[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

2,3,5,8-Tetramethoxy-6,7-dimethyl-1-naphthaldehyde

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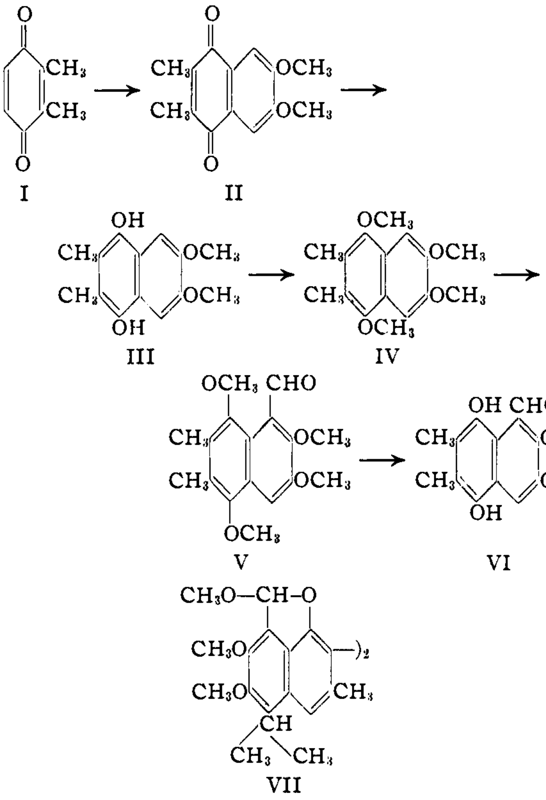
The structure of gossypol has been postulated as 2,2′-bi-1,6,7-trihydroxy-3-methyl-5-isopropyl-8-aldehydonaphthyl.[2] The reactions of gossypol are in agreement with this structure but it is necessary to assume that gossypol has two other tautomeric structures involving the naphthalene ring. No parallel tautomers have been reported among simpler napthalene derivatives so that an attempt to prepare a compound showing such tautomerism has been made. 2,8-Dihydroxy-1-naphthaldehyde contains all the elements of the gossypol molecule directly involved in its tautomerism but has been shown to exist only in the normal aldehyde structure.[3] An additional group in the gossypol molecule which may effect the labilization of the naphthalene nucleus is the hydroxyl group in the 3-position. This investigation now reported involves an attempt to synthesize 2,3,8-trihydroxy-1-naphthaldehyde or one of its derivatives in order to study its tautomerism. Several approaches have all proved unsuccessful in obtaining such a molecule.

In attempting to synthesize 2,3,5,8-tetrahydroxy-6,7-dimethoxy-1-naphthaldehyde (VI), 2,3-dimethyl-6,7-dimethoxy-1,4-naphthoquinone (II) was used as a raw material. This compound has been described by Schroeter, Lichtenstadt and Irenu[4] who oxidized 2,3-dimethyl-6,7-dimethoxynaphthalene (pyroguaiacin methyl ether). Haworth and Mavin[5] have also synthesized this substance by a rather complicated procedure. It was more conveniently obtained by the treatment of an excess of *o*-xyloquinone with 2,3-dimethoxy-1,3-butadiene.[6] The 2,3-dimethyl-6,7-dimethoxy-1,4-naphthoquinone was reduced catalytically to the corresponding hydroquinone (III) which, without isolation, was methylated to give 1,4,6,7-tetramethoxy-2,3-dimethylnaphthalene (IV). The conversion of the hydroquinone methyl ether to the desired aldehyde (V) was accomplished readily by treatment with phosphorus oxychloride and N-methylformanilide. This tetramethoxyaldehyde (V) formed a phenylhydrazone and an oxime in neutral solutions.



Gossypol hexamethyl ether does not form a phenylhydrazone nor an oxime in neutral solution. It is assumed to exist in the acetal form (VII) rather than the normal aldehyde form since it gives aldehyde derivatives of gossypol tetramethyl ether in acetic acid solution because of the loss of the acetal methyl groups by hydrolysis.[7] Since V does give aldehyde derivatives in neutral solution, it is assumed to have the normal aldehyde structure in contrast to gossypol hexamethyl ether. This is, of course, to be expected since V was prepared by the introduction of the aldehyde group into a previoulsy methylated molecule so that there was no possibility of tautomerization.

