

Phenol Dehydrogenations

VIII.* Synthesis of Magnolol

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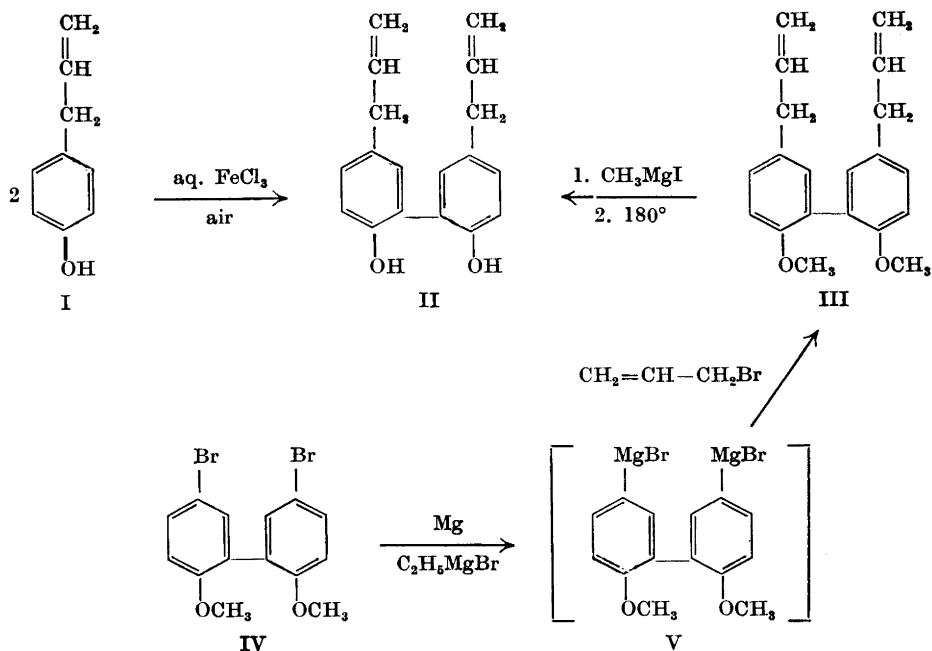
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2,2'-Dimethoxy-5,5'-dibromo-diphenyl (IV) reacted with magnesium in the presence of ethylmagnesium bromide to give the corresponding Grignard compound. This, on treatment with allyl bromide, furnished 2,2'-dimethoxy-5,5'-diallyl-diphenyl (III) which on demethylation with methylmagnesium iodide afforded magnolol (II). Application of the Tschugajew reaction to 2,2'-dimethoxy-5,5'-bis-(ω -hydroxy-*n*-propyl)-diphenyl also furnished magnolol but in this case the product was difficult to obtain in a pure state. Thermal rearrangement of 2,2'-diallyloxy-diphenyl yielded 2,2'-dihydroxy-3,3'-diallyl-diphenyl as the sole identifiable product.

Magnolol, dehydrodichavicol, (II) is a constituent of the bark of some *Magnolia* species¹, and it is interesting to note that chavicol methylether occurs in other species of the same genus². Magnolol was recently³ prepared by dehydrogenation of chavicol (I) with ferric chloride and has now been synthesised by ordinary methods.

2,2'-Dihydroxy-diphenyl was easily brominated to 2,2'-dihydroxy-5,5'-dibromo-diphenyl⁴. This was methylated and the dimethylether (IV) converted into 2,2'-dimethoxy-5,5'-diallyl-diphenyl (magnolol dimethylether) (III) in good yield, using ethylmagnesium bromide as a catalyst according to a method by Short and Wang⁵. It was found necessary, however, to carry out the allylation in tetrahydro-furan solution; in diethylether no reaction took place. 2,2'-Dimethoxy-5,5'-dicarbomethoxy-diphenyl, prepared from magnolol dimethylether¹ was found to be identical with a sample prepared from 2,2'-dimethoxy-5,5'-bis-(ω -carbomethoxy-ethyl)-diphenyl (*cf.* experimental part). Demethylation of magnolol dimethylether with methylmagnesium iodide⁶ furnished crude magnolol which was purified *via* its bis-phenyl-urethan. When the pure urethan was heated in a vacuum it dissociated into phenylisocyanate and magnolol.

