[Contribution from the Medical Research Laboratory, Veterans Administration Hospital, Houston]

THE SYNTHESIS OF 1,2-DIMETHOXY-3-ISOPROPYLBENZENE

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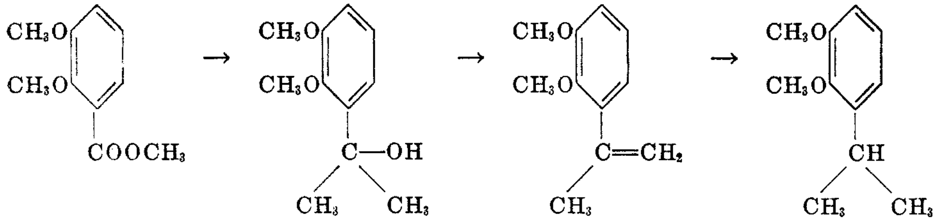
During studies involving the synthesis of 5-isopropyl-6,7-dimethoxy-3-methyl-1-naphthol, to be used as an intermediate in the synthesis of apogossypol hexamethyl ether, it was necessary to prepare in relatively good yield 1,2-dimethoxy-3-isopropylbenzene (VI). This compound (VI) has been synthesized in an over-all yield of 11% from guaiacol (1). This communication reports the synthesis of VI from the commercially available 2,3-dimethoxybenzaldehyde (I) in an over-all yield of 42%.

The oxidation of I to *o*-veratric acid (II) using potassium permanganate has been reported (2) but without yield. This oxidation has now been carried out in a yield of 78% with silver oxide. Esterification of II gave III. The following steps involving the introduction of the isopropyl group parallels those used with methyl 3-methoxysalicylate (1). The tertiary alcohol, dimethyl-(2,3-dimethoxyphenyl)carbinol (IV), was obtained in a yield of 76% by the reaction of III with methylmagnesium bromide. Dehydration of IV to 3-isopropenyl-1,2-dimethoxybenzene (V) was accomplished in a yield of 92% by heating with 20% sulfuric acid. No dehydration occurred when IV alone was heated at 250° for 20 minutes. It is of interest to note that in the other synthesis (1), dimethyl-(3-methoxy-2-hydroxyphenyl)carbinol was dehydrated in good yield by heating at 195–200° for 10 minutes. The olefin (V) was characterized by its reaction with 2,4-dinitrobenzenesulfenyl chloride (3). Reduction of V with Raney nickel gave a quantitative yield of VI.



III IV V VI

Since it has been shown (4) that VI on reaction with acetic anhydride and aluminum chloride gives 4-hydroxy-5-isopropyl-3-methoxyacetophenone, studies were made as to the effect of various reagents on the partial demethylation of VI to 2-hydroxy-3-isopropyl-1-methoxybenzene (VII). It was found that VI is not cleaved by even 3 moles of aluminum chloride on standing at room temperature with benzene as the solvent for 24 hours provided the temperatures during the initial addition and final decomposition are held at 7°. If these temperatures were not controlled a mixture resulted. Likewise, hydrobromic acid-acetic anhydride, hydrobromic acid-acetic acid, and hydrochloric acid-acetic acid yielded a mixture from which it was possible to obtain a dinitrobenzoate having the correct analysis for the desired product. But, as these approaches were not promising, the attempt to get VII in this way was abandoned.

Acknowledgment. The authors are indebted to the Monsanto Chemical Company for a most generous sample of 2,3-dimethoxybenzaldehyde.

EXPERIMENTAL

The analyses reported were carried out by the Huffman Microanalytical Laboratories, Wheatridge, Colorado. All melting points are uncorrected and were made on a Fisher-Johns melting point apparatus. The infrared spectra determinations were made on a Perkin-Elmer Recording Spectrophotometer, Model 21, matched sodium chloride cells, 0.1 mm., with chloroform as the solvent, concentrations 3–5%.

o-Veratric acid (II). To a solution of 340 g. (2.0 moles) of silver nitrate in 2 l. of distilled water, there was added slowly with stirring a solution 88 g. (2.14 moles) of sodium hydroxide in 800 ml. of water. The silver oxide was suction-filtered and washed well with distilled water. The moist silver oxide was transferred to a 6 l. beaker and a solution of 200 g. (4.85 moles) of sodium hydroxide in 4 l. of water was added. With stirring and while maintaining the temperature at 65–70°, there was added dropwise 332 g. (2.0 moles) of freshly distilled I. The mixture was stirred for 20 minutes after the addition of the aldehyde and then filtered. With cooling and stirring, the filtrate was made acid by the slow addition of conc'd hydrochloric acid and then allowed to stand overnight in a refrigerator. The white crystalline material was filtered and air-dried, yield 283 g. (78%). A sample was recrystallized from water, m.p. 120–122°, [literature reports (2) m.p. 122°]. The infrared spectrum showed carboxyl absorption at 1737 cm^{-1}.

