washing well with carbonate solution, dilute acid and water. The ether was evaporated and the residue evaporatively distilled at 170–180° (0.2 mm.) giving 189 mg. (87%) of distillate which solidified upon scratching, m. p. 89–93°. Recrystallization from benzene–petroleum ether gave 155 mg., m. p. 90–103°. Repeated recrystallization from the same solvent slowly raised the m. p. of the keto phenol IXb to 104–105°.

The ultraviolet absorption spectrum (95% alcohol) showed maxima at 225 mμ (log $E = 3.97$) and 279 mμ (3.25) and a minimum at 248 mμ (2.50).

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.8; H, 9.5. Found: C, 79.0; H, 9.5.

α-(4-Hydroxycyclohexyl)-butyric Acid.—Ethyl α-(*p*-hydroxyphenyl)-butyrate[5] was hydrogenated in absolute alcohol solution at 180–185° and 4500–5000 p.s.i. of hydrogen in the presence of Raney nickel.[30,6]

After hydrolysis of the ester with 45% potassium hydroxide, as much as 83% of the mixture of acids was obtained, m. p. 88–110°. Recrystallization of this material from benzene–alcohol gave a 35% recovery of the higher melting isomer (probably *trans*),[6] m. p. 121–125°, and 62% of a mixture, m. p. 88–105°. Further recrystallization of the first crop gave material melting at 122–124° (Ungnade and Morriss,[6] m. p. 123.5–124°).

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.5; H, 9.7. Found: C, 64.1; H, 9.8.

Benzoate of α-(4-Hydroxycyclohexyl)-*p*-methoxybutyrophenone.—A solution of 3.15 g. of the hydroxy acid (m. p. 120–122°) in 10 cc. of acetic acid and 5 cc. of pyridine was treated at room temperature with 3.5 cc. of acetyl chloride for twenty-four hours. The mixture was diluted with water, extracted with ether, evaporated and the crude acetoxy acid converted to the acid chloride with 3 cc. of thionyl chloride in 10 cc. of benzene containing one drop of pyridine for two and one-half hours at room temperature, then working up as described for the corresponding derivative of the aromatic acid.[5] The crude acid chloride was coupled with 6 cc. of anisole in 20 cc. of benzene using 5 cc. of anhydrous stannic chloride, letting stand for one hour at room temperature.[5] The crude acetoxy ketone could not be crystallized and was hydrolyzed with methanolic potassium hydroxide and converted to the benzoate by treating in 20 cc. of pyridine with 3 cc. of benzoyl chloride at room temperature for twelve hours. After hydrolyzing, extracting with ethyl acetate and washing with bicarbonate solution, the benzoate was crystallized from methanol giving 2.95 g. (46%) of product, m. p. 79–85°, and 0.41 g. (6%), m. p. 60–68°. Another recrystallization from methanol gave material as colorless needles or thin plates, m. p. 84–88°, which, though not completely pure, gave a satisfactory analysis.

Anal. Calcd. for $C_{24}H_{28}O_4$: C, 75.8; H, 7.4. Found: C, 75.3; H, 7.4.

3-(*p*-Anisyl)-4-(4′-hydroxycyclohexyl)-3-hexanol (V).—Seven and six-tenths grams of the benzoate was hydrolyzed with methanolic potassium hydroxide, extracted with benzene and dried. The crude hydroxy ketone was added in 100 cc. of dry benzene to the ethylmagnesium bromide from 2.4 g. of magnesium and 10 cc. of ethyl bromide in 100 cc. of dry ether. The tan-colored solid which separated redissolved upon warming; after refluxing for five hours the mixture was cooled and hydrolyzed, washing the ether–benzene layer with dilute acid and water. The solvent was evaporated and the oily residue taken up in a small amount of benzene; after six months standing, crystals were deposited from an aliquot of this solution, corresponding to a total yield of 4 g. (65%), m. p. 105–111°. Recrystallization from benzene–petroleum ether gave colorless prisms of the alcohol V which changed to a powder upon drying, m. p. 110–111°.

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.5; H, 9.9. Found: C, 74.0; H, 10.2.

Some preliminary attempts at selective dehydration were carried out, but the work had to be discontinued in 1942 before definitive results were obtained. Further work on this synthesis is not contemplated at the present time.

Summary

By selective hydrogenation of *meso*-hexestrol monomethyl ether using copper–chromium oxide catalyst, followed by demethylation of the reduction product with methylmagnesium iodide at 185–195°, it has been possible to prepare the two hexahydro-*meso*-hexestrols: Isomer A, m. p. 183–184°, and isomer B, m. p. 134–135°. Oxidation of the monobenzoate and hydrolysis has given the corresponding phenolic ketone. The hexahydrohexestrols have been tested for estrogenic activity. Both are less active than *meso*-hexestrol.

