NOTES

Studies in the Naphthalene Series. II. Synthesis of 6,7-Dimethoxy-3-methyl-1-naphthol

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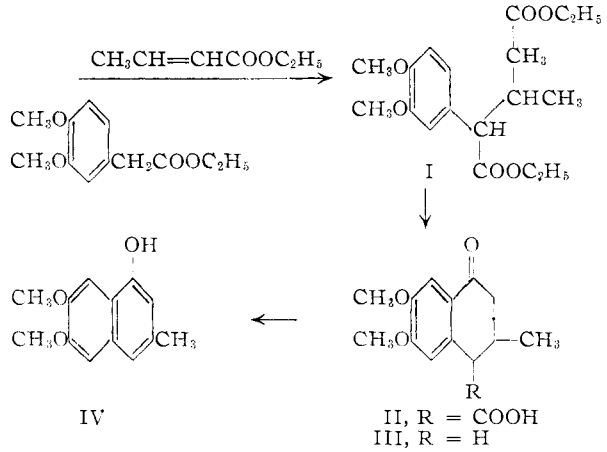
During the course of certain investigations in this Laboratory, it was necessary to synthesize 6,7-dimethoxy-3-methyl-1-naphthol (IV). Two syntheses of 3,4-dihydro-6,7-dimethoxy-3-methyl-1(2)naphthalenone (III), which on dehydrogenation would yield IV, have been reported.[1,2] The melting points of the products reported, as well as that of a common intermediate, do not agree.

The synthesis of III reported here was realized by a procedure different from the above two. Ethyl 3,4-dimethoxyphenylacetate was condensed with ethyl crotonate by the Michael reaction to give diethyl 2-(3',4'-dimethoxylphenyl)-3-methyl glutarate (I) in 76% yield. Ring closure of I to 3,4-dihydro-6,7-dimethoxy-3-methyl-1(2)naphthalenone-4-carboxylic acid (II) was achieved by use of sulfuric or polyphosphoric acid. Although good yields (73%) were obtained in small runs in the ring closure reaction using sulfuric acid, they could not be realized in large runs. For this reason the use of polyphosphoric acid was investigated and it was found that a better synthesis of II was realized by hydrolysis of the ester I to 2-(3',4'-dimethoxyphenyl)-3-methylglutaric acid which when heated with polyphosphoric acid for 1.5 minutes at 90° or 20 minutes at 70° gave the tetralonecarboxylic acid II in good yield. In large-scale runs the latter conditions were employed since it was more convenient and appeared to give a purer product.



The decarboxylation of II to 3,4-dihydro-6,7-dimethoxy-3-methyl-1(2)naphthalenone (III) was achieved by a yield of 47% and all attempts to increase it by changing the conditions met with failure.

Dehydrogenation of the tetralone III proceeded best with sulfur to yield the desired naphthol IV. An alternate synthesis of this compound involved the bromination of III to 2-bromo-3,4-dihydro-6,7-dimethoxy-2-methyl-1(2)naphthalenone and dehydrohalogenation to IV.

The melting point of compound III obtained in this study agrees with that reported by Haworth and Atkinson.[2] In all probability Borsche and Neimann[1] did not completely separate the isomeric compounds formed in the first step of their synthesis; if so, their product III was contaminated with some of the isomeric 3,4-dihydro-6,7-dimethoxy-2-methyl-1(2)naphthalenone.

Experimental[3]

Diethyl 2-(3',4'-Dimethoxyphenyl)-3-methylglutarate (I).—To 375 ml. of ethanol in a 3-neck two-liter flask equipped with a stirrer, separatory funnel and condenser, there was added portionwise 24.6 g. (1.07 moles) of sodium metal. The mixture was then refluxed to complete solution and cooled to room temperature. A mixture of 240 g. (1.07 moles) of ethyl 3,4-dimethoxyphenylacetate[4] and 131 g. (1.15 moles) of freshly distilled ethyl crotonate was added through the separatory funnel with constant stirring. After refluxing for 12 hours, the solution was allowed to stand at room temperature for 3 hours before it was added with stirring to a cold solution of 66 g. of glacial acetic acid in 1200 ml. of water. The glutaric ester separated as an oil and was extracted with ether. The combined ethereal extracts were washed with dilute sodium bicarbonate, then water, dried over anhydrous sodium sulfate and the ether was removed over a steam-bath. Distillation of the resulting oil gave 276 g. (76% yield) of the glutaric ester, boiling at 166–169° (0.25 mm.).

Anal. Calcd. for $C_{18}H_{26}O_6$: C, 63.88; H, 7.75. Found: C, 63.67; H, 7.56.

A study correlating yield of product to the time of refluxing showed that the yield progressively increased from 30% for 4 hours refluxing to 76% for 12 hours. In all runs made, it was possible to recover approximately 50% of the unreacted starting materials.

