washed with anhydrous ether, and dried *in vacuo*. The material obtained melted at 82–84° with decomposition. Several other sulfonium compounds were found to decompose at the same point. The compound was very unstable and could not be recrystallized; hence, analyses were unsatisfactory. The compound burned without leaving a residue, and therefore did not contain aluminum.

Anal. Calcd. for $C_{20}H_{19}SBr$: C, 64.69; H, 5.18. Found: C, 63.80; H, 5.50.

Isolation of Thiophenol.—Ten grams of the sulfide was allowed to react at room temperature for forty-one hours with a solution of 15.33 g. of aluminum bromide in benzene (80 cc.). The ether extracts of the hydrolyzed reaction mixture were diluted to 100 cc. with ether. One cc. of the resulting solution was titrated for mercaptan, and indicated 91% cleavage of the sulfide had occurred. The remaining ether extracts were dried and distilled *in vacuo*. A total of 4.1 cc. of thiophenol (b. p. 89–95° (51 mm.)) was obtained, corresponding to 80.3% cleavage of the benzyl phenyl sulfide.

Isolation of Diphenyl Disulfide.—The washed ether extracts of the reaction mixture were extracted with 10% aqueous sodium hydroxide solution. The alkaline extracts were acidified and extracted with ether. Alcoholic iodine was added to the ether solution until the iodine was no longer decolorized. Evaporation of the ether and recrystallization of the residue from alcohol gave white crystals, m. p. 59–60°, which did not depress the melting point of a known sample of diphenyl disulfide.

Summary

1. Under optimum conditions, benzyl phenyl sulfide (BPS) can be cleaved to thiophenol to the extent of about 30% by hydrogen bromide–glacial acetic acid. Aqueous halogen acids are virtually ineffective in this reaction.

2. Aluminum bromide in benzene or chlorobenzene cleaves BPS rapidly and smoothly; the reaction requires one mole of bromide per mole BPS. It is retarded by water or oxygen-containing solvents.

3. The rate is first order in BPS, and practically independent of the aluminum bromide concentration if this is in excess. The reaction is not affected by molecular oxygen.

The mechanism is believed to involve a rapid coördination of aluminum bromide with BPS, followed by a slow cleavage of the complex.

ROCHESTER, N. Y. RECEIVED JUNE 1, 1948

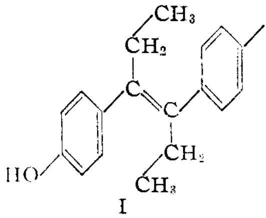
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Hexahydro Derivatives of *meso*-Hexestrol[1]

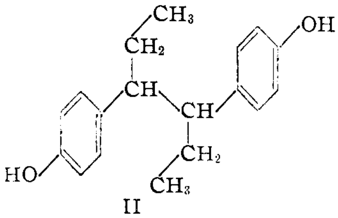
BY A. L. WILDS AND WILLIAM B. MCCORMACK[2]

In attempts to rationalize the high activity of the synthetic estrogens diethylstilbestrol (I) and hexestrol (II), the superficial resemblance of these compounds (as written in the accompanying formulas) to the natural hormone estradiol (III) has frequently been pointed out. While several objections can be raised to this hypothesis, nevertheless, in harmony with it, the more active of the two possible stereoisomers in each case (*trans* I and *meso* II) is that which corresponds more closely to the probable configuration of estradiol. For some time we have been interested in preparing for estrogenic testing the hexahydro derivatives of *meso*-hexestrol (IV) in which one ring is reduced, since these resemble the phenolic alcohol estradiol (III) even more closely than does the diphenol hexestrol (II).

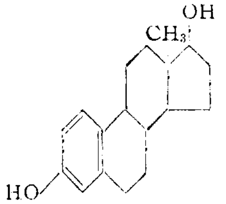
Preliminary attempts in 1940–1941[3] to hydrogenate one ring of *meso*-hexestrol or its monobenzoate did not appear promising, leading to mixtures containing fully hydrogenated as well as unchanged material. A second approach (by A. L. W.) through a synthesis involving the Friedel–Crafts condensation with anisole of α-(4-acetoxycyclohexyl)-butyric acid,[4] obtained by hydrogenation of the readily available ethyl α-(4-hydroxyphenyl)-butyrate,[5,6] was carried as far as the crystalline carbinol (V) when the work had to be discontinued in 1942.