MADISON 6, WIS.

RECEIVED JULY 9, 1948

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF MISSOURI]

Hydrodiethylstilbestrol Compounds. III. The *meso* Octahydro Compounds[1]

BY HERBERT E. UNGNADE AND PAUL W. TUCKER[2,3]

In continuation of our studies on hydrodiethylstilbestrol compounds the partial hydrogenation of *meso*-hexestrol has been investigated in the presence of W-2 Raney nickel catalyst. The separation of the reduction products has presented considerable difficulties due to the formation of complexes between dihydro and perhydrostilbestrol compounds and between *cis* and *trans* isomers of the octahydro compound.

A single octahydro compound (I, m. p. 127–128°) can be isolated from the alkali-soluble portion of the reduction products only after laborious purification by crystallization, sublimation and adsorption of the substance and its benzoate (m. p. 123.5–125°). This compound (I) is identical with the phenolic alcohol B of Wilds and McCormack.[4] It gives a good yield of the perhydrogenation product (II), *meso*-3,4-di-(4-hydroxycyclohexyl)-hexane.[5] While the compound probably has the *trans*-configuration, the perhydrogenation product cannot be regarded as evidence for this structure in view of the results of Wilds and McCormack.[5a]

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[1] Presented before the Division of Organic Chemistry of the American Chemical Society, Chicago, Ill., April, 1948.

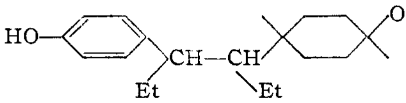
[2] George Breon Fellow, 1946–1948.

[3] From the Ph.D. thesis of Paul W. Tucker, 1948.

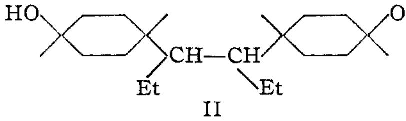
[4] Wilds and McCormack, THIS JOURNAL, **70**, 884 (1948).

[5] Ungnade and Ludutsky, *J. Org. Chem.*, **10**, 307 (1945).

[5a] Wilds and McCormack, THIS JOURNAL, **70**, 4127 (1948).



I

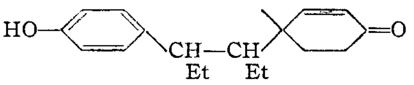


II

On the basis of melting points, mixed melting points and infrared spectra, the phenolic alcohol (I) differs from the octahydro compounds reported previously.[6]

In an attempt to prepare the corresponding *cis* isomer, the crude mixture of *meso*-octahydro compounds has been oxidized with aluminum *t*-butoxide. The resulting ketone on reduction with W-2 Raney nickel catalyst yields a glassy phenolic alcohol (III) which has been purified by chromatographic adsorption and by regeneration from the purified glassy benzoate. The ultraviolet absorption spectra of these compounds coincide with those of the crystalline isomer (I) and its monobenzoate (Figs. 1 and 2).

Inasmuch as a second crystalline *meso* compound has been described by Wilds and McCormack,[4] which presumably has the *cis* configuration, the glassy compound (III) must be regarded as a mixture of *cis* and *trans* isomers. A similar glassy mixture is also obtained from the reduction of the unsaturated phenolic ketone (IV).[7]



IV

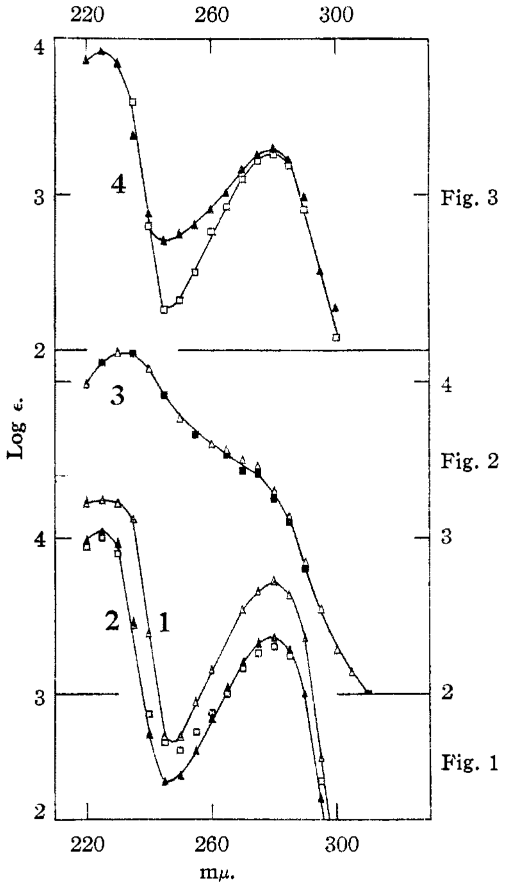
The alcohol (I) has been tested biologically and has been found to be devoid of androgenic activity.