N,N'-Dibenzyl-2-(3',4'-dimethoxyphenyl)-3-methylglutardiamide.—One gram of the glutaric ester and 3–4 ml. of benzylamine was refluxed for 16 hours. Upon cooling a white crystalline material separated. Ether was added to the mixture and the crystalline material filtered, washed with ether and recrystallized from methanol; m.p. 193–194°, yield 1 g. (77%).

Anal. Calcd. for $C_{28}H_{32}N_2O_4$: C, 73.02; H, 7.00; N, 6.08. Found: C, 73.08; H, 7.03; N, 6.07.

3,4-Dihydro-6,7-dimethoxy-3-methyl-1(2)naphthalenone-4-carboxylic Acid (II). (a) **Sulfuric Acid.**—To a cool solution of 133 ml. of concentrated sulfuric acid and 27 ml. of water, there was added with stirring 35 g. of the glutaric ester. When stirred for 10 minutes, a light yellow color developed. The stirred solution was then heated on a steam-bath for 25 minutes. After standing at room temperature for 15 minutes, the acid solution was added slowly with stirring to 1 liter of cold water and allowed to stand overnight in a refrigerator. The crystalline product was filtered (20 g., 73%), dried and recrystallized from chloroform–petroleum ether (30–60°); m.p. 178–180°.

(b) **Polyphosphoric Acid.**—A mixture of 40 g. of the glutaric ester, 40 g. of potassium hydroxide and 250 ml. of water was heated on the steam-bath with stirring for 6 hours. On cooling to room temperature, concentrated hydrochloric

(1) W. Borsche and J. Neimann, *Ann.*, **502**, 264 (1933).

(2) R. D. Haworth and J. R. Atkinson, *J. Chem. Soc.*, 807 (1938).

(3) The microanalyses were carried out by the Huffman Microanalytical Laboratories, Wheatridge, Colorado. The infrared absorption spectra were determined in a Perkin-Elmer spectrophotometer, model 21, with chloroform as the solvent (matched sodium chloride cells, 0.1 mm.); concentration 4–7%. All melting points are uncorrected and were made on a Fisher–Johns melting point block.

(4) J. D. Fulton and R. Robinson, *J. Chem. Soc.*, 1463 (1933).

acid was added in excess with stirring. The resulting oil was extracted with ether, dried over anhydrous sodium sulfate, filtered and concentrated over a steam-bath. When the temperature of the glutaric acid reached 70°, 280 g. of polyphosphoric acid,[5] previously heated to 70°, was added and the mixture stirred for 20 minutes and then poured onto approximately 1 kg. of crushed ice. On standing in the refrigerator overnight, the slightly yellow material was filtered and dried; yield 27 g. (90%). The product was recrystallized from chloroform–petroleum ether (30–60°); m.p. 178–180°. A mixture melting point with the sample prepared by the sulfuric acid procedure gave no depression. This procedure was used for large-scale (100–200 g.) runs and the same yield realized. The infrared spectrum showed the presence of the carbon–oxygen double bond (1668 cm.$^{-1}$) and of the carboxyl group (1703 cm.$^{-1}$).

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.41; H, 5.93.

The yields of crude product obtained on the polyphosphoric acid ring closure under various conditions were: Mixing reactants previously heated separately to 90° and stirring over steam-bath for 2.5 minutes followed by stirring with no heat for 5 minutes, then adding to crushed ice, 51.3%; same as before except heated for 1 minute only, and standing 5 minutes, 62.8%; heating for 2 minutes and immediately adding to ice, 83%; heating for 1.5 minutes and immediately adding to ice, 90%.

3,4-Dihydro-6,7-dimethoxy-3-methyl-1-(2)naphthalenone (III).—A mixture of 25 g. of the tetralonecarboxylic acid, 0.3 g. of cupric oxide and 20 ml. of quinoline was heated in an oil-bath at 200° for 1 hour. After cooling to room temperature it was added with stirring to an excess of cold dilute hydrochloric acid and extracted with chloroform. The chloroform extract was washed successively with dilute sodium bicarbonate, acetic acid and water, then dried over anhydrous sulfate and concentrated to dryness to give 10.3 g. (47% yield) of the desired tetralone. Recrystallization from methanol gave a crystalline material, m.p. 130–132° (reported 132–133°[2]). The infrared spectrum showed the presence of the carbon–oxygen double bond (1662 cm.$^{-1}$).

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.88; H, 7.32. Found: C, 70.66; H, 7.20.

Acidification of the aqueous sodium bicarbonate extract yielded 4 g. of starting material.

It was found that the yield obtained on decarboxylation decreased materially when impure starting material was used. Attempts to increase the yield by (1) using the copper salt of the carboxylic acid, (2) lower or higher temperatures, (3) heating while under vacuum all gave yields lower than that reported above.