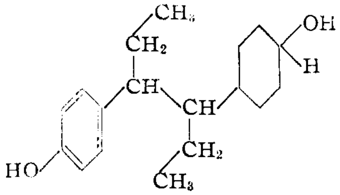
I



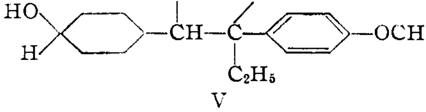
II



III



IV



V

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[1] For a preliminary communication see Wilds and McCormack, THIS JOURNAL, **70**, 884 (1948).

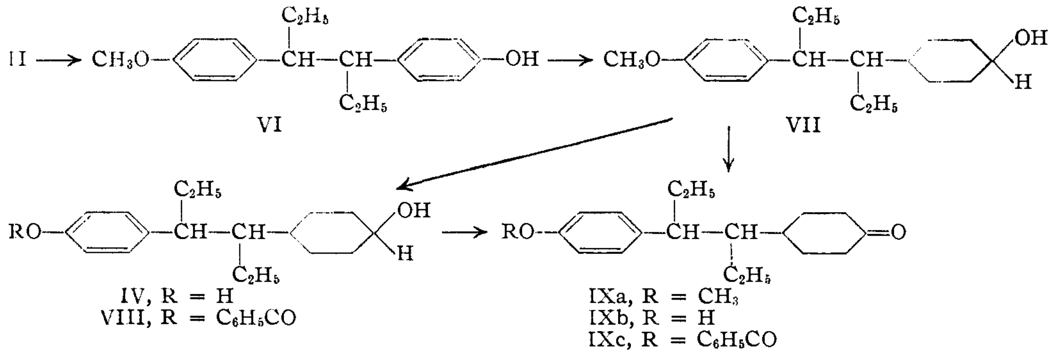
[2] Wisconsin Alumni Research Foundation Research Assistant, 1945–46; American Chemical Society Predoctoral Fellow, 1946–1948.

[3] Carried out by Adrian M. Docken and A. L. Wilds.

[4] Compare Ruggli and Businger, *Helv. Chim. Acta*, **24**, 346, 1112 (1941).

[5] Wilds and Biggerstaff, THIS JOURNAL, **67**, 789 (1945).

[6] Recently the reduction of this compound was carried out independently by Ungnade and Morriss [THIS JOURNAL, **70**, 1898 (1948)].



VI

VII

IV, R = H
VIII, R = C_6H_5CO

IXa, R = CH_3
IXb, R = H
IXc, R = C_6H_5CO

It seemed attractive to investigate the half-reduction of hexestrol monomethyl ether (VI), which is easily prepared in 72% yield from hexestrol, since Musser and Adkins[7] have found that copper–chromium oxide will catalyze the hydrogenation of a phenolic ring but not that of an aromatic ether.[8] When the monomethyl ether VI was treated with hydrogen at 6000–6500 p. s. i. at 240° in the presence of this catalyst, the amount of hydrogen absorbed corresponded to reduction of only one ring. By oxidation of the crude reduction product the methoxy ketone IXa could be isolated as the semicarbazone in yields as high as 52%.

Demethylation of this ketone presented difficulties, principally because of its susceptibility to self-condensation in the presence of the usual strongly acidic reagents. Early attempts to effect demethylation with pyridine hydrochloride[9] appeared encouraging, but the phenolic ketone could not be obtained crystalline by this method even after conversion to the benzoate.

A suitable procedure was found for demethylating the methoxy alcohols (VII) by heating with methylmagnesium iodide at 180–190°.[10] The mixture resulting from such a demethylation of the crude hydrogenation product (VII) could be separated by extraction first with 5% potassium hydroxide and then with Claisen's alkali. The latter fraction afforded a mixture of the two isomeric phenolic alcohols (IV) from which was obtained by crystallization isomer A, m. p. 183–184°, and after purification through the monobenzoate (m. p. 130.5–131.5°), isomer B, m. p. 134–135°. Additional amounts of the latter were also isolated from the aqueous alkaline extract; the total yield of the phenolic alcohols was in the neighborhood of 50–60%, of which the major product was isomer B. The melting point behavior of the latter showed variations which were indicative of several polymorphic forms.

In a private communication Drs. Ungnade and Tucker informed us that they have succeeded in isolating from the partial hydrogenation products of *meso*-hexestrol one of the crystalline hexahydro derivatives, m. p. 127–128°, giving a monobenzoate, m. p. 123.5–125°.[11,12] A direct comparison has shown this to be the same as our isomer B, but slightly less pure.