Experimental[8,9]

Partial Hydrogenation of *meso*-Dihydrodiethylstilbestrol.—*meso*-Hexestrol (50 g.) in 100 ml. of methanol was hydrogenated with 10 g. of Raney nickel at 210° and a starting pressure of 5300 lb. The hydrogenation was interrupted after one half of the amount of hydrogen required for complete reduction was absorbed. The product obtained after removing catalyst and solvent weighed 48 g.

The perhydro compounds (15.3 g.) were removed from the mixture by refluxing with sodium methoxide solution, diluting with water and extracting with benzene. The alkali soluble fraction (35.6 g.) was liberated, extracted, washed and dried.

***dl-m*-3-(4-Hydroxycyclohexyl)-4-(*p*-hydroxyphenyl)-hexane (I).**—The above phenolic material (28.83 g.) was benzoylated according to Schotten–Baumann and the mixture of benzoates (32.3 g.) was digested with benzene. The residue melting at 170–235° weighed 5.8 g. The digest was adsorbed on alumina and eluted with benzene. Fractional crystallization of the residue and the eluted zones from benzene gave 8.15 g. of *meso*-hexestrol dibenzoate, 8.71 g. of solid fractions melting between 117° and 208° and 8.17 g. of glassy material. The solid fraction (m. p. 117–208°) and the glassy material were hydrolyzed separately with 150 cc. of 0.8 *N* aqueous potassium hydroxide. The products of hydrolysis were adsorbed on aluminum oxide from benzene solution and eluted with benzene. The washings contained *meso*-hexestrol. A second fraction obtained by eluting with methanol was crystallized from aqueous methanol, benzene and petroleum ether and melted at 129–130°.



Ultraviolet absorption spectra: Fig. 1.—Curve 1. △, *meso*-hexestrol; curve 2, ▲, *meso*-octahydrostilbestrol (I); □, *meso*-octahydrostilbestrol (III). Fig. 2.—Curve 3. △, benzoate of (I); ■, benzoate of (III). Fig. 3.—Curve 4, ▲, phenolic alcohol B of Wilds and McCormack; □, octahydrostilbestrol of Hoehn and Ungnade.

The new material, presumably a complex, was repeatedly crystallized, sublimed, adsorbed on alumina and again crystallized from various solvents until it appeared homogeneous and melted at 127–128° (from benzene). It gave a single monobenzoate (Schotten–Baumann), m. p. 123.5–125°.

Anal. Calcd. for $C_{25}H_{32}O_3$: C, 78.91; H, 8.48; mol. wt., 380. Found: C, 78.41; H, 8.54; mol. wt. (Rast), 392.

Depending on the method of crystallization, melting points of 130.5–133°, 129–130° and 135–136° could be observed for the same material. This behavior was also observed by Wilds and McCormack and was ascribed to polymorphism by them.[4] The compound did not depress the melting point of a sample of the phenolic alcohol B of these authors,[10] but gave a melting point depression with

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(6) Ungnade and Ludutsky, THIS JOURNAL, **69**, 2629 (1947).

(7) Unpublished work by P. W. Tucker.

(8) All melting points uncorrected.

(9) Analyses by Karl T. Zilch.

(10) We wish to thank Dr. Wilds for a specimen of this substance.

the isomer, m. p. 144–145°, described by Hoehn and Ungnade.[11]

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.08: H, 10.44.

Hydrogenation of *dl-m*-3-(4-Hydroxycyclohexyl)-4-(*p*-hydroxyphenyl)-hexane (I).—A solution of the octahydro compound (0.080 g.) in 100 cc. of methanol was reduced at 210° with 3 g. of Raney nickel by shaking for two and one-half hours at 3000 lb. The product (0.080 g.), isolated in the usual way, gave 0.050 g. of *meso*-3,4-di-(4-hydroxycyclohexyl)-hexane (II) melting at 166–167° after crystallization from ethyl acetate. The mixed melting point with authentic material was 166–167°.

***dl-m*-3-(4-Ketocyclohexyl)-4-(*p*-hydroxyphenyl)-hexane (IV).**—The crude phenolic material from the partial hydrogenation of *meso*-hexestrol (25 g.) was oxidized with 20 g. of aluminum *t*-butoxide and 185 cc. of acetone in 375 cc. of benzene. After refluxing for eight hours, the mixture was decomposed with 40 cc. of water and 100 cc. of 10% aqueous sulfuric acid, shaken and separated after addition of another 300-cc. portion of water. The benzene extract yielded 25 g. of glassy material. Separation of the crude product by means of Girard reagent[12] gave 3.74 g. of ketonic compounds. This mixture was further purified by adsorption on alumina from benzene solution. The benzene eluate (0.80 g.) was non-phenolic. The desired ketone was obtained from the acetone eluate, yield 1.60 g.

