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Steroidal Hormone Relatives. V. The Conversion of Hexestrol to Promethestrol *via* the Mannich Reaction[1]

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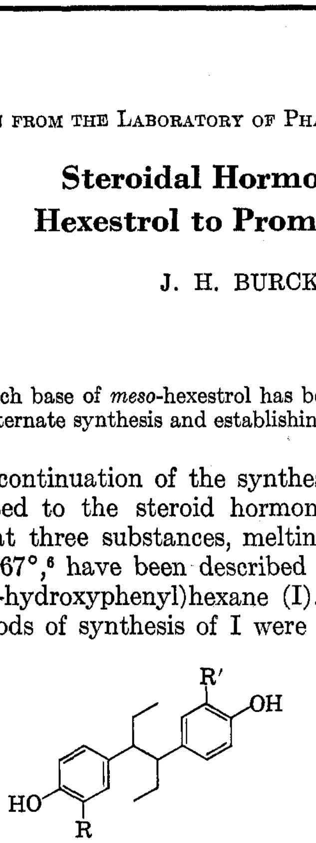
A *bis* Mannich base of *meso*-hexestrol has been prepared and converted through hydrogenolysis to promethestrol, thus affording an alternate synthesis and establishing the configuration of the latter as *meso*.

During a continuation of the synthesis of compounds related to the steroid hormones,[3] it was observed that three substances, melting at 145°,[4] 180°,[5] and 167°,[6] have been described as 3,4-bis-(*m*-methyl-*p*-hydroxyphenyl)hexane (I). Inasmuch as the methods of synthesis of I were not stereospecific it was considered desirable to prepare I from *meso*-hexestrol (II) and thereby to establish unequivocally the identity of the *meso* form of I. Also, in view of the fact that the configuration of the dipropionate of I, which is the important estrogen promethestrol (Meprane) dipropionate, has not definitely been established, there is a further reason for the suggested synthesis.



	R	R′
I	CH_3	CH_3
II	H	H
III	$CH_2N(C_2H_5)_2$	$CH_2N(C_2H_5)_2$
IV	$CH_2N(C_2H_5)_2$	H

Starting with *meso*-hexestrol (II), paraformaldehyde and diethylamine, we proposed to prepare III under the conditions of the Mannich reaction[7] and to subject III, which is a bis-benzylamine, to hydrogenolysis in order to obtain the desired *meso* isomer of I. In attempting the synthesis of Mannich base III, we found that the identity and yield of the product depended upon such variables as the temperature and the proportions of reactants. For a maximum yield of 78% of diamine III, a mixture of two moles of paraformaldehyde and eight moles of diethylamine for each mole of hexestrol was heated at reflux temperature for three hours. No solvent other than the diethylamine was employed. Isolation of III as the dihydrochloride salt gave apparently greater yields but its high melting point did not allow an indication of purity.

The monoamine IV hydrochloride was prepared in 47% yield using molar equivalents of hexestrol and paraformaldehyde and eight molar equivalents of diethylamine and no solvent, or four equivalents of diethylamine with alcohol as solvent. All attempts to introduce four basic groups into hexestrol failed and only diamine III was isolated.

The hydrogenolysis of *meso*-3,4-bis(*m*-diethylaminomethyl-*p*-hydroxyphenyl)hexane (III) was

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(3) J. H. Burckhalter and P. Kurath, *J. Am. Chem. Soc.*, **81**, 395 (1959).

(4) V. Niederl, C. A. Siconolfi, A. Bloom, and C. T. Van Meter, *J. Am. Chem. Soc.*, **70**, 508 (1948); V. Niederl and A. Bloom, U. S. Patents **2,500,855** and **2,520,052** [*Chem. Abstr.*, **44**, 5912 (1950) and **45**, 3421 (1951)].

(5) A. Bloom and V. Niederl, U. S. Patent **2,419,516** [*Chem. Abstr.*, **41**, 5150 (1947)].

(6) S. Tanabe and S. Onishi, *J. Pharm. Soc. Japan*, **70**, 618 (1950) [*Chem. Abstr.*, **45**, 6174 (1951)].

(7) F. F. Blicke, *Org. Reactions*, **1**, 303 (1942).

accomplished using Adkins' copper chromite catalyst at elevated temperature and pressure, according to the method of Caldwell and Thompson.[8] The reduction took place in excellent yield, providing the starting material (III) was pure. Impure base resulted in decreased yields of the bicresol (I) together with increased amounts of oily byproducts. It was also necessary to use a glass liner in the high pressure bomb, as contact between the metal and the catalyst promoted reduction of the latter to copper accompanied by decomposition and discoloration of the product.

The bicresol I, obtained from the hydrogenolysis of diamine III, has been assigned the *meso* configuration since it was prepared from *meso*-hexestrol. It melts at 164–165° which compares favorably with the 166–167° given by Tanabe and Onishi.[6] Their material must be identical with I and be assigned the *meso* configuration, while the 145°-melting compound of Niederl *et al.*[4] may be either the racemic modification or a polymorphic form of the *meso*. It would also appear that the melting point of 180° mentioned in Niederl's earliest patent[4] was in error or it represents a higher melting modification of I.

In order to determine the configuration of the commercial promethestrol dipropionate (Meprane Dipropionate) which is the diester of the bicresol I, the diester[9] was saponified to yield a product melting at 162–164°, which did not depress the melting point of the bicresol obtained from the hydrogenolysis of the Mannich diamine (II). The dipropionates of the two bicresols were also found to be identical. Thus, promethestrol has been synthesized from *meso*-hexestrol and its configuration has been established as *meso*.