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Following an observation that β -(4-methoxy-phenyl)-propanol on dehydration by the Tschugajew method furnished chavicol methylether, although in poor yield, an attempt was made to synthesise magnolol in a similar way. β -(4-Hydroxy-phenyl)-propanoic acid was iodinated in ammonia to β -(4-hydroxy-3-iodo-phenyl)-propanoic acid which was converted into its methyl-ether-methylester. This was then coupled by the Ullman procedure to give 2,2'-dimethoxy-5,5'-bis(ω -carbomethoxy-ethyl)-diphenyl, which was reduced with lithium aluminum hydride to the corresponding diol. This product was converted into its bis-methylxanthate, which on heating furnished oily, crude 2,2'-dimethoxy-5,5'-diallyl-diphenyl. On demethylation with methylmagnesium iodide this material yielded a phenol which, however, failed to crystallise. The paper chromatographic behaviour of the product indicated that it consisted essentially of magnolol.

Finally, the di-allylether of 2,2'-dihydroxy-diphenyl was subjected to thermal rearrangement. The resulting phenolic product, on paper chromatographic examination, appeared to be rather inhomogeneous but it obviously contained no magnolol. Methylation of the crude rearrangement product followed by oxidation with permanganate furnished a fair yield of 2,2'-dimethoxy-3,3'-dicarboxy-diphenyl. The rearrangement obviously proceeds essentially in the normal way to give the bis-*ortho* allylated product.

EXPERIMENTAL

Melting points are uncorrected

2,2'-Dihydroxy-5,5'-dibromo-diphenyl: A solution of bromine (120 g) in chloroform (700 ml) was added dropwise with stirring at room temperature to a solution of 2,2'-dihydroxy-diphenyl (70 g) in chloroform (700 ml). After concentration to about 200 ml and cooling, a first crop of crystals (112 g) was obtained. A second crop (8 g) was recovered from the mother liquors. Yield 120 g (93 %). After one recrystallisation from ethanol-water the product melted at 186–189° (lit.⁷ m. p. 188–189°).

2,2'-Dimethoxy-5,5'-dibromo-diphenyl: Dimethyl-sulphate (25 g) was added in portions with stirring to a solution of 2,2'-dihydroxy-5,5'-dibromo-diphenyl (23 g) in 10 % sodium hydroxide (100 ml). A white crystalline product precipitated. Yield 22.1 g (89 %). The product was recrystallised from 95 % ethanol, m. p. 127–129° (lit.⁴ m. p. 129–130°).

2,2'-Dimethoxy-5,5'-diallyl-diphenyl (Magnolol dimethylether): Ethyl bromide (29.2 g) was added in portions to magnesium turnings (13.1 g) in tetrahydrofuran (250 ml) dried over sodium. The formation of the Grignard compound was initiated by adding a crystal of iodine and heating gently. When all the ethyl bromide (and half of the magnesium present) had reacted, the mixture was chilled in ice and a solution of 2,2'-dimethoxy-5,5'-dibromo-diphenyl (50 g) in dry tetrahydrofuran (250 ml) was added drop by drop with stirring. The reaction mixture was then stirred at room temperature for another 24 h. Allyl bromide (97 g) was now added with stirring. The reaction mixture was refluxed for 3 h, chilled, and then 2 N hydrochloric acid (300 ml) was added in portions. The tetrahydrofuran phase was separated and the water phase extracted with ether. The nonaqueous phases were combined, washed with water, dried and evaporated yielding a yellow oil (37 g). This was distilled in a nitrogen atmosphere, the main fraction (27.8 g) boiling at 165°/0.7 mm. Yield 70 % (lit.¹ b.p. 186°/5 mm).