In order to compare the methylation product of the tetrahydroxyaldehyde (VI) with V and with gossypol hexamethyl ether, the preparation of VI was attempted. Demethylation of the tetramethoxyaldehyde to the tetrahydroxyaldehyde (VI) failed. Even when the reaction was carried out in an atmosphere of sulfur dioxide, oxidation occurred so readily that no product could be isolated. Attempted demethylations of 6,7-dimethoxy-2,3-dimethyl-1,4-naphthoquinone, of 1,4 - diacetoxy - 2,3 - dimethyl - 6,7 - dimethoxynaphthalene, and of 2,3,5,8-tetramethoxy-6,7-dimethyl-1-naphthonitrile led to reaction mixtures from which no pure product could be isolated.

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(1) An abstract of a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry; Eastman Kodak fellow 1943-44.

(2) Adams, Morris, Geissman, Butterbaugh and Kirkpatrick, THIS JOURNAL, **60**, 2193 (1938).

(3) Adams and Burney, *ibid.*, **63**, 1103 (1941).

(4) Schroeter, Lichtenstadt and Irenu, *Ber.*, **51**, 1587 (1918).

(5) Haworth and Mavin, *J. Chem. Soc.*, 1485 (1932).

(6) Johnson, Jobling and Bodamer, THIS JOURNAL, **63**, 135 (1941).

(7) Adams and Geissman, *ibid.*, **60**, 2166 (1938).

Experimental[8]

2,3-Dimethyl-6,7-dimethoxy-1,4-naphthoquinone (II).—A mixture of 20 g. of pure *o*-xyloquinone[9] (2 moles) (recrystallized twice from petroleum ether (b. p. 30–60°) after two vacuum steam-distillations) and 8.25 g. of 2,3-dimethoxy-1,3-butadiene[6] (1 mole) was heated at 140° in a sand-bath for thirty-six hours. During this time the reaction mixture solidified to a mass of white and brown-orange crystals. The solid was broken up and refluxed with 100 ml. of ethanol for half an hour. The white needles (xylohydroquinone) went into solution but the orange crystals were not appreciably soluble. After cooling, the precipitate was collected on a filter and washed with a small amount of ethanol. The filtrate was diluted with water and extracted with ether. The combined ethereal solution was then extracted with aqueous sodium hydroxide. The ethereal solution was dried and the small amount of orange solid obtained on evaporation of the ether was combined with that previously obtained and the quinone recrystallized from a large volume of glacial acetic acid using Darco. The quinone separated as small, silky, orange-yellow needles which melted at 248–249° (reported 241–242°, uncor.).[4,6] The yield varied from 13 to 14 g. (77–82.5%).

In order to obtain satisfactory yields, it was necessary that the *o*-xyloquinone be as pure as possible. An attempt to effect the condensation at steam-bath temperature for forty-eight hours was unsuccessful. The addition was unsuccessful in a solvent such as ethanol or xylene.

The alkaline solution obtained by the extraction of the ether layer mentioned above was acidified with hydrochloric acid and the acid solution and the precipitate were extracted with ether. The ethereal solution was dried over anhydrous sodium sulfate and the ether removed by distillation. In this way 8 g. of crude *o*-xylohydroquinone was obtained. The material was reoxidized to *o*-xyloquinone according to the directions of Underwood and Walsh[10] for the oxidation of hydroquinone to quinone.

1,4,6,7-Tetramethoxy-2,3-dimethylnaphthalene (IV).—A suspension of 23.6 g. of the quinone in 400 ml. of methanol was treated with hydrogen at 1500 lb. initial pressure in the presence of Raney nickel catalyst at 50°. The exothermic reduction was complete in less than one hour. The contents of the bomb, including the catalyst, were transferred rapidly, while still hot, to a 2-liter three-necked flask which had been previously flushed with nitrogen and which contained 108 g. of freshly distilled dimethyl sulfate and 1 g. of sodium hydrosulfite. The hydrogenation bomb was rinsed with two 50-ml. portions of boiling methanol and this solution added to the main portion. The flask was cooled in an ice-bath and a rapid stream of oxygen-free nitrogen passed through the solution. In spite of these precautions, there was always a little yellow color, indicating that some oxidation to the quinone had taken place. To the cooled, stirred mixture, a solution of 96 g. of potassium hydroxide in 500 ml. of water was added very slowly. After the addition was complete the reaction mixture was allowed to warm to room temperature, then heated on a steam-bath for two hours, and allowed to stand overnight. The reaction mixture was cooled, filtered, and the precipitate was extracted continuously in a Soxhlet extractor with absolute ethanol for twenty-four hours. The extract was cooled and the crystals collected by filtration and recrystallized from ethanol, m. p. 151–152°; yield, 18.5 g. (73%).

