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

HYDRODIETHYLSTILBESTROL COMPOUNDS. I. THE PERHYDRO COMPOUNDS[1]

HERBERT E. UNGNADE AND ANNA LUDUTSKY[2]

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A perhydrodiethylstilbestrol, m.p. 189–190° (I) has been obtained in good yield by the hydrogenation of diethylstilbestrol over Raney nickel catalyst (1, 2). Another isomer, m.p. 167° (II) was reported by Lane and Wallis (3). The present investigation was undertaken in order to determine the configuration of these and the other possible isomers.

The two known dihydric alcohols (I) and (II) have been prepared in quantity and have been converted to the diketones (VII) and (VIII) by oxidation with chromic acid. A mixture of the two ketones gave a melting point depression. If one assumes that the configuration around carbons 3 and 4 of the hexane chain of hexestrol is unaffected by chemical changes involving the cyclohexane rings, the diketone (VIII) should be the *meso* compound since the diol (II) from which it was obtained was a reduction product of *meso*-hexestrol (3). On the same basis the diketone (VII) should be a racemate because the hydrogenation of diethylstilbestrol and its derivatives with Raney nickel gives predominantly racemic dihydro compounds (1, 4). Further evidence for this configuration was obtained by reducing *racemic*-dihydrodiethylstilbestrol with Raney nickel catalyst. The product consisted of a mixture of (I) and a new isomer (III).

The hydroxyl groups in the perhydro isomer (I) have been assigned the *trans* configuration on the basis of the following evidence. (I) was the main product when the racemic diketone (VII) was reduced with sodium and alcohol.[3] It was stable when heated with sodium in xylene at 175°, and was the main product when the isomer (III) was inverted under the same conditions.[4] No trace of the isomer (I) was found when the *racemic* diketone (VII) was reduced with platinum in acetic acid.[3] The isolation of the compound (I) was particularly easy, due to its small solubility in ether and the great tendency to be adsorbed on sodium sulfate.

The isomer (III), m.p. 129–130° was obtained by hydrogenation of *racemic*-hexestrol with Raney nickel. It was also formed in the exhaustive hydrogenation of diethylstilbestrol. When oxidized with chromic acid it gave the *racemic* diketone (VII). At least one hydroxyl group in the isomer (III) must have the *cis* configuration because the compound could be rearranged to (I) by heating with sodium.[4] The second hydroxyl group was given the *trans* configuration

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[1] Abstracted from a portion of a thesis by Anna Ludutsky to be submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] George Breon Fellow, 1943–1945.

[3] *trans* Isomers are favored by reduction in neutral or basic media, *cis* isomers in acid media (5).

[4] When heated with sodium, *cis*-alkylcyclohexanols rearrange to the *trans* forms or to equilibrium mixtures in which the *trans* forms usually predominate (6).

since the compound could be adsorbed on sodium sulfate like the di-*trans* isomer (I), and could be benzoylated in good yield although under more vigorous conditions. It differed in this respect from the di-*cis*-diol (IV) described below.

The ease of benzoylation of the three perhydro isomers was thus in the order which would be expected on the basis of the configuration, namely (I) *trans-trans* > (III) *cis-trans* > (IV) *cis-cis*.[5]

When the *racemic* diketone (VII) was reduced with platinum in acetic acid the glassy product had the composition of a monoacetate. Hydrolysis of this ester was effected by treating with methylmagnesium iodide. The resulting product consisted of a single new perhydro isomer (IV), a non-crystallizable glass, which was chromatographically uniform and could not be adsorbed on sodium sulfate from an ether solution. Attempts to purify this substance by sublimation in a high vacuum led to partial dehydration. When the new isomer was heated with sodium it underwent dehydration to give an unsaturated alcohol instead of the expected inversion.[4] Prolonged benzoylation of the diol gave only a small amount of dibenzoate. The main product consisted of an unsaturated compound. Benzoyl chloride in pyridine caused some dehydration even under relatively mild conditions, such as heating to 50°.

The oxidation of the dihydric alcohol (IV) gave only a very small yield of the diketone (VII), although normally the *cis*-alkylcyclohexanols are oxidized more easily than the *trans* isomers (8). The apparent anomaly is due to the competing dehydration which causes the formation of acids as main products of the oxidation.

The foregoing results are taken as evidence for the *cis-cis* configuration of the new dihydric alcohol (IV).[6] The relationship of the compounds in the racemic series is shown in Figure 1.

The Lane and Wallis compound (II) (3) was obtained in good yield from the perhydrogenation of *meso*-hexestrol with Raney nickel. It was accompanied by a new perhydrodiethylstilbestrol isomer (V), m.p. 124–125° and a small amount of phenolic material. Both isomers gave a good yield of the *meso* diketone (VIII) on oxidation with chromic acid. The configuration of the hydroxyl groups was assigned as in the racemic series largely on the basis of the mode of formation of the alcohols,[3] their rearrangement by heating with sodium,[4] their ease of esterification[5] and dehydration.[6,7]

The dihydric alcohol (II) was the only product when the *meso* diketone (VIII) was reduced with sodium and alcohol. It was also formed in good yield by inversion of (V) with sodium in xylene at 175° and did not rearrange on heating with

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[5] In alkylcyclohexanols the *trans* isomers esterify more rapidly and their esters are saponified more readily than the corresponding *cis* isomers (7).