***dl-m*-3-(4-Hydroxycyclohexyl)-4-(*p*-hydroxyphenyl)-hexane (III).**—The above ketone (0.66 g.) dissolved in 50 cc. of methanol was reduced with 3 g. of Raney nickel at room temperature. Slightly more than the theoretical amount of hydrogen was taken up in four hours. The crude product (0.6 g.) was purified by adsorbing on aluminum oxide from benzene solution. The main product, a clear glass, (0.45 g.) was obtained from the acetone eluate.

Monobenzoate.—The alcohol (III) (0.45 g.) dissolved in 50 cc. of 5% aqueous sodium hydroxide was benzoylated with 0.4 cc. of benzoyl chloride. The crude product (0.6 g.) was adsorbed on alumina from benzene solution. The main product was obtained in the benzene eluate, yield 0.16 g.

The glassy alcohol (III) was regenerated from the benzoate by hydrolyzing with 0.1 *N* sodium ethoxide solution.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.20; H, 10.21. Found: C, 78.28; H, 10.32.

Absorption Spectra

The infrared absorption spectrum of the alcohol (I) has been found to differ from that of the previous octahydrostilbestrol compounds.[6,13]

Ultraviolet absorption spectra of the octahydro compounds (I) and (III), the specimen of Dr. Wilds and the compound prepared by Hoehn[11] have been determined and show a characteristic band at 280 mμ which can be used as a test for purity. The average molecular extinction of the octahydro compounds at this wave length is approximately half as large as the extinction of the dihydro compound (Figs. 1 and 3). The absorption curves of the two described benzoates nearly coincide (Fig. 2). The ultraviolet absorption spectra were determined in 95% alcohol at concentrations of around 0.00018 mole per liter with a Beckmann spectrophotometer. Readings were taken at 5 mμ intervals.[14]

Summary

A single pure isomer of *meso*-octahydrostilbestrol has been isolated from the products of the partial hydrogenation of *meso*-hexestrol. The catalytic reduction of the corresponding ketone yields a glassy substance which probably represents a mixture of *cis* and *trans* isomers. The compounds have been characterized by derivatives and absorption spectra.

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[11] Hoehn and Ungnade. THIS JOURNAL, **67**, 1617 (1945).

[12] Girard and Sandulesco, *Helv. Chim. Acta*, **19**, 1095 (1936).

[13] Infrared absorption spectrum by Agatha Johnson and Foil Miller, University of Illinois.

[14] Ultraviolet absorption spectra by Dr. E. E. Pickett and P. W. Tucker, University of Missouri.

COLUMBIA, MISSOURI RECEIVED JULY 10, 1948

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Derived Steroids. II. Structure of Products Derived from 3-Magnesio Halides[1]

BY ROBERT H. BAKER AND EDWARD N. SQUIRE[2]

Prior to our work, 3-cholesteryl Grignard reagents had been subjected only to carbonation and oxidation. Marker[3] referred to the acid so obtained as "*d,l,*" and showed the oxidation product to be a mixture of α and β-forms of cholesterol. Since we have used the Grignard reagent extensively to make compounds of biological interest[4] in the cholestene[1] and 17-oxygenated androstene[5] series, it was of importance to investigate the stereochemical pattern of its reactions.

The ionic nature of the carbon–magnesium bond and the allylic nature of 3-cholesteryl derivatives offers the possibility of a particular derivative being either 3-α or β or 6-*i* or mixtures of these. Neither 5-cholestene-3-carboxylic acid nor any of its derivatives gives evidence of being a mixture. Extensive fractional crystallization and/or chromatography of the acid, the methyl ester or the series of amides reported herein demonstrate a striking homogeneity of each compound. Furthermore, only one compound, the anilide, has a positive rotation, 0.5°. Saturation of the double bond increased the positive rotation of both the anilide and the dipropylamide. Since a number of these compounds react with one equivalent of perbenzoic acid, the *i*-steroid structure is untenable.

The reaction of the cholesteryl Grignard with cholesteryl chloride is even more complex since both reagents are allyl-like and either 3-3′, 3-6′, or, less likely, 6-6′ linkages might be encountered. Although the product, bicholesteryl, has a specific rotation +30°, neither half of the molecule seems to have the *i*-steroid structure since it

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[1] For the first paper see Baker and Squire, THIS JOURNAL, **70**, 1487 (1948).

[2] Junior Fellow of the National Institute of Health.

[3] Marker, Oakwood and Crooks, THIS JOURNAL, **58**, 481 (1936).

[4] Squire and Squire, *J. Bact.*, **55**, 766 (1948).

[5] Baker and Squire, forthcoming publication.