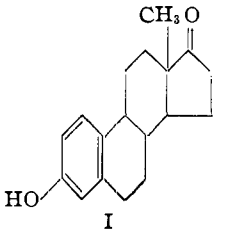
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WALLACE AND TIERNAN COMPANY, INC.]

1-Methyl-3-ethyl-4-(*p*-hydroxyphenyl)-Δ^3-cyclohexenylethylcarbinol, an "Open-Model" of Estradiol

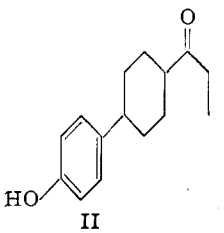
BY MARTIN RUBIN AND HENRY WISHINSKY

In a recent publication the synthesis of 4-(*p*-hydroxyphenyl)-hexahydropropiophenone, II, was described.[1] This compound was suggested as an "open-model" of estrone, I. An investigation in this Laboratory directed toward the same objective has resulted in the preparation of 1-methyl-3-ethyl-4-(*p*-hydroxyphenyl)-Δ^3-cyclohexenylethylcarbinol, III, which may be considered as an "open model" of estradiol.

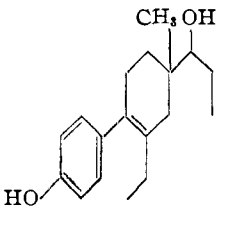
For the preparation of III the readily available γ-methyl-γ-carboxypimelic acid[2] was utilized. Dieckman cyclization of ethyl γ-methyl-γ-carbethoxypimelate gave ethyl 1-methyl-3-carbethoxy-4-ketocyclohexanecarboxylate, IVb, in good yield. Alkylation with ethyl iodide in the usual way followed by acid hydrolysis afforded 1-methyl-3-ethyl-4-ketocyclohexanecarboxylic acid, Va. From the complex mixture resulting from the condensation of Va with the Grignard reagent from *p*-bromanisole, the crystalline acid VIa could be obtained by fractional distillation of the methyl esters of the acidic portion of the reaction mixture followed by dehydration and saponification of the intermediate hydroxy ester. The position of the double bond in the acid VIa is indicated by its characteristic resistance to catalytic hydrogenation. Conversion of the acid VIa to the propionyl derivative, VII, was effected by reaction of its acid chloride with diethyl zinc. 1-Methyl-1-propionyl-3-ethyl-4-(*p*-methoxyphenyl)-Δ^3-cyclohexene, VII, was not stable to acidic demethylation reagents. Demethylation with potassium hydroxide in ethylene glycol[3] at 200–220° caused simultaneous reduction of the carbonyl group.[4] The phenol, III, was characterized as the crystalline *p*-nitrobenzoate.