[6] In all cases reported by Vavon (9) the *cis* isomers of the 2- and 4-alkylcyclohexanols were dehydrated more easily than the *trans* isomers although his results hardly lead one to predict the relatively great ease of dehydration of this perhydrostilbestrol isomer.

[7] The authors realize that none of these criteria in themselves are considered absolute proof since there are exceptions to the rule (10). It appears, on the other hand, that there is little doubt of the validity of the configurations when all methods are in agreement as in his case.

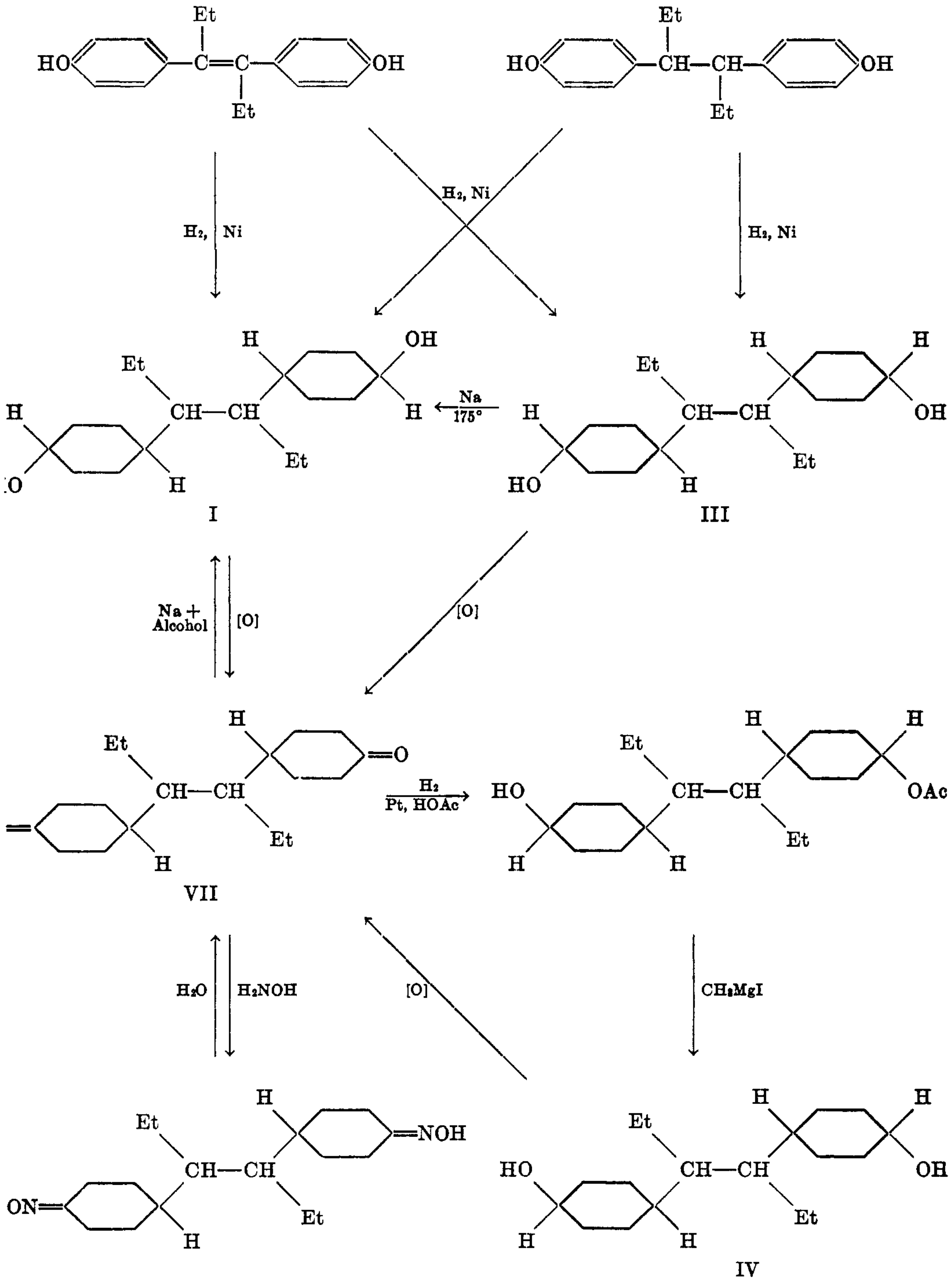
H₂, Ni
H₂, Ni
H₂, Ni
Na 175°
I
III
Na + Alcohol
[O]
[O]
H₂ Pt, HOAc
VII
H₂O
H₂NOH
[O]
CH₃MgI
IV

FIG. 1

sodium under the same conditions. Both of the isomers (II) and (V) were readily adsorbed on sodium sulfate from an ether or benzene solution and formed dibenzoates in good yield. On the basis of this evidence (II) was assigned the *trans-trans* and (V) the *cis-trans* configuration.