Ungnade and Tucker[13] found that hydrogenation of their phenolic alcohol with Raney nickel at 210° gave the 169° perhydro derivative of *meso*-hexestrol in 63% yield. Since this had previously been assigned the *trans-trans* configuration[14] on the basis of the rules of von Auwers and Skita and of Vavon, it was concluded that isomer B had the *trans* configuration in the hydrogenated ring. A repetition of this perhydrogenation, however, has shown that this evidence is not valid, since we found that *both* isomers A and B gave the 169° (presumably *trans–trans*)[14,15] diol as the major product and some of the 124° (presumably *cis–trans*)[14] diol; the relative amounts were similar from both isomers A and B. Thus, a not too unexpected equilibrium is established between the isomers during hydrogenation, perhaps through the ketone. It was found that hydrogenation of the keto ether IXa under neutral conditions followed by demethylation gave predominately isomer B, while under acidic conditions mainly isomer A resulted; this suggests that isomer A may have the *cis* and isomer B the *trans* configuration.[16]

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[7] Musser and Adkins, This Journal, **60**, 664 (1938).

[8] We are indebted to Dr. Homer Adkins for directing our attention to this selectivity.

[9] Prey, *Ber.*, **74**, 1219 (1941); **75**, 350, 445 (1942).

[10] Model experiments with 4-cyclohexylcyclohexanol gave 95% recovery of the alcohol under these conditions; the pyridine hydrochloride method, however, was unsuitable, probably because of dehydration of the alcohol. The interesting observation was made that phenolic ethers are more readily cleaved by the latter reagent than are phenolic benzoates. Thus, after heating hexestrol dibenzoate with pyridine hydrochloride at 210° for five hours, 68% of the dibenzoate was recovered unchanged, while in forty minutes hexestrol monomethyl ether was quantitatively cleaved to hexestrol. From hexestrol monomethyl ether benzoate after one hour at 210° was obtained mainly hexestrol monobenzoate.

[11] Ungnade and Tucker, This Journal, **70**, 4132 (1948); see also Abstracts of 113th Meeting, American Chemical Society, Chicago, Ill., April 19–23, 1948, page 16L.

[12] See also Ungnade and Ludutsky, This Journal, **69**, 2629 (1947), for the hexahydro derivatives of racemic hexestrol.

[13] Private communication.

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

[15] In our opinion these assignments of configuration are also open to question, particularly in view of the insolubility and ease of isolation of the 169° isomer, for example from equilibrated mixtures.

[16] The possibility that some change in configuration at the bridge carbon atoms (from the *meso* to racemic series) might have occurred with either isomer A or B, under the drastic conditions necessary for hydrogenating the mono ether VI, is excluded since each gave the same perhydro derivatives which result from *meso*-hexestrol. In addition both isomers were obtained from the pure keto ether IXa, and each has been reconverted by methylation and oxidation to this same ketone.

Oxidation of the monobenzoate of the alcohol phenols (VIII) gave the crystalline benzoate (IXc) of the phenolic ketone. Although the latter was very susceptible toward self-condensation, it was possible to cleave the ester by mild alkaline hydrolysis to the crystalline phenolic ketone (IXb), m. p. 104–105°.

Physiological tests are being carried out with the phenolic alcohols IV under the direction of Drs. R. K. Meyer and Elva G. Shipley of the Department of Zoology. Preliminary assays in ovariectomized rats indicate isomer B, m. p. 134–135°, to be active in about 10 γ doses, compared to around 1 γ for *meso*-hexestrol. Isomer A, m. p. 183–184°, was inactive in 200 γ doses but seems to be active at 500 γ levels. Thus, it is clear that both isomers are considerably less active than *meso*-hexestrol.[17] Further physiological tests are underway with IV and the ketone IXb.

On the basis of their relative physiological activities, it would appear that isomer B may correspond in configuration to the natural estradiol and isomer A to its less active stereoisomer. If the current views on the stereochemical configuration of natural estradiol are accepted (namely that the 17-hydroxyl is *cis*[17a] and the C-14 hydrogen *trans* to the C-13 methyl group) then isomer B may correspond to the *cis* configuration. Further evidence is needed before the configurations can be assigned.

Experimental[18]

***meso*-Hexestrol Monomethyl Ether (VI).**—This compound was prepared, with some modification, by the method of Bretschneider.[19] To a solution of 200 g. of *meso*-hexestrol[20] in 1700 cc. of methanol and 890 cc. of 1 *N* aqueous sodium hydroxide was added 69 cc. of dimethyl sulfate below 10° over a ten-minute period with stirring. After eighty minutes an additional 245 cc. of 1 *N* sodium hydroxide and 23 cc. of dimethyl sulfate was added and stirring was continued for two hours at 10°. The product was isolated by acidifying and extracting with ether. Washing with 5% potassium hydroxide removed 39.4 g. (20%) of unreacted hexestrol, m. p. 181–184.5°. By treatment of the ether solution with 800 cc. of 10% sodium hydroxide saturated with salt, the monoether salt was precipitated; the ether layer was decanted through a filter, and the aqueous suspension washed with several portions of ether. Acidification of the salt suspension gave after filtering and drying 152.5 g. (72%) of the monomethyl ether, m. p. 118.5–120°. Distillation of 146 g. of the monoether at 200–210° (0.7 mm.) from a two-bulb flask gave 137 g., m. p. 119–120° (reported,[19] m. p. 120–121°).

