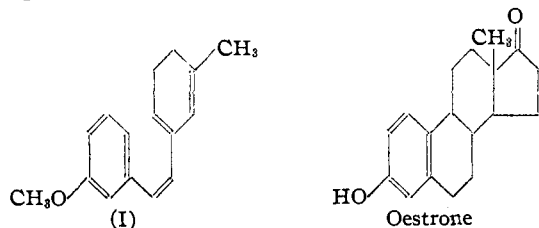


[CONTRIBUTION FROM THE PEDIATRIC RESEARCH LABORATORY OF THE JEWISH HOSPITAL OF BROOKLYN]

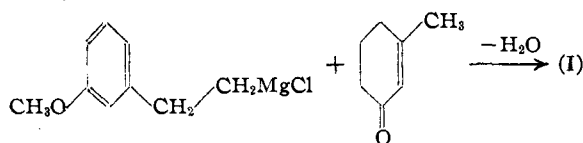
Synthesis of Derivatives of Symmetrical Diphenylethane Related to Materials Occurring Naturally. II. 3,4-Dihydro-5-methyl-3'-methoxydibenzyl, a Compound Related to Oestrone in Structure

BY SAMUEL NATELSON AND SIDNEY P. GOTTFRIED

Because of its relationship to oestrone¹ and possible conversion to this valuable sex hormone, 3,4-dihydro-5-methyl-3'-methoxydibenzyl was prepared in this investigation.



This compound was formed readily by the action of *m*-methoxyphenethylmagnesium chloride on the readily available 1-methylcyclohexen-1-one-3.²



Methylcyclohexenone prepared from formaldehyde and acetoacetic ester in good yield should be a valuable starting material for the synthesis of substances of the steroid type. It has a potential quaternary methyl group and an active ketonic group as is evident from its structure.

m-Methoxyphenethyl chloride was prepared in good yield by the following series of reactions. *m*-Nitrobromobenzene was reduced to the amine, and a procedure was worked out for the conversion of *m*-bromoaniline to *m*-bromophenol in over 80% yield. Since this paper was written, Smith and Haller³ have published a method for obtaining *m*-bromophenol in good yield. These authors also found fault with the procedures in the literature⁴ and obtained *m*-bromophenol by the conversion of *m*-bromophenyl diazonium borofluoride to *m*-bromophenyl acetate and saponification of this product. Their over-all yield is not as good as that obtained from the

procedure described herein, nor is their procedure as simple. The procedure depends upon the removal of nitrogen from the diazonium salt by strong acid (20% sulfuric acid) and the removal of the phenol from the sphere of action by steam so as to prevent coupling.

The *m*-bromophenol was methylated and its Grignard reagent condensed with ethylene oxide to yield *m*-methoxyphenethyl alcohol. This was converted smoothly by thionyl chloride to *m*-methoxyphenethyl chloride.

Treatment of I with 80% sulfuric acid in the cold resulted in rapid polymerization. Milder conditions are being studied to cyclize the compound and leave the double bond next to the methyl group open for building up the five-membered ring.

Experimental Part

***m*-Bromoaniline.**—For the preparation of large quantities the following procedure is recommended. In a 5-liter flask *m*-bromonitrobenzene (203 g., 1 mole) was added to 360 g. (excess) of mossy tin (tech.) and 700 cc. of water. The mixture was heated almost to boiling and concentrated hydrochloric acid was added drop by drop until 500 cc. had been added. The acid is added slowly at first and more rapidly as the reaction proceeds. Refluxing is continued for two hours. The reaction mixture is cooled, made strongly alkaline with 50% sodium hydroxide (about 550 g.) and steam distilled. The distillate is extracted with ether, dried over anhydrous sodium sulfate and vacuum distilled; yield 158 g., m. p. 17°, b. p. 130° (12 mm.).

***m*-Bromophenol.**—*m*-Bromoaniline (150 g.) is mixed with one liter of 5 *N* hydrochloric acid and diazotized with 62 g. of sodium nitrite in saturated solution at 0° with vigorous stirring. The excess nitrous acid is decomposed with solid urea. The diazotized material, kept cold, is dropped into 20% sulfuric acid through which a rapid stream of steam is passing and which is heated by an auxiliary heater to prevent excessive condensation. The addition and heating is maintained at such a rate as to allow for no material increase in volume. The distillate is extracted with ether, dried, and vacuum distilled; yield 142 g., m. p. 33°, b. p. 138° (12 mm.).

***m*-Bromoanisole.**—*m*-Bromophenol (142 g.) is dissolved in a solution of 45 g. of sodium hydroxide in 350 cc. of water. Dimethyl sulfate is added with mechanical stirring and heating on a water-bath until 120 g. (excess) has been added. The reaction mixture is now acid; 15% alkali is added until the mixture is just alkaline and heating is continued. More alkali is added if necessary

(1) Fieser, "Chemistry of Natural Compounds Related to Phenanthrene," Reinhold Publishing Corp., New York, 1936, p. 200.

(2) Knoevenagel and Klages, *Ann.*, **281**, 97 (1895); Hageman, *Ber.*, **26**, 884 (1893); Rabe and Pollack, *ibid.*, **45**, 2926 (1912).

(3) Smith and Haller, *THIS JOURNAL*, **61**, 143 (1939).