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.29. Found: C, 69.80; H, 7.36.

2,3,5,8-Tetramethoxy-6,7-dimethyl-1-naphthaldehyde (V).—The procedure used for the introduction of the aldehyde group was essentially that used by Wood and Bost[11] for the preparation of 2-ethoxy-1-naphthaldehyde. A mixture of 5.5 g. of 1,4,6,7-tetramethoxy-2,3-dimethylnaphthalene, 3.8 g. of N-methylformanilide[12] and 4.4 g. of phosphorus oxychloride was refluxed for eight hours on a steam-bath. The reaction mixture was poured into about 75 ml. of cold water while stirring vigorously. A red oil which separated at first soon solidified to a light red solid. This was collected by filtration and, after washing with water, was recrystallized from ethanol using Norite. Fine, white needles were obtained, m. p. 135–136°; yield, 4.1 g. (67%).

Anal. Calcd. for $C_{17}H_{20}O_5$: C, 66.87; H, 6.93. Found: C, 66.87; H, 6.96.

Phenylhydrazone of V.—In the usual manner, in ethanolic solution, the phenylhydrazone was obtained as white crystals which, after recrystallization from ethanol, melted at 156–157°.

Anal. Calcd. for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64. Found: C, 70.22; H, 6.72.

Oxime of V.—The oxime was obtained by reaction of the aldehyde with hydroxylamine hydrochloride and sodium acetate in ethanol as white crystals which, after recrystallization from dilute ethanol, gave needles which melted at 155–156°.

Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63. Found: C, 63.97; H, 6.65.

2,3,5,8-Tetramethoxy-6,7-dimethyl-1-naphthonitrile.—A solution of 0.3 g. of the oxime in 5 ml. of acetic anhydride was refluxed for one hour and then poured into 50 ml. of ice-water. When all the acetic anhydride had hydrolyzed, the white solid which remained was collected by filtration. After recrystallization from ethanol, white needles were obtained which melted at 122.5–123°.

Anal. Calcd. for $C_{17}H_{19}NO_4$: C, 67.79; H, 6.36. Found: C, 67.86; H, 6.40.

1,4-Diacetoxy-2,3-dimethyl-6,7-dimethoxynaphthalene.—2,3-Dimethyl-6.7-dimethoxy-1,4-naphthoquinone was reductively acetylated in the usual manner. After recrystallization from methanol, a 91% yield of white rods was obtained. The material melted at 180.5–181°.

Anal. Calcd. for $C_{18}H_{20}O_6$: C, 65.03; H, 6.07. Found: C, 65.27; H, 6.10.

Summary

1. 2,3,5,8-Tetramethoxy-6,7-dimethyl-1-naphthaldehyde has been prepared and characterized. The attempted demethylation of this aldehyde to 2,3,5,8-tetrahydroxy-6,7-dimethyl-1-naphthaldehyde was unsuccessful.

2. The demethylations of 6,7-dimethoxy-2,3-dimethyl-1,4-naphthoquinone, of 1,4-diacetoxy-2,3-dimethyl-6,7-dimethoxynaphthalene, and of 2,3,5,8 - tetramethoxy - 6,7 - dimethyl-1-naphthonitrile also failed.

3. The aldehyde (V) formed derivatives in neutral solution in contrast to gossypol hexamethyl ether.

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[8] All melting points corrected unless specified otherwise.

[9] The authors wish to express their appreciation to Merck and Co., Inc., for the kind gift of large amounts of 3-nitro-*o*-xylene. Reduction by the method of Smith and Opie, *J. Org. Chem.*, **6**, 427 (1941), followed by oxidation according to the method of Emerson and Smith, THIS JOURNAL, **62**, 141 (1940), gave a satisfactory yield of xyloquinone.

[10] Underwood and Walsh, "Organic Syntheses," Coll. Vol. **2**, 395 (1941).

[11] Wood and Bost, *ibid.*, **20**, 11 (1940).

[12] Fieser and Jones, *ibid.*, **20**, 66 (1940).