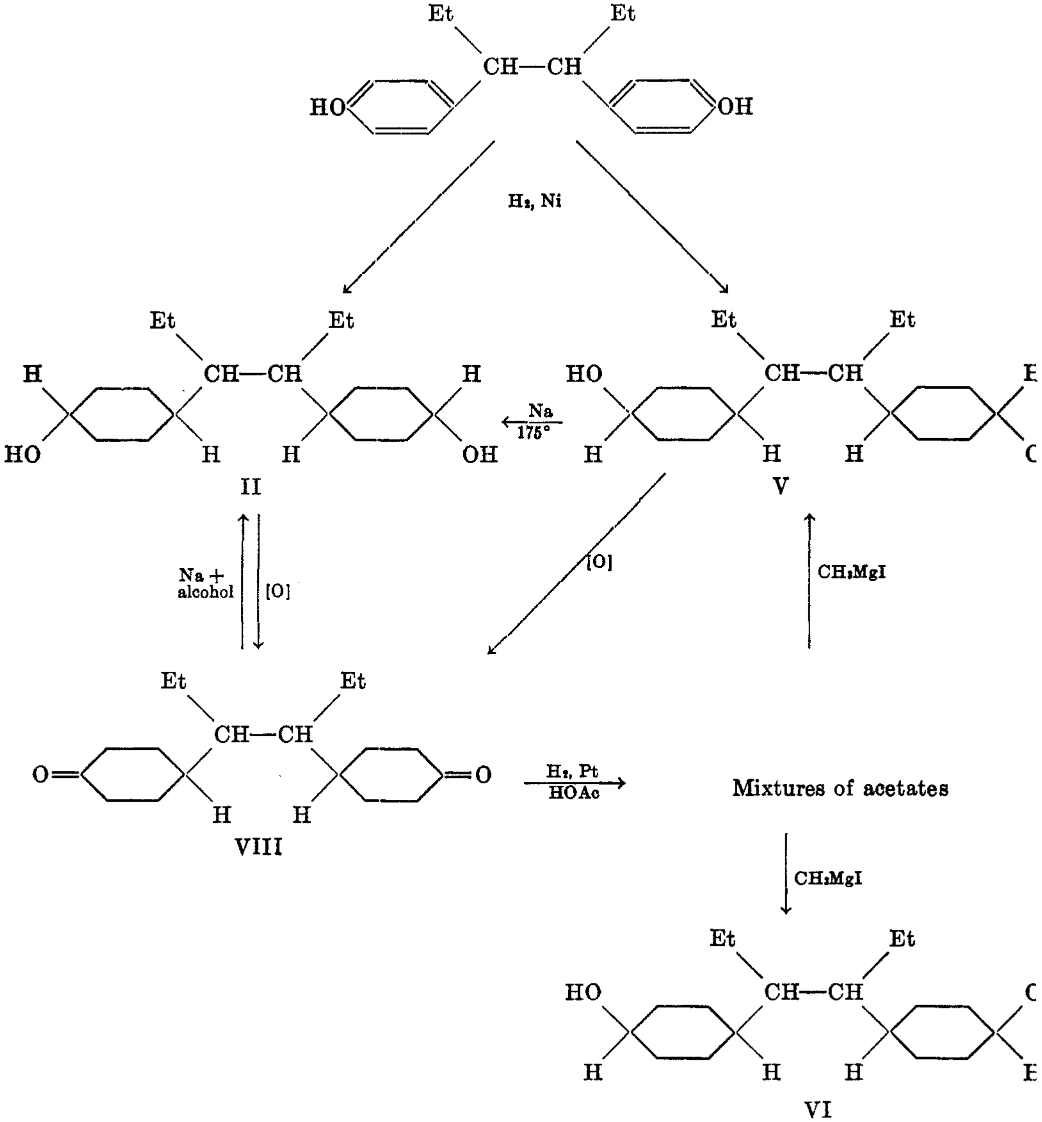

FIG. 2

The product from the reduction of the *meso* diketone (VIII) with platinum in acetic acid solution was deacetylated with methylmagnesium iodide. The resulting glass was a mixture of isomers from which the *cis-trans* isomer (V) could be separated. The remaining glassy perhydrodiethylstilbestrol (VI) could not be crystallized. It was homogeneous and could not be adsorbed on sodium sulfate. Vigorous benzoylation, by heating at 85° with benzoyl chloride in pyridine for a period of eight days, gave an unsaturated substance and only a minute trace of solid which is believed to be the dibenzoate. At lower temperatures no dibenzoate was formed.

The diol (VI) is regarded as the *cis-cis* isomer by analogy with the compound (IV) in the racemic series. The behavior of the two series of compounds appears to be identical with exception of the formation of the *cis-trans* isomer in the reduction of the *meso* diketone with platinum in acetic acid. This difference has no particular bearing on the configurations of the compounds involved since the relative amount of *cis* compounds in such reductions depends on the rate of reduction.[8]

The reactions of the isomers in the meso series are summarized in Figure 2.

Attempts to separate mixtures of the perhydro isomers by digitonin were unsuccessful since none of the six isomers formed an insoluble digitonide under the usual conditions.