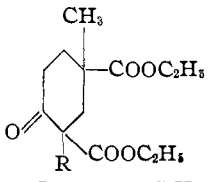
I



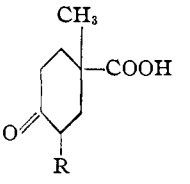
II



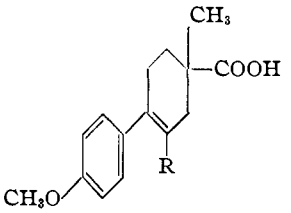
III



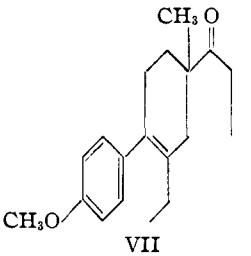
IV a, R = C_2H_5
b, R = H



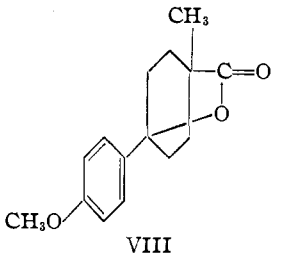
Va, R = C_2H_5
b, R = H



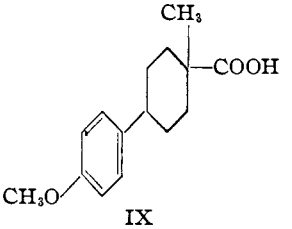
VI a, R = C_2H_5
b, R = H



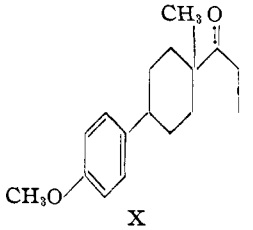
VII



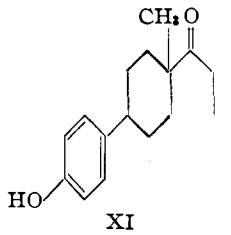
VIII



IX



X



XI

For the preparation of the lower homolog, 1-methyl-4-(*p*-hydroxyphenyl)-hexahydropropiophenone, XI, ethyl 1-methyl-3-carbethoxy-4-ketocyclohexanonecarboxylate, IVb, was converted by acid hydrolysis to 1-methyl-4-ketocyclohexanecarboxycyclic acid, Vb. This compound could also be prepared by pyrolysis of the anhydride of γ-methyl-γ-carboxypimelic acid. The reaction of the methyl ester of 1-methyl-4-ketocyclohexanecarboxylic acid with the Grignard reagent from *p*-bromoanisole gave rise to the unsaturated acid VIb and the lactone VIII.[5]

(1) Johnson and Offenhauer, THIS JOURNAL, **67**, 1045 (1945).
(2) Bruson and Riener, THIS JOURNAL, **64**, 2850 (1942).
(3) Corse, U. S. Patent, 2,325,307 (1943).
(4) Rubin, THIS JOURNAL, **66**, 2075 (1944).
(5) The formation of an acid as a product of the addition of a Grignard reagent to an alicyclic keto ester has been previously ob-

In contrast to its homolog, VIa, the unsaturated acid, VIb, was readily reduced by catalytic hydrogenation. Conversion of the reduced acid, IX, to the ketone, X, proceeded satisfactorily in the manner described for the homolog. 1-Methyl-4-(*p*-hydroxyphenyl)-hexahydropropiophenone, X, could be demethylated by a mixture of hydrobromic and acetic acids to the phenol, XI.

The estrogenic activity of some of the compounds described above have been determined by Dr. C. F. Geschickter. Compound VII was inactive by the Allen–Doisy assay at a threshold level of 100 γ. Compound XI was active at a level of 5 mg. The threshold level for estradiol by this same test is 1 γ.

Experimental

Ethyl γ-Methyl-γ-carbethoxypimelate.—The continuous esterification for thirty hours of 436 g. of γ-methyl-γ-carboxypimelic acid[2] by heating with ethanol, carbon tetrachloride and sulfosalicylic acid[6] gave 416 g. (80%) of ester, b. p. 128–131° at 0.1 mm.

Anal. Calcd. for $C_{16}H_{26}O_6$: C, 59.58; H, 8.67. Found: C, 59.10; H, 8.33.

Ethyl 1-Methyl-3-carbethoxy-4-ketocyclohexanecarboxylate (IVb).—Dieckmann cyclization[7] of 302 g. of γ-methyl-γ-carbethoxypimelate gave 192 g. (75%) of product, b. p. 125–130° at 0.2 mm. It gave the characteristic violet color with ferric chloride solution.

Anal. Calcd. for $C_{13}H_{20}O_5$: C, 60.92; H, 7.85. Found: C, 61.03; H, 7.97.

1-Methyl-4-ketocyclohexanecarboxylic Acid (Vb). A. From γ-Carboxy-γ-methylpimelic Acid.—A mixture of 15 g. of γ-carboxy-γ-methylpimelic acid and 30 g. of acetic anhydride was heated under reflux for four hours. The excess acetic acid was then removed by distillation *in vacuo* and the residue heated at 200–220° at 30 mm. until the evolution of carbon dioxide was complete. Immediate distillation of the residue gave 5 g. (47%) of the product as a clear viscous oil, bath temp. 250–280° at 0.7 mm. On cooling the material rapidly crystallized and was purified by recrystallization from benzene–petroleum ether mixture. After two recrystallizations it melted at 78–79°.