Methyl o-veratriate (III). To a solution of 546 g. (3.0 moles) of the acid II dissolved in 900 ml. of 1,2-dichloroethane and 288 g. (9.0 moles) of methanol, there was added dropwise with stirring 45 ml. of conc'd sulfuric acid. Stirring then was discontinued and the mixture was refluxed for 15 hours at which time two distinct layers had formed. The dichloroethane layer was separated and washed with dilute sodium bicarbonate and water. Addition of conc'd hydrochloric acid to the sodium bicarbonate extract gave 35 g. of II. The dichloroethane extract was dried over sodium sulfate, filtered, and the solvent was removed under house vacuum at 50°. Distillation of the residue at 180–185°/50 mm. gave 476 g. (81%) of light yellow crystals. A sample was recrystallized from petroleum ether (90–120°), m.p. 49–50°; [literature (2) reports m.p. 47°]. The infrared spectrum showed carbonyl absorption at 1720 cm^{-1}.

The N-benzylamide derivative was prepared in a yield of 50% by the directions of Wild (5) and was recrystallized from dilute methanol, colorless crystals, m.p. 132–134°.

Anal. Calc'd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32.

Found: C, 70.79; H, 6.28.

Dimethyl-(2,3-dimethoxyphenyl)carbinol (IV). To the Grignard reagent prepared from 55 g. (2.25 moles) of magnesium and 215 g. of methyl bromide (2.25 moles) in 2 l. of anhydrous ether, there was added dropwise under reflux an etheral solution of 196 g. (1.0 mole) of the ester III. The mixture was stirred for 4 hours, allowed to stand overnight, and was decomposed by the addition of a solution of 160 g. ammonium chloride in 1 l. of water. The mixture was extracted with ether and after drying the etheral extract over anhydrous sodium sulfate and concentration on a steam-bath, it was distilled at 97°/0.5 mm. to give a colorless liquid, n_D^{20} 1.5244.

The infrared spectrum showed hydroxyl absorption at 3530 cm^{-1}.

Anal. Calc'd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.23.

Found: C, 67.38; H, 8.17.

In those cases where iodine was used to initiate the formation of the Grignard reagent or where dilute hydrochloric acid was used for the decomposition, a mixture of the alcohol IV and the olefin V was obtained. The product IV is stable, when pure, at high temperatures since heating at 250° for 20 minutes caused no dehydration.

3-Isopropenyl-1,2-dimethoxybenzene (V). A mixture of 51 g. of the alcohol IV and 70 ml. of 20% sulfuric acid was heated with good stirring under reflux for 6 hours. After cooling, the mixture was extracted with ether and the etheral extract was washed with dilute sodium bicarbonate and water. The etheral solution was dried over sodium sulfate, the ether was removed over a steam-bath, and the product was distilled at 84°/1.4 mm. to give 43 g. (92%) of a colorless liquid, n_D^{20} 1.5295.

The infrared spectrum of this compound showed strong terminal methylene group absorption at 902 cm^{-1} which disappeared on hydrogenation.

Anal. Calc'd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92.

Found: C, 74.27; H, 7.89.

In large scale runs compound V was prepared from the ester III in a yield of 88% without the isolation of IV. The Grignard solution was decomposed with dilute hydrochloric acid and extracted with ether. After drying and evaporation of the ether, the crude product was dehydrated by heating with 20% sulfuric acid and worked up as above.

A solution of 1 g. of 2,4-dinitrobenzenesulfenyl chloride and 1 g. of the oelfin (V) in 25 ml. of glacial acetic acid was heated on a steam-bath for 15 minutes. After cooling in the refrigerator the product was filtered and recrystallized several times from methanol to give yellow crystals; m.p. 125–127°. No atetmpt was made to ascertain if isomers were formed although the product did not change in m.p. during the several recrystallizations. The product formed was a 1:1 adduct accompanied by the elimination of hydrogen chloride.

Anal. Calc'd for $C_{17}H_{16}N_2O_6S$: C, 54.25; H, 4.29.

Found: C, 54.18; H, 4.31.

1,2-Dimethoxy-3-isopropylbenzene (VI). The olefin V (50 g.) was hydrogenated in a Parr low-pressure hydrogenator using Raney nickel as the catalyst and without a solvent. The hydrogenation was complete within 30 minutes after which the catalyst was removed and washed well with ether. The filtrate, after removal of the ether over a steam-bath, was distilled at 84°/3 mm.; n_D^{20} 1.5069, [literature reports (1) b.p. 119–21°/24 mm., n_D^{20} 1.5068]; yield 48 g. (95%).

The product was further identified by nitration to give a compound of m.p. 51–53° [literature (1) reports m.p. 53°].

Cleavage of VI. To a suspension of 9.3 g. of anhydrous aluminum chloride in 30 ml. of dry benzene, there was added with shaking and without cooling 5 g. of VI in one portion. After standing overnight at room temperature, the mixture was decomposed with dilute hydrochloric acid and was extracted with ether. After drying over sodium sulfate, the etheral extract was concentrated over a steam-bath and distilled at 107°/10 mm. to give 2.5 ml. of a colorless liquid, n_D^{20} 1.5263. The product was characterized as the 3,5-dinitrobenzoate according to the directions of Wild (6) and was recrystallized from methanol, colorless crystals, m.p. 150–152°.

Anal. Calc'd for $C_{17}H_{16}N_2O_7$: C, 56.66; H, 4.48; N, 7.78.

Found: C, 56.50; H, 4.42; N, 7.89.

SUMMARY

The synthesis of 1,2-dimethoxy-3-isopropylbenzene from 2,3-dimethoxybenzaldehyde in an over-all yield of 42% is reported.

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