EXPERIMENTAL[9]

The perhydrogenation of diethylstilbestrol. trans-Diethylstilbestrol (40 g.) dissolved in 100 cc. of methanol by refluxing was shaken with Raney nickel (10 g.) at 210° under 270 atm. initial hydrogen pressure until the pressure remained constant. The resulting solution was filtered and the solvent removed. The glassy residue was refluxed with 300 cc. of ether. The perhydro compound (I), *dl*-3,4-di-(4'-hydroxycyclohexyl)hexane, separated as an insoluble precipitate; yield 43%, m.p. 184–186°.

Dibenzoate. The perhydro compound (0.3 g.) dissolved in pyridine (5 cc.) was benzoylated with 0.3 cc. of benzoyl chloride at room temperature. The mixture was worked up after standing for forty hours. The product was crystallized from methanol and from petroleum ether (85–100°) and melted at 141–142°.

Anal. Calc'd for $C_{32}H_{42}O_4$: C, 78.32; H, 8.67.
Found: C, 78.17; H, 8.85.

The solution remaining after removal of the ether-insoluble isomer was distilled to remove the ether and the residue crystallized from benzene-petroleum ether. The product melting at 97–104° (15 g.) was refluxed for eight hours with 2 g. of sodium methoxide in 50 cc. of methanol.[10]

The mixture was then diluted with water and the alkali-insoluble material extracted with benzene. One crystallization from benzene-petroleum ether (60–80°) gave a product which melted at 110–114° and did not depress the melting point of the *cis-trans* isomer (III). (Yield 10.5 g.)

The presence of the *cis-trans* isomer (III) could also be demonstrated by benzoylation of the crude alkali-insoluble glass. The material (3.55 g.) was dissolved in 20 cc. of dry pyridine and 5 cc. of benzoyl chloride and the mixture was maintained at 95° for eight days. The benzoate was worked up in the usual way. One crystallization from methanol gave a product (2.77 g.) which melted at 85–115°. It possessed a uniform chromatogram. Re-

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[8] Higher rates of hydrogenation favor the *cis* forms (11).

[9] Analyses by Anna Ludutsky.

[10] This procedure, first used by W. M. Hoehn, represents the only good method to remove the phenolic material which is present. Aqueous alkali or Claisen alkali remove only part of the phenols.

crystallization from petroleum ether (28–38°) gave a crystalline product melting at 98–104°. Mixed melting point with the benzoate of (III) 104–106°.

In view of the rather drastic conditions and long period of time required for the hydrogenation of diethylstilbestrol (1, 2), it was hoped that the reaction could be promoted by reducing in the presence of the sodium salt of diethylstilbestrol. In all cases investigated previously this method proved successful (12). With diethylstilbestrol, however, the salt, even in small amounts inhibited the hydrogenation, which stopped at the dihydro or octahydro stage. The same was true for the monomethyl ether of diethylstilbestrol. In the latter case the application of the method was particularly attractive since it could offer an easy way to prepare pure octahydro compounds if it were successful (13).

The dihydro compound normally produced in the hydrogenation of *trans*-diethylstilbestrol is the racemate (1, 4). If, however, the reduction is carried out in the presence of the sodium salt a fair amount of the *meso* compound is obtained. It is interesting to note that the hydrogenation of *trans*-diethylstilbestrol with Raney nickel alloy and sodium hydroxide (14) also leads to some (30%) *meso*-hexestrol. The results are described in the following.

trans-Diethylstilbestrol (50 g.) dissolved in 100 cc. of methanol was treated with 0.05 g. of sodium and the resulting solution was reduced with 10 g. of Raney nickel. The reduction required five hours at 210° at an average pressure of 310 atm. The product was taken up in benzene, washed with dilute hydrochloric acid and water, and dried by distilling the benzene-water azeotrope. Colorless crystals separated on cooling of the dry benzene solution, m.p. 95–105°, yield 9.5 g. Many crystallizations raised the melting point to 176–178°. Mixed with *meso*-hexestrol (m.p. 185–186°) the substance melted at 178–180°. The respective dibenzoates, prepared by the method of Foreman and Miller (15) melted at 232–233° (from the hydrogenation) and 236–237° [from synthetic *meso*-hexestrol (4)] and the mixture melted at 233–234°.

The mother liquor from the crude *meso*-hexestrol (m.p. 95–105°) was treated with petroleum ether (60–80°) and on cooling deposited 6.31 g. of colorless solid melting at 107–114°. When mixed with *racemic*-hexestrol (m.p. 125–126°) it melted at 107–117°. The dibenzoate of *racemic*-hexestrol melted at 120–122°,[11] the same derivative from the reduction product (m.p. 107–114°) melted at 120–122° and the mixture melted at 120–122°.

A second reduction attempt with 10 g. of diethylstilbestrol, 0.01 g. of sodium, and 100 cc. of methanol conducted at an average pressure of 360 atm. gave 10.7 g. of a glass which contained no perhydro compounds but gave 4.26 g. of crystalline material melting at 50–55° when crystallized from benzene and petroleum ether (60–80°). This substance gave a positive Folin test and resembled the octahydro compounds (1).