2-Bromo-3,4-dihydro-6,7-dimethoxy-3-methyl-1(2)naphthalenone.—To a solution of 5.0 g. (0.023 mole) of the tetralone in 100 ml. of chloroform, there was added dropwise with stirring over a period of 30 minutes a solution of 1.2 ml. (0.023 mole) of bromine in 35 ml. of chloroform. The resulting solution was allowed to stir while in a hood for an additional 12 hours, after which the chloroform was evaporated over a steam-bath. On standing overnight, the oil obtained solidified and was recrystallized from ligroin (90–120°) to give 6.1 g. (90% yield) of colorless crystals m.p. 118–120°. The infrared spectrum showed the presence of the carbon–oxygen double bond (1673 cm.$^{-1}$).

Anal. Calcd. for $C_{13}H_{15}BrO_3$: C, 52.19; H, 5.05; Br, 26.71. Found: C, 52.33; H, 4.96; Br, 26.55.

6,7-Dimethoxy-3-methyl-1-naphthol (IV).—(a) An intimate mixture of 12.5 g. (0.057 mole) of the tetralone III and 1.85 g. (0.057 mole) of sulfur was heated in an oil-bath at 245° for 1 hour, at the end of which time the evolution of hydrogen sulfide had ceased. The product was then distilled at 160–165° (0.5 mm.). The distillate which solidified in the receiver was removed with ether and after evaporation of the solvent, crystallized first from toluene–petroleum ether (30–60°) and then from ligroin (90–120°); white crystals, m.p. 140–142°, yield 10 g., 80%.

(b) A solution of 5 g. of 2-bromo-3,4-dihydro-6,7-dimethoxy-3-methyl-1(2)naphthalenone in 30 ml. of N,N-dimethylaniline was heated under reflux for 30 minutes. After cooling this solution was poured with stirring onto a mixture of crushed ice and an excess of hydrochloric acid. The red precipitate was filtered, dried and recrystallized from ligroin (90–120°) to give 1 g. (27% yield) of colorless crystals, m.p. 140–142°. A mixture melting point with the sample prepared above gave no depression. When a solution of the bromoketone in N,N-dimethylaniline was heated on the steam-bath for 1 hour and worked up, only starting material was recovered.

The infrared spectra of the two samples were identical and showed the presence of the hydroxyl group (sharp band at 3620 cm.$^{-1}$ and a broad band at 3430 cm.$^{-1}$).

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.59; H, 6.66.

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(5) Victor Chemical Works, Chicago, Illinois.

Osazone Formation from Mixtures of Glucose and Fructose[1]

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In recent studies on the metabolism of carbon-14 *d*-glucose and *d*-fructose[4] where both sugars were present in the same medium, we have found it necessary to compute the relative contribution of each of these to the osazone formed from the media. Both hexoses form the same osazone, but react at different rates.[5] Maquenne[6] first proposed that the rate of osazone formation might be used as a means of differentiating sugars, and reported that in the course of an hour 1 g. of fructose formed 0.70 g. of osazone compared with 0.32 g. formed from a corresponding quantity of glucose. Garard and Sherman[7] have noted that glucose does not react quantitatively with phenylhydrazine to form glucosazone. Only under the most carefully controlled conditions could yields greater than 70% (max. yield 81%) be obtained. Van Laer and Lombaers[8] have attributed the difference in the reaction of glucose and fructose to the second stage, or oxidation of the adjacent alcohol to a carbonyl.

Neuberg[9] has reported that fructose and methylphenylhydrazine will react to give an 81% yield on heating in a boiling water-bath for only 10 minutes. Glucose forms an osazone with this reagent only after prolonged heating.[10] Methylphenylhydrazine has therefore been suggested as a specific reagent for fructose. We have found this reagent to be of little value for our purpose. Methylphenylosazones are more difficult to form than the corresponding phenylosazones. We have been unable to prepare crystalline methylphenylosazones from

(1) This work was supported in part by the United States Atomic Energy Commission.

(2) Schering Fellow of the Endocrine Society, 1953–1954.

(3) Post-Doctoral Fellow of the United States Public Health Service, 1951–1953.

(4) A. E. Renold, A. B. Hastings and F. B. Nesbett, *J. Biol. Chem.*, in press.

(5) E. Fischer, *Ber.*, **17**, 579 (1884).

(6) M. Maquenne, *Compt. rend.*, **112**, 799 (1891).

(7) D. D. Garard and H. C. Sherman, THIS JOURNAL, **40**, 955 (1918).

(8) M. H. van Laer and R. Lombaers, *Bull. soc. chim. Belg.*, **30**, 296 (1921).

(9) C. Neuberg, *Ber.*, **37**, 4616 (1904).

(10) P. B. Hawk, B. L. Oser and W. H. Summerson, "Practical Physiological Chemistry," 12th ed., Blakiston, Philadelphia, Pa., 1947, p. 65.