The **monomethyl ether benzoate** of *meso*-**hexestrol** was prepared by the Schotten–Baumann procedure, using 1 g. of the monoether, 60 cc. of 5% potassium hydroxide, 20 cc. of dioxane and 2.1 cc. of benzoyl chloride. The product (1.36 g. or 100%), m. p. 141–144° (soft at 137°) was recrystallized from alcohol–benzene (4:1) as small white needles, m. p. 145–146°.

Anal. Calcd. for $C_{26}H_{28}O_3$: C, 80.4; H, 7.3. Found: C, 80.6; H, 7.3.

dl-*m*-**3-(*p*-Methoxyphenyl)-4-(4′-ketocyclohexyl)**-hexane (**IXa**).[21]—Before hydrogenation a methanolic solution of the monomethyl ether of hexestrol was refluxed overnight with Raney nickel, the solvent removed and the product dried at 90°. A mixture of 17.1 g. of the monoether, 80 cc. of purified dioxane[22] and 8 g. of copper–chromium oxide catalyst[23] in a 270-cc. bomb filled with hydrogen to 4000–4200 p.s.i. was heated at 240° (reaching a pressure of 6000–7000 p.s.i.) until the hydrogenation was complete; the time required varied from one and one-half to six hours depending somewhat upon the pressure.[24] After cooling, the drop in pressure corresponded to 100–140% of the theoretical for reduction of one ring. The catalyst was removed by filtration, washed with alcohol and the solution was concentrated to a viscous oil, finally under reduced pressure. The oil was oxidized by dissolving in 200 cc. of glacial acetic acid and treating with a solution of 8 g. of chromium trioxide in 3 cc. of water and 45 cc. of acetic acid at 15–20°. After standing thirty minutes, 10 cc. of methanol was added and after another fifteen minutes the bulk of the solvent was removed under reduced pressure. The pasty residue was treated with warm water and taken up in dilute hydrochloric acid and ether. The ether layer was washed with acid, sodium carbonate solution (1.15 g. of crude acidic material obtained) and water. The ether solution was concentrated and the residue heated for twenty minutes with 6.75 g. of semicarbazide hydrochloride, 65 cc. of alcohol and 7 cc. of pyridine. The solution was concentrated to about 40 cc., cooled, diluted with water and the mixture was filtered. The gummy solid was digested with cold alcohol, giving 10.5 g. (51%) of the semicarbazone, m. p. 204–206° dec. The non-ketonic fraction, after washing to remove semicarbazide hydrochloride, amounted to 5.95 g. of oil; no additional crystalline semicarbazone could be obtained after reoxidation. On other runs the yield varied from 40–52%, averaging 46%.

For analysis a sample of the **semicarbazone of IXa** was boiled with water and then recrystallized from a large volume of hot alcohol, giving small colorless platelets, m. p. 208–209° dec.

Anal. Calcd. for $C_{20}H_{31}O_2N_3$: C, 69.5; H, 9.1. Found: C, 69.5; H, 9.0.

For small runs the semicarbazone (1 g.) was hydrolyzed by heating at reflux with a solution of oxalic acid (2 g. in 20 cc. of water) for five hours. The mixture was extracted with ether, washed with sodium carbonate solution, evaporated and the residue crystallized by dissolving in petroleum ether (40–60°) and evaporating to give 0.81 g. (97%) of a powder, m. p. 58–61°. Larger runs gave poorer results even though alcohol was used as a solvent. Thus, when 11.1 g. of semicarbazone was heated for six hours with 200 cc. of 75% alcohol containing 22 g. of oxalic acid, 0.31 g. (m. p. 199–204°) of semicarbazone was recovered. The ketone (after ether extraction) was distilled giving 5.43 g. (59% yield), b. p. 182–190° (1 mm.), after a forerun of ethyl oxalate. Upon cooling, the distillate solidified (m. p. 51–60°) and was recrystallized from petroleum ether (40–60°) giving 3.90 g. of ketone, m. p. 56–60°.

In one run the crude ketone from the oxidation was distilled directly, giving a total of 53% of material in the fraction b. p. 140–160° (0.4 mm.), m. p. 48–52° to 53–56°. By repeated recrystallization from petroleum ether (40–60°) the melting point of the keto ether IXa was raised to 62–63.5°.