Anal. Calcd. for $C_8H_{12}O_3$: C, 61.51; H, 7.75. Found: C, 61.27; H, 7.60.

B. From IVb.—A mixture of 10 g. of IVb, 20 cc. of glacial acetic acid, 5 cc. of concentrated hydrochloric acid and 3 cc. of water was refluxed for five hours. After removal of the low boiling fractions the product, 4.8 g. (78%), was collected at 130–135° at 0.5 mm. It crystallized rapidly in the receiver, m. p. 78–79°.

Methyl 1-Methyl-4-ketocyclohexanecarboxylate.—The esterification of the acid by diazomethane in the usual manner gave a quantitative yield of the ester, b. p. 80–83° at 0.2 mm.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.50; H, 8.29. Found: C, 63.97; H, 8.38.

Ethyl 1-Methyl-3-ethyl-3-carbethoxy-4-ketocyclohexanecarboxylate (IVa).—To 11.5 g. of sodium sand in 300 cc. of toluene was added 130 g. of IVb. After the initial reaction the mixture was stirred and refluxed until all of the sodium had reacted. One hundred grams of ethyl iodide was added, and stirring and refluxing was continued for fourteen hours. The mixture was cooled, washed with water and extracted with cold 5% sodium hydroxide until a ferric chloride test of the toluene solution indicated the absence of any unreacted starting material. The solution was then washed with water until free of alkali, concentrated and distilled. The product, 131 g. (92%), was a clear colorless oil, b. p. 120–125° at 0.1 mm.

Anal. Calcd. for $C_{15}H_{24}O_5$: C, 63.36; H, 8.50. Found: C, 63.46; H, 8.07.

1-Methyl-3-ethyl-4-ketocyclohexanecarboxylic Acid (Va).—A mixture of 130 g. of IVa, 400 cc. of glacial acetic acid, 80 cc. of concentrated hydrochloric acid and 32 cc. of water was heated under reflux for eighteen hours. The solvents were then removed by distillation *in vacuo*. The residue, on fractionation gave 75 g. (88%) of product, b. p. 140–150° at 0.1 mm.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76; mol. wt., 184.2. Found: C, 64.75; H, 8.20; mol. wt., 185.5.

Methyl 1-Methyl-3-ethyl-4-ketocyclohexanecarboxylate.—Esterification of the acid with diazomethane in the usual way gave a quantitative yield of the ester, b. p. 95° at 0.05 mm.

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.5; H, 9.09. Found: C, 66.4; H, 8.98.

1-Methyl-3-ethyl-4-(*p*-methoxyphenyl)-Δ^3-cyclohexenecarboxylic Acid (VIa).—The Grignard reagent from 35 g. of *p*-bromoanisole and 4.9 g. of magnesium was added dropwise to a cold, well stirred solution of 32 g. of Va in 250 cc. of ether. When the addition was complete the mixture was refluxed for two hours and then decomposed in the usual way with dilute sulfuric acid. The ether layer was separated and extracted with 5% sodium hydroxide solution. The alkaline extracts were cautiously acidified in the cold and extracted with ether. The ether extract was dried and concentrated *in vacuo* and the residue treated with ethereal diazomethane solution in excess. After one hour the excess diazomethane was decomposed by the addition of concentrated hydrochloric acid, the ether solution washed with water and with sodium hydroxide solution. The ethereal layer was then concentrated and the residue fractionated using a 25-cm. Vigreux column. After a forerun of methyl 1-methyl-3-ethyl-4-ketocyclohexanecarboxylate, 13 g. of carbinol, b. p. 150–160° at 0.1 mm. was obtained. The analysis indicates the presence of a small amount of the dehydrated material.

Anal. Calcd. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.53. Found: C, 71.55; H, 8.52.

Dehydration of this carbinol was effected by the thionyl chloride pyridine procedure.[8] The product of this reaction was saponified without further purification by refluxing overnight with 10% sodium hydroxide solution in 50% methanol. After the distillation of the methanol the alkaline solution was extracted once with ether, cooled and acidified with hydrochloric acid. The oily acid which separated was extracted with ether and the extracts concentrated *in vacuo*. On trituration with a small amount of methanol in the cold, the residue crystallized. On recrystallization from dilute methanol the product, 7 g. (15%), melted at 123–124°.