Hydrogenation of racemic-hexestrol. *racemic*-Hexestrol was prepared from its dimethyl ether (1) (10 g.) by demethylation with 70 cc. of hydriodic acid (*d* 1.5), 70 cc. of acetic acid, and 50 cc. of acetic anhydride. The crude product (91%) melted at 124–125° after crystallizing from benzene.

A solution of 8 g. of this compound in 100 cc. of methanol was completely hydrogenated with 3 g. of Raney nickel at 210° under a pressure of 350 atm. The ether-insoluble part of the products (6.25 g., m.p. 130–177°) was refluxed for five hours with a solution of sodium methoxide prepared from 50 cc. of methanol and 2 g. of sodium. The mixture was poured into water and the non-phenolic solid filtered off (yield 5.81 g.). Three grams of this material on crystallization from benzene gave 1.6 g. of a white solid melting at 177–183°. It was purified by dissolving in benzene and allowing the solution to stand for several days over anhydrous sodium sulfate. The adsorbant was filtered and washed out with water. The remaining insoluble perhydro compound melted at 185–187°. Its mixed melting point with the perhydro isomer (I) (m.p. 187–188°) was 185–187°.

The filtrate from the crystallization was evaporated to half of its volume and allowed to stand over anhydrous sodium sulfate. The product left after washing out the sodium

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[11] Wessely and Welleba (16) give 116.5° for the pure optical isomers.

sulfate weighed 1.33 g., m.p. 123–126°. The pure compound (III) was obtained after crystallization from benzene-petroleum ether (60–80°), m.p. 129–130°. Mixed melting point with the isomer (I) (m.p. 187–188°) 125–135°.

Anal. Calc'd for $C_{18}H_{34}O_2$: C, 76.51; H, 12.14.
Found: C, 76.29; H, 12.39.

Dibenzoate. The perhydro compound (III) (0.5 g.) was heated for forty-eight hours at 100° with 3 cc. of anhydrous pyridine and 1 cc. of benzoyl chloride. The mixture was worked up in the usual manner and gave 1.04 g. of solid material which was crystallized from methanol and then from petroleum ether (60–80°). It melted at 110–111°. Mixed melting point with the dibenzoate of (I) (m.p. 141–142°) 99–125°.

Anal. Calc'd for $C_{32}H_{42}O_4$: C, 78.32; H, 8.67.
Found: C, 78.13; H, 8.85.

Inversion of dl-r-3-(4^t-hydroxycyclohexyl)-4-(4^c-hydroxycyclohexyl)hexane (III). The dihydric alcohol (III) (0.3 g.) was refluxed for forty-eight hours with 0.08 g. of sodium and 5 cc. of xylene at 175°. Unchanged sodium was removed by adding alcohol and the mixture diluted with water. Part of the product separated as an insoluble precipitate (0.05 g.). The remainder was extracted with benzene, freed from solvent and treated with ether. The yield of precipitate was 0.13 g. After crystallization from benzene the product melted at 183–185°. Mixed melting point with the isomer (I) (m.p. 187–188°) 185–187°.

When the perhydro compound (I) (0.3 g.) was treated in the same manner 0.1 g. was recovered unchanged. The remainder of the product was a glass which could not be crystallized. It was not unsaturated, *i.e.*, it did not decolorize bromine in carbon tetrachloride or exhibit the blue fluorescence in ultraviolet light which is characteristic for the unsaturated compounds in this series.

dl-3,4-Di-(4-ketocyclohexyl)hexane (VII). Various methods were used in order to convert the perhydro compounds (I) and (III) to the diketone (VII). The most consistent results were obtained when the alcohols were oxidized with chromic acid in benzene and acetic acid (17). The diketone was obtained in one of two crystalline modifications melting at 67–68° or 74–75°. Recrystallization of the higher-melting form or resolidification of the melt usually produced the lower-melting form of the diketone. The higher-melting modification was obtained sometimes by slow crystallization at room temperature. The diketone can be purified by sublimation at 2 mm.

Anal. Calc'd for $C_{18}H_{30}O_2$: C, 77.64; H, 10.87.
Found: 77.50; H, 11.00.

Dioxime. Hydroxylamine sulfate (8 g.) was dissolved in 24 cc. of water and 16 cc. of 10% aqueous sodium hydroxide. To this solution was added a solution of 0.79 g. of the diketone in 15 cc. of ethanol. Ethyl alcohol was then added dropwise until the mixture became homogeneous. The dioxime began to precipitate immediately. The precipitate was filtered, washed until neutral, and dried, m.p. 173–177°; yield 0.87 g. (95%). After recrystallization from chloroform and petroleum ether (28–38°) it melted at 179–180° (dec.). This material contained one molecule of water of crystallization. The loss in weight by heating to 110° was 5.87%. Calc'd for $C_{18}H_{32}N_2O_2 \cdot H_2O$: 5.52%.

Anal. Calc'd for $C_{18}H_{32}N_2O_2$: C, 70.06; H, 10.46.
Found: C, 69.93; H, 10.42.