(4) Diels and Bunzl, *Ber.*, **38**, 1486 (1905).

to keep the reaction mixture strongly alkaline. The mixture is heated for one hour longer, cooled and extracted with ether. The ether is evaporated and the material is vacuum distilled; yield 138 g., b. p. 105° (16 mm.).

***m*-Methoxyphenethyl Alcohol.**—A Grignard reagent is prepared from 17 g. of magnesium, 120 g. of *m*-bromoanisole and 400 cc. of anhydrous ether. When the magnesium has almost completely dissolved, 35 g. of ethylene oxide (excess) in twice its volume of ether is added through the dropping funnel, cooling the flask in running water. The mixture is refluxed for thirty minutes; 200 cc. of benzene (anhydrous) is added, about three-fourths of the ether is distilled off, and the residue is refluxed for one hour longer (temperature 60°). The mixture is decomposed with diluted sulfuric acid in crushed ice. The ether layer is dried with sodium sulfate, and the ether is evaporated. The residue is vacuum distilled: b. p. 148° (13 mm.); yield 60 g.

Anal. Calcd. for C₉H₁₂O₂: C, 71.05; H, 7.89. Found: C, 70.83; H, 7.96.

***m*-Methoxyphenethyl Chloride.**—*m*-Methoxyphenethyl alcohol (50 g.) is dissolved in 300 cc. of ether; with cooling (in an ice-bath) and stirring 55 g. (excess) of thionyl chloride in an equal volume of ether is added slowly. The mixture is then stirred for one-half hour. The ether is evaporated on a steam-bath and the residue is vacuum distilled: yield 45 g.; b. p. 122° at 18 mm.

Anal. Calcd. for C₉H₁₁OCl: Cl, 20.80. Found: Cl, 20.91.

3,4-Dihydro-5-methyl-3'-methoxydiphenylethane.—*m*-Methoxyphenethylmagnesium chloride is prepared from 45 g. of *m*-methoxyphenethyl chloride and 7 g. of magnesium as described for *m*-methoxybromobenzene. The Grignard reagent is added in the cold to methyl-

cyclohexenone in ether, and allowed to stand overnight. The reaction mixture is worked up as usual: yield 32 g.; b. p. 184° (10 mm.).

Anal. Calcd. for C₁₈H₂₀O: C, 84.21; H, 8.77. Found: C, 83.69; H, 8.96.

1-Methylcyclohexene-1-one-3.—Ethyl acetoacetate (520 g., 4 moles) is mixed with 150 g. (2 moles) of 40% formaldehyde; 10 cc. of piperidine in 50 cc. of alcohol is added drop by drop with mechanical stirring. The flask is allowed to warm to 30° but prevented by running water from going higher. After complete addition (one hour), the material is allowed to stand overnight.

The upper water layer is separated and the lower oily layer is washed with water several times. The oily layer is mixed with 2 liters of 15% sulfuric acid, glass beads added and the mixture is refluxed for fifteen hours. The mixture is cooled, neutralized with ammonium hydroxide and saturated with ammonium sulfate. The methylcyclohexenone is extracted with ether, the ether is dried with anhydrous potassium carbonate and evaporated. The methyl cyclohexenone is distilled at atmospheric pressure, collecting from 195–202°; yield 180 g. Methylcyclohexenone is light sensitive and should be kept in a dark colored bottle. About 10–15% is lost on each distillation due to polymerization.

Summary

Starting with readily available materials, 3,4-dihydro-5-methyl-3'-methoxydiphenylethane has been synthesized. This compound is structurally related to oestrone and attempts are being made to convert it to this sex hormone.

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RECEIVED FEBRUARY 1, 1939

[CONTRIBUTION FROM JACKSON LABORATORY OF E. I. DU PONT DE NEMOURS AND COMPANY]

Reactions of 3-Hexene. II. Condensations with Aromatic Hydrocarbons and Phenols

BY LOUIS SPIEGLER AND J. M. TINKER

3-Hexene, which behaves normally in common addition reactions, was condensed with hydrocarbons and phenols using a series of catalyzers, such as sulfuric acid, anhydrous hydrogen fluoride, dihydroxyfluoboric acid (H₃BO₂F₂), perchloric acid, zinc chloride, and anhydrous aluminum chloride. Depending upon the molal ratio of the reactants, 1, 2 or 3 secondary hexyl groups could be introduced into the respective aromatic hydrocarbon or phenol. All of the condensation products were non-crystallizable oils. Inability to obtain pure crystalline products probably was due to the formation of mixtures resulting from partial isomerization under the conditions em-

ployed. It is believed, however, that the results obtained are truly indicative of the characteristic reactions of 3-hexene.

Experimental

Table I indicates the methods and reactants used and the yields and products formed from reaction of 3-hexene, or derivatives obtainable from it, with hydrocarbons.

Oxidation of 4-chloro-(1'-ethylbutyl)-benzene (No. 3 in Table I) with sodium dichromate and 50% sulfuric acid at 110–125° yielded *p*-chlorobenzoic acid, m. p. 239–241°. No change in melting point was observed when mixed with pure *p*-chlorobenzoic acid. Similarly oxidation of 1-methyl-4-(1'-ethylbutyl)-benzene (No. 4) with dilute potassium permanganate gave terephthalic acid; dimethyl ester, m. p. 140–142°.