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(17) A fairer test might be to compare the optically active antipodes of isomer B with *meso*-hexestrol; we hope to effect this resolution in the future and also to prepare the ketone similar to IXb except with a five-membered alicylic ring.

(17a) This conclusion that the 17-hydroxyl has the β-orientation for the natural hormone, rather than α as previously believed, is based upon a reinterpretation of the evidence available; see Fieser and Fieser, *Experientia*, in press.

(18) All m. ps. are corrected.

(19) Bretschneider, Bretschneider and Ajtai, *Ber.*, **74**, 583 (1941)

(20) Wilds and McCormack, *J. Org. Chem.*, in press.

(21) Following the notation of Ungnade and Ludutsky,[14] *m* is used to indicate this compound is derived from *meso*-hexestrol.

(22) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1941, 2nd ed., p. 369.

(23) Lazier and Arnold, "Organic Syntheses," Coll. Vol. II, 142 (1943).

(24) A starting pressure (cold) of 2900 p. s. i. gave poor results (10% yield of semicarbazone).

Anal. Calcd. for $C_{19}H_{28}O_2$: C, 79.1; H, 9.8. Found: C, 78.7; H, 9.6.

Demethylation Experiments. (a) Hexestrol Monomethyl Ether and Pyridine Hydrochloride.—To define the mildest conditions for effecting demethylation with this reagent, a series of runs was carried out at various temperatures, resulting in the following procedure. A mixture of 0.5 g. of the monomethyl ether and 1.5 g. of pyridine hydrochloride was heated (air condenser) at 210° for forty minutes. After cooling, the mixture was poured into 100 cc. of water, using a little alcohol to rinse the flask. The resulting solid was washed and dried, giving 0.50 g. of hexestrol, m. p. 180–184°. When the temperature was 175° and the time of heating three and one-half hours, demethylation was incomplete.

(b) Hexestrol Monomethyl Ether and Methylmagnesium Iodide.—To the Grignard reagent from 51 mg. of magnesium and 0.16 cc. of methyl iodide in 3 cc. of ether was added 200 mg. of the monomethyl ether and the mixture was heated in an oil-bath at 170–180° for one and one-half hours. The cooled reaction mixture was treated with dilute acid and ether, and the latter was extracted thoroughly with 5% potassium hydroxide, giving upon acidification 166 mg. (87%) of hexestrol, m. p. 179.5–181.5°.

(c) Attempts to Demethylate the Keto Ether (IXa).—A mixture of 0.5 g. of the keto ether (IXa) and 10 g. of pyridine hydrochloride was heated at 200–215° for eighty minutes, then poured into water, giving 0.42 g. of an amorphous, powdery solid, m. p. about 65–100°. Analyses for methoxyl indicated at least 80–90% demethylation. Evaporative distillation of 0.40 g. of the solid at 200–260° (0.05 mm.) gave 0.25 g. of an oil which could not be crystallized as such or after conversion to the benzoate or 3,5-dinitrobenzoate. Other runs under varied conditions also failed to give the crystalline keto phenol.

***cis* and *trans* *dl-m*-3-(*p*-Hydroxyphenyl)-4-(4′-hydroxycyclohexyl)-hexane (Hexahydrohexestrol IV). (a) Directly from Hexestrol Monomethyl Ether.**—Ten grams of *meso* hexestrol monomethyl ether was reduced as described above. To the crude hydrogenation product after evaporation of the solvent was added the Grignard reagent prepared from 2.56 g. of magnesium and 6.5 cc. of methyl iodide in 50 cc. of dry ether. The solution was heated in an oil-bath to 115° allowing the ether to escape, then attached to a gas buret and heated at 185–195° for two and one-half hours (total evolution of gas was 750 cc. or 85%). Upon cooling, the vitreous solid was decomposed with ice and dilute hydrochloric acid and extracted with ether. The ether was washed with four portions of 5% potassium hydroxide; acidification and extraction gave 4.33 g. of a dark-colored glass (this is considered separately below).[25] Further extraction with eight to ten portions of Claisen alkali,[26] followed by acidification and extraction with ether gave 3.82 g. of a colorless semi-solid mass. The neutral material remaining in the original ether solution amounted to 1.30 g. of dark brown glass.

Digestion of the material from the Claisen's alkaline extracts with hot benzene gave 0.57 g. (6%) of isomer A as a white powder,[27] m. p. 182–183° with softening at 179°. Concentration of the benzene solution gave an additional 2.25 g. (23%) of colorless solid, m. p. 124–144° (cloudy liquid, clear at 150°), which was crude isomer B, bringing the total yield of the alcohol–phenol isomers to 29% from this fraction. In other runs this varied from 15 to 42% (with additional material in the 5% potassium hydroxide-soluble fraction considered below).