The purity of the diketone (VII) was further established by regeneration from its purified dioxime. The dioxime (0.5 g.) was dissolved in 10 cc. of 1:4 hydrochloric acid and the mixture warmed on the steam-bath for one hour. The cooled solution was extracted with benzene, the benzene solution was washed with water and distilled. The residue (0.3 g.) was crystallized from petroleum ether, m.p. 62–63°. Sublimation in a vacuum and recrystallization raised the melting point to 64–65°. Mixed with the original diketone (m.p. 67–68°) it melted at 74–75° (remelt 67–68°).

Reduction of the diketone (VII) *with sodium and alcohol.* The diketone (0.5 g.) was dissolved in 13 cc. of absolute ethyl alcohol in a 100-cc. round-bottom flask attached to a reflux condenser. Sodium (1 g.) was added in small pieces through the condenser. After all the sodium had reacted, the mixture was refluxed on a water-bath for one hour and allowed to stand overnight. A crystalline substance (0.10 g.) separated after addition of water. The main product was obtained by extracting the filtrate with benzene. (Yield 0.35 g.). For purification the substance was adsorbed on sodium sulfate from benzene solution. On regeneration it melted at 186–188°. The mixed melting point with the di-*trans* isomer (I) was 186–188°. It has not been possible to isolate the impurity which contaminates the reduction product.

dl-3,4-Di-(4^c-hydroxycyclohexyl)hexane (IV). A solution of 3 g. of the diketone (VII) in 10 cc. of acetic acid and 1.5 cc. of hydrochloric acid containing 0.1 g. of platinum oxide catalyst was hydrogenated at room temperature under a pressure of approximately 35 mm. (above atmospheric pressure).[12] The reaction was stopped when the theoretical amount of hydrogen was absorbed. The catalyst was filtered, water added to the filtrate and the cloudy solution was extracted with benzene. The benzene solution was washed until neutral and distilled. The residual glass (3.11 g.) could not be crystallized. It was purified by sublimation from a molecular still at 1 × 10^{-4} mm.

Anal. Calc'd for the monoacetate $C_{20}H_{36}O_3$: C, 74.01; H, 11.09.
Found: C, 74.07; H, 11.04.

An ether solution (20 cc.) of the monoacetate (2.13 g.) was added dropwise to methylmagnesium iodide prepared from 1 g. of magnesium and 6.0 g. of methyl iodide. After the addition, the solution was refluxed for one hour. The reaction mixture was decomposed by pouring it cautiously into iced 30% sulfuric acid. The resulting solution was extracted with ether, and the ether solution was washed with saturated sodium bisulfite solution, with 10% aqueous sodium carbonate solution, and with water until neutral. The product was obtained as a glass when the solvent was distilled and finally completely removed *in vacuo*.

Anal. Calc'd for $C_{18}H_{34}O_2$: C, 76.81; H, 12.14.
Found: C, 76.86; H, 12.26.

After distillation from a molecular still at 1 × 10^{-4} mm. the compound was partially dehydrated (positive test for unsaturation).

Anal. Found: C, 77.67; H, 12.28.

The perhydro compound (IV) was occasionally accompanied by a small amount of crystalline material melting at 157–158° (from Skellysolve C) which was completely unaffected by chromic acid. In view of this stability toward oxidation it is regarded as one of the isomers of the di-tertiary alcohol which results from the addition of the Grignard reagent to any unchanged diketone.

Anal. Calc'd for $C_{20}H_{38}O_2$: C, 77.42; H, 12.26.
Found: C, 76.57; H, 12.52.

Dibenzoate. Benzoyl chloride (2 cc.) was added to the dihydric alcohol (IV) (2.08 g.) dissolved in 10 cc. of dry pyridine. The mixture was maintained at 100° for eight days. The product, isolated in the usual way, consisted of 3.3 g. of a glass which gave 0.58 g. of crystals when crystallized from petroleum ether (60–80°). Both the solid and the mother liquor were adsorbed separately on aluminum oxide from this same solvent.[13] The mother liquor contained a non-crystallizable glass (1.96 g.) with a blue fluorescence (U. V.) which decolorized a chloroform solution of bromine.

Anal. Found: C, 78.36; H, 9.43.

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[12] The catalytic hydrogenations in acetic acid were carried out in a ground glass flask which was attached to the shaker of a standard Parr hydrogenation apparatus. The glass outlet tube was connected to a gas burette of 2000 cc. capacity. Both acetic acid and hydrochloric acid used in these reactions were purified by distillation from an all glass apparatus.

[13] All chromatographic separations were carried out with purified petroleum ether. The adsorbent was reagent aluminum oxide (General Chemical Company) and the bands were frequently visible in ultraviolet light. The preferred method of elution consisted of washing through the column (flowing chromatogram).

The solid material could be separated into two fractions. The lower zone gave 0.15 g. of the dibenzoate which melted at 137–138° after crystallization from petroleum ether (28–38°).

Anal. Calc'd for $C_{32}H_{42}O_4$: C, 78.32; H, 8.67.
Found: C, 78.06; H, 9.12.

When mixed with the dibenzoates of (I) (m.p. 140–141°) and (III) (m.p. 110–111°) the new benzoate gave a melting point depression (119–135° and 97–125°).