2,2'-Dimethoxy-5,5'-dicarbomethoxy-diphenyl from magnolol dimethylether: On oxidation with potassium permanganate, magnolol dimethylether furnished 2,2'-dimethoxy-5,5'-dicarboxy-diphenyl, m. p. above 310°. Treatment with diazomethane afforded the dimethylester, m. p. 174–175° (lit.⁴ m. p. 173–174°). Mixed with 2,2'-dimethoxy-5,5'-dicarbomethoxy-diphenyl obtained from 2,2'-dimethoxy-5,5'-bis-(ω -carbomethoxy-ethyl)-diphenyl (*cf.* below) the product melted at 173–175°.

2,2-Dihydroxy-5,5'-diallyl-diphenyl (Magnolol): A solution of magnolol dimethylether (10 g) in absolute ether (50 ml) was added with stirring to a solution of methylmagnesium iodide made from magnesium turnings (1.6 g) and methyl iodide (9.7 g) in absolute ether (100 ml). The ether was then removed by distillation and the temperature of the reaction flask slowly raised to 180° and kept at this level for 1 h. During the heating, gas was evolved. Small portions of water were then cautiously added to the glassy residue, followed by 2 N hydrochloric acid (75 ml). The mixture was then extracted with ether and the ether solution shaken with 2 N sodium hydroxide. Starting material (3.4 g) was recovered from the ether phase. The alkaline solution was acidified and extracted with ether. The ether extract was washed with water, dried and evaporated yielding a red-brown syrup (5.0 g). This was dissolved in benzene (50 ml) and filtered through a thin layer of aluminum oxide. The solution was evaporated and the remaining syrup distilled in a nitrogen atmosphere, yielding a main fraction (2.2 g) which boiled at 178–180°/1.0 mm. This material did not readily crystallise when scratched but crystallised immediately on seeding with magnolol obtained by dehydrogenation of chavicol³. Allowing for recovered starting material the yield was 37 %.

Purification of magnolol: Magnolol was purified *via* its bisphenylurethan (m. p. 143–144°) as described in a previous paper³. On thermal decomposition the phenylurethan afforded magnolol which was resublimed twice, m. p. 100.5–101.5° (lit.¹ m. p. 103°).

β -(3-Iodo-4-hydroxy-phenyl)-propanoic acid: Potassium iodide (400 g) and iodine (127 g) were dissolved in water and diluted to 1 000 ml. This solution (230 ml) was added drop by drop with stirring to a solution of β -(4-hydroxy-phenyl)-propanoic acid (20 g) in conc. ammonia (2 400 ml). The ammonia was evaporated in a vacuum and the volume of the solution reduced to about 400 ml. This solution was acidified stepwise with 10 N hydrochloric acid. The strongly discoloured material (2 g) precipitated first was discarded. The main fraction (26.9 g) consisted of reddish crystals. Extraction of the mother

liquor with ether gave additional material (4 g). The combined products were digested with hot benzene (150 ml) and the solution was filtered. On cooling, crystals (25.2 g), m. p. 103–108°, were obtained and concentration of the mother liquor yielded a second crop (2.7 g). Yield 79 %. For analysis a sample was extracted four times with hot ligroin and the residue was recrystallised from the same solvent, m. p. 112–113° (with sintering at 104°). (Found: I 43.30; equiv. wt. 291 (titration). Calc. for $C_9H_9O_3I$: I 43.45; equiv. wt. 292).

Methyl- β -(3-iodo-4-methoxy-phenyl)-propanoate: β -(3-Iodo-4-hydroxy-phenyl)-propanoic acid (21 g) was treated overnight with an excess of diazomethane in ether. Excess reagent was then destroyed with acetic acid, the solution was evaporated and the residue recrystallised from methanol, m. p. 42–43°. (Found: I 39.29. Calc. for $C_{11}H_{13}O_3I$: I 39.64.)

2,2'-Dimethoxy-5,5'-bis-(ω -carbomethoxy-ethyl)-diphenyl: Methyl- β -(3-iodo-4-methoxy-phenyl)-propanoate (20 g) was heated with copper bronze (60 g). At 225° a sudden reaction took place and the temperature rose to 285°. After cooling, the mixture was exhaustively extracted with acetone. The acetone was evaporated and the remaining syrup distilled in a vacuum. The main fraction, boiling at 234°/1.0 mm, crystallised on standing. Yield: 7.0 g (58 %). Recrystallised from 95 % ethanol, the product melted at 66–67°. (Found: C 68.10; H 6.99. Calc. for $C_{22}H_{26}O_6$: C 68.37; H 6.78.)