Further crystallization of **isomer A** from benzene and then several times from 50% alcohol–water gave small transparent platelets, m. p. 183–184°.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.2; H, 10.2. Found: C, 78.2; H, 9.9.

The crude isomer B was best purified by conversion to the monobenzoate. A solution of 1.7 g. of material, m. p. 129.5–133°, in 100 cc. of 5% potassium hydroxide and 34 cc. of dioxane was shaken with 3.6 cc. of benzoyl chloride for five minutes. The gummy solid which resulted was extracted with ether, washing with sodium carbonate solution and water. Removal of the ether and drying at 90° under reduced pressure gave 2.43 g. of solid, m. p. 107–119°, which upon recrystallization from 125 cc. of benzene–petroleum ether (1:4) yielded 1.21 g. of solid, m. p. 127–129°, and 1.13 g. of gummy residue in the filtrate. (Saponification and recrystallization of this residue yielded some of isomer A.) Further recrystallization of the monobenzoate of isomer B raised the m. p. to 129.5–130.5°.

Saponification of 0.83 g. of the monobenzoate with 25 cc. of 5% alcoholic potassium hydroxide at room temperature overnight gave 0.64 g. of the crude alcohol–phenol which upon recrystallization from benzene and drying at 90° to remove benzene of crystallization afforded 0.56 g. of **isomer B** as short, colorless needles, m. p. 134–135°, and an additional 0.02 g., m. p. 131–134°. The ultraviolet absorption spectrum in 95% alcohol showed maxima at 224.5 mμ (log $E = 3.95$) and 279 mμ (3.24), a minimum at 245 mμ (2.12) and an inflection at 284 mμ (3.16).

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.2; H, 10.2. Found: C, 78.2; H, 10.0.

(b) From the Keto-ether (IXa).—A solution of 0.5 g. of the distilled keto-ether in 5 cc. of absolute alcohol was hydrogenated at atmospheric pressure first in the presence of 0.4 g. of 5% palladium-on-carbon catalyst[28] and then 100 mg. of Adams platinum oxide; the total hydrogen uptake was 88% for one mole. From petroleum ether a small amount (0.01 g.) of crude solid was obtained, m. p. 101–125°, but the major portion was an oil (0.39 g.). This was demethylated by heating at 170–180° for two hours with the Grignard reagent from 0.15 g. of magnesium and 0.40 cc. of methyl iodide, then hydrolyzed and extracted with ether. Washing the ether with four portions of 5% potassium hydroxide extracted a negligible amount of material; by extraction with Claisen alkali a total of 0.325 g. of viscous oil was obtained which gave upon recrystallization from benzene 0.27 g. of solid, mainly isomer B, m. p. 122–124°. Purification as the monobenzoate gave 0.12 g. (18% yield from the keto-ether) of the derivative of isomer B, m. p. and mixed m. p. 129–129.5°. The remaining material was a mixture.

Hydrogenation of 0.5 g. of the keto-ether with a total of 0.2 g. of platinum oxide in 14 cc. of glacial acetic acid containing 1 cc. of concentrated hydrochloric acid gave absorption of 115% for one mole. A portion of the product crystallized from petroleum ether (0.07 g., m. p. 129–136°) with the remainder (0.39 g.) an oil. Demethylation as before gave 0.29 g. of viscous oil from the Claisen alkali extraction. By crystallization from benzene this afforded 0.12 g. of crude isomer A, m. p. 175–179° (soft. 172°), 0.08 g., m. p. 171–177° and 0.01 g., m. p. 150–160°. Further recrystallization gave material melting at 182.5–184° which showed no m. p. depression when mixed with isomer A from (*a*).

(c) Polymorphism of Isomer B. Comparison With the Material of Ungnade and Tucker.—Considerable variation in melting point, suggestive of several polymorphic forms, was observed for isomer B. One sample melted at 144–146°, while another, regenerated from monobenzoate of m. p. 128–129°, melted at 136° when first obtained and at

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[25] It appeared initially that 5% potassium hydroxide would not extract appreciable amounts of the hexahydrohexestrols. This is true for the product from the reduction and demethylation of the pure methoxy ketone (see b) and also for the pure isomers A and B. Partition experiments with the latter showed that about 10% of isomer A and 20% of isomer B were extracted by the alkali when 25 mg. of the pure alcohol phenol in 15 cc. of ether was extracted with four 5-cc. portions of 5% potassium hydroxide. With the material obtained here by demethylation of the crude hydrogenation mixture, however, significant amounts, particularly of isomer B, were extracted by the aqueous alkali.

