophan methyl ester, followed by the catalytic hydrogenation of the coupling product. Treatment of the resulting dipeptide ester with ammonia gave the diketopiperazine.

If the antibacterial action of gramicidin were due solely to the presence of D-leucine or L-tryptophan residues, the synthetic diketopiperazine might have been expected to exhibit some inhibition of the growth of organisms affected by gramicidin. It has been found, however, that the diketopiperazine, when tested at concentration levels of 1 to 10 μg. per ml. of culture medium, shows no appreciable action on *Escherichia coli*, *Staphylococcus aureus*, *Clostridium welchii* or *Brucella abortus*, and only a slight antibacterial effect was noted with *Streptococcus hemolyticus*. Control experiments with gramicidin, at 1 and 5 μg. per ml., showed complete inhibition of the growth (in 12 hours) of *S. hemolyticus*. Further experiments on the antibacterial activity of peptide derivatives related to gramicidin and tyrocidine are in progress.

Experimental

N-Carbobenzoxy-D-leucyl-L-tryptophan Methyl Ester.—Three grams of carbobenzoxy-D-leucinhydrazide[3] was dissolved in a mixture of 25 ml. of water, 10 ml. of glacial acetic acid and 5 ml. of concentrated hydrochloric acid. The solution was chilled to 0° and, with shaking, there was added, in small portions, a solution of 0.7 g. of sodium nitrite in 10 ml. of water. The azide separated as an oil and was extracted with ether. The ethereal solution was washed successively with cold water, cold aqueous bicarbonate solution, and again with cold water. The ethereal layer (60 ml.) was dried briefly over sodium sulfate and added to a solution of 2.5 g. of L-tryptophan methyl ester[4] in 60 ml. of ether. The reaction mixture was left at room temperature for eighteen hours, and then washed successively with dilute hydrochloric acid, water, aqueous bicarbonate solution, and water. After being dried over sodium sulfate, the solution was concentrated to a small volume under reduced pressure. The careful addition of petroleum ether (30–60°) gave a sirup which crystallized readily. After recrystallization from ethyl acetate–petroleum ether, the substance (2.7 g.) melted at 125–127°.

Anal. Calcd. for $C_{26}H_{31}O_5N_3$: N, 9.0. Found: N, 9.2.

D-Leucyl-L-tryptophan Diketopiperazine.—One gram of the above carbobenzoxydipeptide ester was dissolved in a mixture of 15 ml. of methanol and 0.2 ml. of glacial acetic acid and was hydrogenated at atmospheric pressure in the presence of palladium black. The hydrogenation required two hours, after which time the catalyst was removed by filtration. The filtrate was added to 30 ml. of methanol which had previously been saturated with dry ammonia at 0°. The mixture was left at room temperature for two days, then concentrated under reduced pressure, and the resulting crystalline product was dissolved in 10 ml. of hot absolute alcohol. On chilling the alcoholic solution, 0.56 g. of the diketopiperazine crystallized; m. p. 218–219° (dec.).

Anal. Calcd. for $C_{17}H_{21}O_2N_3$: C, 68.2; H, 7.1; N, 14.0. Found: C, 67.9; H, 7.1; N, 14.0.

(1) Hotchkiss, *J. Biol. Chem.*, **141**, 171 (1941).
(2) Gordon, Martin and Synge, *Biochem. J.*, **37**, 86 (1943).
(3) This compound was prepared in the manner described for the L-form by Bergmann, *et al.*, *J. Biol. Chem.*, **109**, 325 (1935).
(4) Abderhalden and Kempe, *Z. physiol. Chem.*, **52**, 207 (1907).

DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY
YALE UNIVERSITY
NEW HAVEN, CONNECTICUT RECEIVED DECEMBER 1, 1947

Indole from Formyl-toluidine

BY ALEXANDER GALAT AND HARRIS L. FRIEDMAN

Of the numerous methods of preparation of indole described in the literature, ring closure of *o*-formyltoluidine is the most direct and convenient. Tyson[1] has shown that yields up to 79% may be obtained with potassium alkoxides, whereas sodium alkoxides give little or no product. This is a peculiarity of the formyl group, for the higher acyl derivatives are readily dehydrated by sodium alkoxides.[2]

The use of potassium metal in the dehydration of *o*-formyltoluidine adds both expense and an element of danger to large scale preparations. It occurred to us that if the potassium *ion* had a catalytic effect in the reaction, it would be possible to use an inexpensive potassium salt with sodium alkoxide.

This possibility was tested as follows: sodium (4.6 g.) was dissolved in 100 ml. of anhydrous methanol and 27 g. of *o*-formyltoluidine was added. Complete solution resulted on warming.

(1) Tyson, THIS JOURNAL, **63**, 2024 (1941).
(2) Madelung, *Ber.*, **45**, 1130 (1912).