Reduction, dehydration and demethylation: Reduction of 2,2'-dimethoxy-5,5'-bis-(ω -carbomethoxy-ethyl)-diphenyl with lithium aluminum hydride afforded a viscous oil boiling at 252°/3.7 mm. A sample was converted into the bis-methylxanthate by the Tschugajew procedure (cf. Ref.⁸). On pyrolysis at 250°, an oil (b. p. 165–175°/1 mm) was obtained which on treatment with methyl magnesium iodide (cf. magnolol above) furnished an alkali soluble syrup [2.4 g from 10 g 2,2'-dimethoxy-5,5'-bis-(ω -carbomethoxy-ethyl)-diphenyl]. Samples of this product were chromatographed in the same way as the rearrangement product of 2,2'-diallyloxy-diphenyl (cf. below) and a spot was obtained with the same R_F -value (0.76) and colour reaction with diazotised benzidine as a blank of 2,2'-dihydroxy-5,5'-diallyl-diphenyl (magnolol). The product obviously contained magnolol but refused to crystallise.

2,2'-Dimethoxy-5,5'-dicarbomethoxy-diphenyl: On alkaline hydrolysis, 2,2'-dimethoxy-5,5'-bis-(ω -carbomethoxy-ethyl)-diphenyl afforded the corresponding dicarboxylic acid, m. p. 221–222° which on oxidation with permanganate gave 2,2'-dimethoxy-5,5'-dicarboxy-diphenyl, m. p. above 310°. Dimethylester, m. p. 174–175° (lit.¹ 172°).

2,2'-Diallyloxy-diphenyl: 2,2'-Dihydroxy-diphenyl (13 g) in dry xylene (200 ml) was added to metallic potassium (5.5 g) suspended in the same solvent (100 ml) with vigorous stirring under reflux. A pale yellow salt was formed. The mixture was refluxed for 2 h and then potassium carbonate (5 g) was added. Allyl bromide (34 g) was added drop by drop and the reaction mixture was refluxed for a further 2 h. The filtered solution was extracted with 2 N sodium hydroxide, washed with water and evaporated. The residual oil was distilled in a vacuum, the main fraction (11.8 g) boiling at 142°/0.8 mm. Yield 64 %. (Found: C 80.46; H 6.91. Calc. for $C_{18}H_{18}O_2$: C 81.17; H 6.81).

Rearrangement of 2,2'-diallyloxy-diphenyl: 2,2'-Diallyloxydiphenyl (4 g) was heated at 250° for 10 min. The alkali soluble reaction product (3.8 g) was analysed by paper chromatography. A Whatman No. 1 filter paper was immersed in a solution of dimethylsulphoxide (10 %) in benzene and dried at room temperature for 15 min. A mixture of benzene (10 parts), ligroin (10 parts) and dimethylsulphoxide (0.5 parts) was used as the mobile phase. The chromatogram was run against a blank of magnolol prepared from 2,2'-dimethoxy-5,5'-diallyl-diphenyl (cf. above) and developed with diazotised benzidine⁹. The crude product gave the following spots: I (R_F 0.90, yellowish-brown, main spot), II (R_F 0.64, red-brown), III (R_F 0.43, red-brown), IV (R_F 0.15, red-brown). No trace of magnolol (R_F 0.76, yellowish-brown) was obtained.

On methylation with dimethyl sulphate and alkali the product yielded a neutral oil b. p. 155–156°/1.0 mm. This crude material was oxidised with potassium permanganate yielding an acid, m. p. 207–208° in agreement with the reported⁴ melting point for 2,2'-dimethoxy-3,3'-dicarboxy-diphenyl (208–209°). (2,2'-Dimethoxy-5,5'-dicarboxy-diphenyl melts¹ above 300°.)

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