[26] Equal portions of 40% aqueous potassium hydroxide and methanol.

[27] In some runs all of the product was soluble in benzene and isomer A was best separated by repeated crystallization of the mixture from 50% alcohol-water.

[28] Mozingo, "Organic Syntheses," **26**, 78 (1946), procedure C.

143–147° a day later. In another case, material of m. p. 132.5–134.5° upon drying at 80° (0.01 mm.) changed to m. p. 132.5–142°. Vacuum sublimation in one case gave material melting at 128–129.5° and in another at 133–134°. Polymorphism also was indicated by the following: insertion of a sample at 25° gave m. p. 132.5–133.5°; insertion at 129° gave complete melting; after cooling the sample remelted at 127–128°, and in another case at 130–134.5°. On the microscope hot stage, insertion at 50° gave m. p. 132.5–134.0° with no previous change visible; when inserted at 130° the sample melted completely, resolidified and remelted at 134.5–137°. With the purest samples this transition temperature was as high as 131–132°. Thus, there is evidence for at least two and probably three polymorphic forms for isomer B.

A sample of the octahydrodiethylstilbestrol (*meso* series) of Ungnade and Tucker[11,29] was compared with our isomer B. In our apparatus this sample was found to melt at 130–132° with sintering at 128°, when inserted at 115° (reported[11] m. p. 127–128°). A mixture with our isomer B melted at 130–133°. On the hot stage their sample (inserted at 100°) melted at 131–132°; inserted at 128° it melted completely, resolidified and remelted at 132–133.5°. A mixture with isomer B melted at 126–130° and remelted at 133.5–135°.

(**d**) **Benzoyl Derivatives of Isomers A and B.**—Schotten–Baumann benzoylation as described above for isomer B gave the **monobenzoate of isomer A** as a colorless powder from petroleum ether, m. p. 68.5–70°. From one of the recrystallizations a second form melting at 103.5–105° was obtained. Further recrystallization gave the lower form.

Anal. Calcd. for $C_{25}H_{32}O_3$: C, 78.9; H, 8.5. Found: C, 79.0; H, 8.6.

The purest sample of the **monobenzoate of isomer B** obtained by direct recrystallization from petroleum ether-benzene melted at 130–131°. After chromatography on alumina followed by fractional elution with benzene and benzene–ether (9:1) and recrystallization, the m. p. was 130.5–131.5°.

The ultraviolet absorption spectrum in 95% alcohol showed a maximum at 232 mμ (log E = 4.28) and an inflection around 264 mμ (3.65).

Anal. Calcd. for $C_{25}H_{32}O_3$: C, 78.9; H, 8.5. Found: C, 79.0; H, 8.3.

A sample of the monobenzoate of Ungnade and Tucker,[29] for which we found the m. p. 120–126° (reported[11] 122–123°) gave the mixed m. p. 121.5–128.5° with our pure sample. It is, therefore, the same compound but slightly impure.

Isomers A and B were converted to the dibenzoates by treating with excess benzoyl chloride in pyridine solution at 25° for five hours and 90° overnight. The **dibenzoate of isomer A** crystallized from methanol as a colorless powder, m. p. 134.5–135.5°. On one occasion a lower melting form was obtained, m. p. 121.5–123°; seeding the melt with the higher form caused resolidification with remelting at 133.5–136°.

Anal. Calcd. for $C_{32}H_{36}O_4$: C, 79.3; H, 7.5. Found: C, 79.2; H, 7.4.

The **dibenzoate of isomer B** was recrystallized from ethanol, m. p. 142–143°.

Anal. Calcd. for $C_{32}H_{36}O_4$: C, 79.3; H, 7.5. Found: C, 79.2; H, 7.4.

Hydrogenation of Isomer A.—A solution of 200 mg. of isomer A (m. p. 181.5–183.5°) in 15 ml. of absolute alcohol was hydrogenated in the presence of 3 g. of Raney nickel[30] at 210° and a hydrogen pressure (hot) of 5100 p.s.i. for three hours. The product was isolated by concentrating the alcoholic solution and adding ether, giving 112 mg. of solid, m. p. 157–166°. An additional 66 mg. of solid, m. p. 115–119°, was obtained from benzene–petroleum ether. Recrystallization of the first crop from alcohol and then ethyl acetate gave 59 mg., m. p. 168.5–170°, and an additional 26 mg., m. p. 165–168°. A mixed m. p. of the first crop with an authentic sample of perhydro-*meso*-hexestrol of m. p. 169–170° (*trans–trans?*)[14,15] showed no depression (m. p. 169–170°). Recrystallization of the original second crop from benzene gave 48 mg., m. p. 121.5–123°, giving no depression with the perhydro diol of m. p. 123–124° (*cis–trans?*).[14,15]