The upper zone of the chromatogram consisted of a by-product (0.10 g.) which has not been identified as yet. It melted at 100–102°.

Anal. Found: C, 72.26; H, 7.16.

When the benzoylation was carried out by heating for eight days at 50° only a small amount of the dibenzoate was formed but the unsaturated compound was also present.

Oxidation of (IV). Chromic acid oxidation of the diol (IV) (1 g.) in the manner described for its isomers gave 0.33 g. of a glassy substance which was soluble in sodium bicarbonate solution, and 0.37 g. of alkali-insoluble glass. The acidic material (0.33 g.) could be further separated by chromatographic adsorption into a saturated acid fraction (0.2 g.) and a fluorescent fraction (0.02 g.) (blue U. V. fluorescence) which took up bromine from a chloroform solution.

The original oxidation product (0.25 g.) reacted with hydroxylamine to give 0.05 g. of an oxime which melted at 96–98°. Recrystallization from benzene and petroleum ether (60–80°) raised the melting point to 178–179°. Mixed melting point with the dioxime of (VII) (179–180°) 179–180°.

Attempted inversion of (IV). The dihydric alcohol (IV) was refluxed for forty-eight hours with 0.06 g. of sodium and 5 cc. of xylene at 175°. The product, obtained in the usual way, was a glass (0.2 g.). Its ether solution was allowed to stand over sodium sulfate but no adsorption occurred. After heating with sodium for an additional six days under identical conditions a glass resulted (0.2 g.) which could not be adsorbed on sodium sulfate. The ether solution was adsorbed on a column of aluminum oxide. The lower fluorescent (U. V.) zone was freed from solvent, yield 0.1 g.

Anal. Calc'd for $C_{18}H_{32}O$: C, 81.72; H, 12.00.
Found: C, 81.01; H, 12.01.

The upper zone (0.07 g.) was not further investigated.

meso-3,4-Di-(4^t-hydroxycyclohexyl)hexane (II). *meso*-Hexestrol (8 g.), prepared by the method of Docken and Spielman (4), was exhaustively hydrogenated in 100 cc. of methanol with 3 g. of Raney nickel at 210° (380 atm.). The product (7.3 g.) was dissolved in ether. The perhydro compound (II), which began to precipitate at once, melted at 161–163°, yield 2.84 g. It was crystallized from ethyl acetate, m.p. 166–167° (3).

Anal. Calc'd for $C_{18}H_{34}O_2$: C, 76.51; H, 12.14.
Found: C, 76.24; H, 12.74.

Dibenzoate. The diol (II) (0.26 g.) was benzoylated in the usual way. The reaction was complete in forty-eight hours at room temperature. The product was washed with methanol (yield 0.33 g., m.p. 133–135°) and then crystallized from petroleum ether (60–80°). It melted at 139–140°. Mixed melting point with the dibenzoate of the *racemic*-di-*trans* isomer (I) 118–130°, with the dibenzoate of the *racemic*-di-*cis* isomer (IV) 115–125° and with the benzoate of the *cis-trans* isomer (III) 99–114°.

Anal. Calc'd for $C_{32}H_{42}O_4$: C, 78.32; H, 8.67.
Found: C, 78.23; H, 8.91.

dl-m-3(4^c-Hydroxycyclohexyl)-4-(4^t-hydroxycyclohexyl)hexane (V). The ether solution remaining after the removal of the perhydro compound (II) (above) was evaporated to dryness. The glassy residue (5.0 g.) was refluxed for eight hours with sodium methoxide solution prepared from 50 cc. of methanol and 1 g. of sodium. The reaction mixture was diluted with water and extracted with benzene. The benzene extract was washed with water and distilled, and the residual alkali-insoluble glass was crystallized from benzene-petroleum ether (60–80°), yield 2.0 g., m.p. 108–114°. After several crystallizations from the same solvent mixture the pure dihydric alcohol (V) melted at 124–125°. Mixed with the *meso*-di-*trans* isomer (II) (m.p. 166–167°) and the *cis-trans* isomer (III) (m.p. 129–130°) it gave melting point depressions (118–148° and 103–114°).

Anal. Calc'd for $C_{18}H_{34}O_2$: C, 76.51; H, 12.14.
Found: C, 76.06; H, 12.52.

Dibenzoate. The above diol (V) (0.3 g.) did not react with benzoyl chloride in pyridine by standing at room temperature for forty-eight hours. The starting material (0.3 g.) was recovered unchanged. The dibenzoate was formed when the perhydro compound (V) (0.3 g.) was heated at 85° with pyridine (3 cc.) and benzoyl chloride (0.5 g.) for five days. The resulting glass was purified chromatographically. The single, homogeneous product was a glass, yield 0.2 g.

Anal. Calc'd for $C_{32}H_{42}O_4$: C, 78.32; H, 8.64.
Found: C, 77.96; H, 9.00.