EXPERIMENTAL

Meso-3,4-bis(m-diethylaminomethyl-p-hydroxyphenyl)hexane (III). A mixture of 5.4 g. (0.02 mole) of *meso*-hexestrol, 1.32 g. (0.044 mole) of paraformaldehyde and 12 g. (0.16 mole) of diethylamine was heated at reflux temperature for 3 hr. The excess diethylamine was removed under reduced pressure and the residue dissolved in 25 ml. of hot methyl alcohol. After the solution was cooled overnight in the refrigerator, 6.9 g. (78% yield) of a white crystalline product was collected, m.p. 107–110°. After recrystallization from methyl alcohol, it melted at 113–114°.

Anal. Calcd. for $C_{28}H_{44}N_2O_2$: C, 76.32; H, 10.06. Found: C, 76.38; H, 10.27.

Dry hydrogen chloride gas was passed into an alcoholic solution of the diamine (III) to precipitate the *hydrochloride of* III, m.p. >300° dec. For analysis, it was recrystallized from alcohol containing a small amount of methyl alcohol.

Anal. Calcd. for $C_{28}H_{44}N_2O_2.HCl$: C, 65.48; H, 9.03; Cl, 13.81. Found: C, 65.08; H, 9.30; Cl, 13.62.

The methyl alcoholic filtrate remaining after base III had been separated was evaporated to dryness, and the residue was dissolved in anhydrous ether. Dry hydrogen chloride, when passed into the solution, precipitated 1.8 g. of white solid which melted over a wide range. When triturated with hot water, 0.4 g. (5% yield) of IV hydrochloride (*vide infra*) was obtained, m.p. 220–222°.

3-(m-Diethylaminomethyl-p-hydroxyphenyl)-4-(p-hydroxyphenyl)hexane (IV) *hydrochloride*. A mixture of 5.4 g. (0.02 mole) of *meso*-hexestrol, 0.6 g. (0.02 mole) of paraformaldehyde and 12 g. (0.16 mole) of diethylamine was heated at reflux temperature for 3 hr. The excess diethylamine was removed under reduced pressure and the residue dissolved in 25 ml. of hot methyl alcohol. After cooling the solution overnight in the refrigerator, the diamine III separated. It was recrystallized from petroleum ether (86–100°) to give 1.2 g. (14% yield) of by-product III, m.p. 113–114°.

The solvent was removed from the methyl alcohol filtrate, the residual oil was dissolved in ether, and dry hydrogen chloride was passed into the solution to precipitate a white solid. After trituration of the substance with acetone and drying 3.3 g. (47% yield) of IV hydrochloride was obtained, m.p. 222–223°. After recrystallization from alcohol, it melted at 226–226.5°.[10]

Anal. Calcd. for $C_{23}H_{33}NO_2.HCl$: C, 70.47; H, 8.74; Cl, 9.05. Found: C, 70.12; H, 8.79; Cl, 9.07.

A total of 1.3 g. (24%) of unreacted hexestrol was recovered from the ether and petroleum ether filtrates.

The *free base* (IV) was liberated from an aqueous solution of the salt by means of sodium carbonate. The solid was recrystallized from benzene and petroleum ether (86–100°), m.p. 130–131°.

Anal. Calcd. for $C_{23}H_{33}NO_2$: C, 77.70; H, 9.36. Found: C, 77.71; H, 9.41.

Meso-3,4-bis-(m-methyl-p-hydroxyphenyl)-hexane (I). *From* III. The general method of Caldwell and Thompson[8] was followed. A solution of 2.2 g. (0.005 mole) of *meso*-3,4-bis-(*m*-diethylaminomethyl-*p*-hydroxyphenyl)hexane (III) in 25 ml. of absolute alcohol contained in a glass liner was subjected to hydrogenolysis in the presence of copper chromite catalyst at 170° and at about 200 atmospheres of pressure for 4 hr. The mixture was then cooled, filtered, and evaporated to dryness. The solid residue was dissolved in 300 ml. of ether, the solution washed successively with 5% hydrochloric acid and water, and dried over sodium carbonate. After filtration, the ethereal solution was distilled to leave a solid residue. Recrystallized from alcohol, 1.42 g. (95% yield) of white powder was obtained, m.p. 164–165°.

From promethestrol dipropionate. A mixture of 1 g. of promethestrol dipropionate and 10 ml. of Claisen solution (100 g. of potassium hydroxide dissolved in 100 ml. of water, cooled, and then diluted with an equal volume of methyl alcohol) was heated on the steam bath for 10 min. After the solution was allowed to stand overnight, it was diluted with 100 ml. of water, filtered, and then acidified with mineral acid. The white solid precipitate was recrystallized from dilute alcohol, m.p. 162–164°. When mixed with the product from the previous preparation, it gave no depression in melting point.

Meso-3,4-bis(m-methyl-p-propionoxyphenyl)hexane. From 1 g. of I, obtained from the diamine III, and propionic anhydride, the dipropionate of I was prepared in the usual manner. After three recrystallizations from dilute alcohol, it melted at 114–115°.[4,11] Mixed with promethestrol dipropionate,[9] it gave no depression in melting point.

LAWRENCE, KAN.

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[8] W. T. Caldwell and T. R. Thompson, *J. Am. Chem. Soc.*, **61**, 765 (1939).

[9] Obtained through the courtesy of Dr. B. J. Brent, Reed and Carnick, Jersey City 6, N. J.

[10] First prepared by Dr. R. Meyer in this laboratory.

[11] Note that this agrees with that reported in ref. 4, although the melting point of the unesterified phenol (I) is given as 145° instead of 164°.