Hydrogenation of Isomer B.—Hydrogenation of 200 mg. of isomer B (m. p. 134–135°) under similar conditions gave 102 mg., m. p. 153–163°, from alcohol–ether and 70 mg., m. p. 107–117°, from benzene–petroleum ether. Recrystallization of the higher melting fraction as above gave 55 mg., m. p. 167–169° undepressed by an authentic sample of the 169° perhydro diol and 17 mg., m. p. 163–167°. From the lower melting crop was obtained 56 mg., m. p. 118–120°; further recrystallization gave the m. p. 120–121.5°, undepressed when the solid was mixed with an authentic sample of the 124° perhydro diol.

Investigation of the 5% Potassium Hydroxide-Soluble Fractions.—The total amount of material soluble in 5% potassium hydroxide obtained from the hydrogenation and demethylation of hexestrol monomethyl ether (see above) amounted to 31, 43, 43 and 36% of the total material reduced in four different runs. Part of this material could be crystallized from benzene giving solids melting from 72–95° to as high as 148–153°, and amounting to 24, 42, 32 and 19%, respectively, of the total material hydrogenated. Conversion of 10 g. of these solids to the monobenzoate gave 13.1 g. of crude benzoate, m. p. 115–121° (to a cloudy liquid, not clear at 130°). By digestion with hot alcohol and filtering, 0.79 g. (5%) of crude hexestrol dibenzoate was obtained, m. p. 224–230°;[31] further recrystallization gave material melting at 228–230°, which was not depressed in m. p. when mixed with authentic hexestrol dibenzoate. From the main alcohol filtrate after concentrating and adding benzene–petroleum ether (1:3) was obtained 6.1 g. of the **monobenzoate of isomer B**, m. p. 129–130° (mixed m. p. undepressed), 1.7 g., m. p. 128–129° and 0.7 g., m. p. 126–128°, totalling 62%.

From another run the alkali-soluble material was recrystallized from benzene giving in the third crop material melting at 169–176° and after another recrystallization, m. p. 178–182°. This material (0.41 g.) was converted to the dibenzoate and crystallized from ether giving a total of 0.46 g. of solid, m. p. 122.5–123.5°, which proved to be the lower polymorphic form of **isomer A dibenzoate**. Another recrystallization gave the higher form, m. p. 134.5–135.5° (mixed m. p. 135–136°).

Benzoate of *dl-m*-**3-(**p**-Hydroxyphenyl)-4-(4′-ketocyclohexyl)-hexane (IXc).**—A mixture of the monobenzoate (VIII) of isomers A and B (0.64 g.) was oxidized in 20 cc. of glacial acetic acid with 0.25 g. of chromium trioxide in 0.2 cc. of water and 3 cc. of acetic acid, allowing to stand at 15–20° for thirty minutes, then adding 5 cc. of methanol. After removing the solvent under reduced pressure, the mixture was extracted with ether and dilute acid, and washed with sodium carbonate and water. Evaporation of the ether gave 0.52 g. (82%) of solid benzoate IXc, m. p. 105–111°; recrystallization from benzene–petroleum ether and cooling to −10°, gave 0.44 g., m. p. 107.5–111°. Further recrystallization from methanol gave the benzoate of the phenolic ketone melting at 112.5–113.5°.

The ultraviolet absorption spectrum (95% alcohol) showed a maximum at 231 mμ (log E = 4.28) and an inflection around 264 mμ (3.63).

Anal. Calcd. for $C_{25}H_{30}O_3$: C, 79.3; H, 8.0. Found: C, 79.1; H, 8.1.

dl-m-**3-(**p**-Hydroxyphenyl)-4-(4′-ketocyclohexyl)-hexane (IXb).**—To 300 mg. of the benzoate IXc was added 15 cc. of a 5% solution of potassium hydroxide in methanol and the mixture was allowed to stand at room temperature. After six minutes, all of the solid had dissolved and after ten minutes water was added and the clear solution was acidified with hydrochloric acid, then made basic with sodium carbonate. The mixture was extracted with ether,

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[29] We wish to thank Dr. Ungnade for sending this sample.

[30] Mozingo, "Organic Syntheses," **21**, 15 (1941).

[31] Under similar Schotten-Baumann conditions, pure hexestrol gave 54-64% yields of hexestrol dibenzoate.

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.

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[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]

[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).