Rearrangement of dl-m-3(4^c-hydroxycyclohexyl)-4-(4^t-hydroxycyclohexyl)hexane (V). When the rearrangement of this substance was attempted by heating with sodium in xylene at 175° for forty-eight hours the starting material was recovered unchanged. A similar attempt with aluminum isopropoxide also failed. The inversion was successful when the diol (V) (0.2 g.) was heated with sodium (0.06 g.) in xylene (5 cc.) at 175° for eight days. Part of the product (0.05 g.) was insoluble in the reaction mixture, m.p. 157–159°. After crystallization from ethyl acetate it melted at 164–165° [mixed with (II), m.p. 163–165°]. The benzene extract of the remaining solution gave a glass (0.15 g.) which was separated into 0.05 g. of (II), m.p. 160–162° and unchanged starting material (V).

When the isomer (II) was treated under identical conditions, half of it was recovered from the reaction mixture.

meso-3,4-Di-(4-ketocyclohexyl)hexane (VIII). The diols (II) and (V) were oxidized with chromic acid as described for the *racemic* diketone (VII). Both gave the same product (VIII) in yields of 76–80%, m.p. 85–86° and 86–87°, mixed m.p. 85–86°. The mixture with the *racemic* diketone (VII) melted at 57–70°.

Anal. Calc'd for $C_{18}H_{30}O_2$: C, 77.64; H, 10.87.
Found: C, 77.49; H, 11.07.

A benzene-insoluble acid, m.p. 235–238° was isolated as a by-product (7%) when a larger amount of the dihydric alcohol (II) was oxidized.

Dioxime. The diketone (VIII) gave a 91% yield of crude dioxime melting at 179–180° (dec.). Its melting point was unchanged after crystallization from chloroform-petroleum ether (28–38°). Mixed with the dioxime of the *racemic* diketone (VII) it melted at 155–173°.

Anal. Calc'd for $C_{18}H_{32}N_2O_2$: C, 70.06; H, 10.46.
Found: C, 69.85; H, 10.75.

Reduction of the meso diketone (VIII) *with sodium and alcohol.* The diketone (VIII) (0.4 g.) was reduced as described above. Part of the product (0.1 g.), m.p. 163–167°, was insoluble in the reaction mixture, mixed melting point with the diol (II) 165–167°. The remainder of this substance (0.15 g.) was removed from the benzene extract of the reaction mixture by adsorption on anhydrous sodium sulfate. It did not depress the melting point of the diol (II).

meso-3,4-Di-(4^c-hydroxycyclohexyl)hexane (VI). Hydrogenation of the diketone (VIII) (1.3 g.) with platinum oxide catalyst in acetic acid solution gave 1.3 g. of a glass.

Anal. Calc'd for the monoacetate $C_{20}H_{36}O_3$: C, 74.01; H, 11.09.
Found: C, 74.92; H, 11.81.

After reaction with methylmagnesium iodide the glass weighed 1.13 g. It was dissolved in benzene and petroleum ether (60–80°) and allowed to crystallize. The precipitate (0.4 g.) melted at 97–100°. After recrystallization from the same solvent mixture it melted at 122–123° [mixed melting point with the diol (V) 122–123°]. The amount of the *cis-trans* isomer (V) obtained in this reduction varied from 12 to 38%.[8] The remainder of the original solution was allowed to stand over anhydrous sodium sulfate but no adsorption occurred. The glass (VI) remaining after removing the solvent was chromatographically uniform.

Anal. Calc'd for $C_{18}H_{32}O_2$: C, 76.51; H, 12.14.

Found: C, 76.12; H, 11.97.

Benzoylation. The above diol (VI) (0.25 g.) was heated with benzoyl chloride (0.5 cc.) and pyridine (3 cc.) for eight days at 85°. The reaction mixture was worked up as usual and the resulting glass (0.3 g.) adsorbed on a column of aluminum oxide. The lower zone corresponded to the dibenzoate in a similar separation described for the benzoate of the isomer (IV). A minute amount of crystalline material, m.p. 79–80° (micro) separated from 0.01 g. of the glass in which it was contained. A second fraction (0.15 g.) was unsaturated and easily identified by its blue fluorescence in ultraviolet light.

Anal. Found: C, 78.48; H, 9.48.

The third fraction (0.1 g.) of non-fluorescent glass may possibly consist of the monobenzoate.

Anal. Calc'd for $C_{25}H_{36}O_3$: C, 77.66; H, 9.92.

Found: C, 76.90; H, 10.14.

When the benzoylation was carried out at 55° the reaction mixture from 0.81 g. of diol contained 0.83 g. of unsaturated fluorescent glass, 0.23 g. of saturated glass (upper zone) and no dibenzoate.

Attempted inversion of (VI). Heating with sodium for eight days at 175° converted the diol (VI) (0.39 g.) to a glass which could be separated into two glassy fractions by chromatographic adsorption. The main product (0.25 g.) was unsaturated. It gave the usual blue fluorescence and absorbed bromine from a chloroform solution. The second saturated fraction (0.01 g.) was not further investigated.

SUMMARY

Six pure perhydrostilbestrol isomers have been prepared and characterized.

Experimental evidence has been presented on which the configurations of the six isomers are based.

The two di-*cis* compounds are difficult to benzoylate and tend to dehydrate partially even under mild conditions.

COLUMBIA, MO.

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