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.45; H, 8.24.

This material was resistant to catalytic hydrogenation with an active platinum catalyst at room temperature and 30 pounds pressure.

1-Methyl-1-propionyl-3-ethyl-4-(*p*-methoxyphenyl)-Δ^3-cyclohexene (VII).—To 7 g. of VIa in 50 cc. of dry benzene was added 10 cc. of purified thionyl chloride and a drop of pyridine. After standing overnight at room temperature the excess reagent and benzene were removed by distillation *in vacuo*. The residue was dissolved in 100 cc. of dry toluene and treated dropwise at 0–5° with an excess of diethyl zinc in toluene. The mixture was allowed to warm

served. *Cf.* Nenitzescu and Cioranescu, *Ber.*, **75**, 1765 (1942). It is likely that the acid is formed by the action of excess Grignard reagent on an intermediate lactone. *Cf.* Cox, THIS JOURNAL, **66**, 865 (1944). Treatment of the lactone, VIII, with methylmagnesium iodide gave rise to some unsaturated acid, VIb.

(6) "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 246.

(7) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 116.

(8) Chuang, Tien and Ma, *Ber.*, **69**, 1499 (1936).

to room temperature and at the end of four hours was decomposed by the addition of ethanol and cold dilute hydrochloric acid. The toluene layer was washed with alkali, concentrated and the residue distilled. The product, 7 g., b. p. 150–155° at 0.1 mm. could not be obtained analytically pure by fractionation with the apparatus at hand. The ketone group proved to be too inert for the characterization of the compound by the usual carbonyl reagents.

1-Methyl-3-ethyl-4-(*p*-hydroxyphenyl)-Δ^3-cyclohexenylethylcarbinol (III).—A mixture of 5 g. of the ketone, 5 g. of potassium hydroxide and 150 cc. of ethylene glycol was refluxed at 200–220° for four hours. The solution was then poured onto ice, acidified with hydrochloric acid, diluted with 500 cc. of water and extracted with ether. The ethereal extracts were washed with water, concentrated and the residue taken up in 50 cc. of benzene. The phenolic material was extracted from the benzene solution by shaking with 5% sodium hydroxide in 50% alcohol solution. The alcohol was removed from the alkaline extract by distillation and the aqueous residue acidified with hydrochloric acid. The oil was then extracted with ether, the extracts concentrated and the residue distilled. The product, a pale yellow glass, b. p. 175–180° at 0.1 mm. (3 g., 60%) could not be crystallized. A portion was converted to the *p*-nitrobenzoate, m. p. 127–128°.

Anal. Calcd. for $C_{25}H_{29}O_5N$: C, 70.88; H, 6.90. Found: C, 70.95; H, 7.40.

1-Methyl-4-(*p*-methoxyphenyl)-cyclohexenecarboxylic Acid (VIb).—To the Grignard reagent from 35 g. of *p*-bromoanisole and 2.8 g. of magnesium in ether was added an ethereal solution of 34.0 g. of methyl 1-methyl-4-ketocyclohexanecarboxylate. The mixture was refluxed for two hours, cooled and decomposed with cold dilute sulfuric acid. The ether layer was separated, washed with water and extracted with cold 5% sodium hydroxide solution until free of acidic material. The alkaline extracts were cooled and acidified with hydrochloric acid. The oil which separated crystallized on standing in the refrigerator overnight. It was then separated by filtration. Since a test of a portion of the product indicated that it contained an appreciable quantity of neutral material, it was redissolved in ether. Acidic material was removed from the ethereal solution by extraction with cold 5% alkali. Acidification of the alkaline extracts gave 12 g. of crystalline product. After four recrystallizations from methanol it melted at 137–137.5°. The material decolorized potassium permanganate solution.

Anal. Calcd. for $C_{16}H_{18}O_3$: C, 73.17; H, 7.37; mol. wt., 246.3. Found: C, 73.58; H, 7.78; mol. wt., 249.0.

Lactone of 1-Methyl-4-hydroxy-4-(*p*-methoxyphenyl)-cyclohexanecarboxylic Acid (VIII).—The combined ethereal solutions of the neutral material was concentrated in a boiling water-bath *in vacuo*. A low boiling fraction, b. p. 75° at 0.1 mm., which consisted largely of anisole was removed. The residue was dissolved in boiling petroleum ether (60–90°). The material which precipitated on cooling was separated by filtration. On recrystallization from petroleum ether the product, 6 g. melted at 114–115°.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.17; H, 7.37. Found: C, 73.26; H, 7.34.

The product was saturated to potassium permanganate solution. It was insoluble in cold alkali, dissolved slowly on refluxing with alkali and was reprecipitated by acidification with mineral acids. The lactone (VIII) could be converted to the unsaturated acid (VIb) by saponification with aqueous alkali followed by distillation of the water *in vacuo*. The gelatinous residue was heated with potassium acid sulfate and dry tetralin for one hour. The tetralin was removed by distillation *in vacuo* and the residue treated with dilute hydrochloric acid. The crystalline precipitate after four recrystallizations from methanol, melted at 137–137.5°.

1-Methyl-4-(*p*-methoxyphenyl)-cyclohexanecarboxylic Acid (IX).—A solution of 6.5 g. of 1-methyl-4-(*p*-methoxyphenyl)-Δ^3-cyclohexenecarboxylic acid in 100 cc. of glacial acetic acid absorbed the theoretical quantity of hydrogen in fifteen minutes using Adams platinum oxide catalyst at a pressure of 2 atms. at room temperature. The catalyst was removed by filtration and the solvent removed by distillation *in vacuo*. The product after three recrystallizations from petroleum ether melted at 112–115°. No further attempt was made to separate the isomers.

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.46; H, 8.12.

Methyl 1-Methyl-4-(*p*-methoxyphenyl)-cyclohexanecarboxylate.—Reaction of the acid with diazomethane in the usual manner gave a quantitative yield of the ester, b. p. 140–145° at 0.1 mm.

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.33; H, 8.60.

1-Methyl-1-propionyl-4-(*p*-methoxyphenyl)-cyclohexane.—In the same manner as described above for the homologous compound, (IX) was converted to the acid chloride and treated with diethyl zinc. The product of the reaction was a clear mobile oil, b: p. 140–145° at 0.03 mm. As in the case of (VII) the product was contaminated with a more highly oxygenated material and could not be obtained in analytical purity.

1-Methyl-4-(*p*-hydroxyphenyl)-hexahydropropiophenone (XI).—A mixture of 1.0 g. of ketone, 10 cc. of 40% hydrobromic acid and 25 cc. of glacial acetic acid was refluxed for three hours. The acids were removed by distillation *in vacuo* and the residual oil dissolved in 10% sodium hydroxide solution. The clear alkaline solution was shaken with 1 cc. of benzoyl chloride and the benzoate which separated immediately removed by filtration. On recrystallization from dilute ethanol it melted at 96–97°.

Anal. Calcd. for $C_{23}H_{26}O_3$: C, 78.82; H, 7.48. Found: C, 78.64; H, 7.42.

The benzoate was refluxed for twelve hours with 50 cc. of 5% sodium hydroxide in 50% alcohol. The alcohol was removed by distillation, the aqueous residue cooled, extracted with ether to remove a little unsaponified material, acidified with hydrochloric acid and extracted with ether. The ethereal extract was washed with bicarbonate solution until free of benzoic acid, and was then concentrated. The residue crystallized rapidly. On recrystallization from benzene–petroleum ether the product (0.6 g., 60%) melted at 142–143°.

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.80; H, 8.83.

Acknowledgment.—We wish to thank Mrs. L. Howells for assistance during the course of this work.

Summary

The preparation of 1-methyl-3-ethyl-4-(*p*-hydroxyphenyl)-Δ^3-cyclohexenylethylcarbinol an "open-model" of estradiol, has been described. By the same general procedure 1-methyl-4-(*p*-hydroxyphenyl)-hexahydropropiophenone, related to an "open-model" of estrone, has been prepared.

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