10% sodium hydroxide and Claisen's extraction of a ligroin solution. Upon acidification of the two alkaline solutions, 9.5 g. (41.5%) of product, m. p. 150–152°, was obtained. This agreed by mixed melting point and analysis with the rearranged product I obtained by the direct condensation above. Further attempts to prepare the ether using potassium, potassium carbonate and acetone or a pyridine medium produced varying quantities of the same rearrangement product.

Attempted Preparation of Triphenylmethyl Ether of 4,6-Dibromo-*o*-cresol IX.—Ten grams of the 4,6-dibromo-*o*-cresol was treated with 1.5 g. of sodium in dry ether and 10 g. of triphenylchloromethane was added. After refluxing and carrying out the usual steps of recovery, no ether could be obtained but a large portion of the original brominated *o*-cresol and triphenylcarbinol was recovered.

Preparation of the Triphenylmethyl Ether of 4-Bromo-*o*-cresol VIII.—Eleven grams of 4-bromo-*o*-cresol was dissolved in 45 ml. of pyridine (dried and distilled from barium oxide) and 15 g. of triphenylchloromethane was added. After heating the mixture for ten hours, water and ether were added and the ether layer was washed with dilute hydrochloric acid, then with 10% sodium hydroxide and finally with water. After drying the ether layer and evaporation, the residue was taken up in ligroin (70–90°) and washed with Claisen's solution. No product was removed by the alkaline washing but from the ligroin layer, a product was obtained which was recrystallized from alcohol. A yield of 11.25 g. or 48.7%, m. p. 113.5–114°, was obtained.

Anal. Calcd. for $C_{26}H_{21}OBr$: Br, 18.61. Found: Br, 18.74, 18.65.

Attempted rearrangement of this ether in glacial acetic acid-sulfuric acid mixtures by dry hydrogen chloride or by zinc chloride was unsuccessful. Only small portions of triphenylcarbinol could be recovered in each case.

Conclusions

Condensation products have been obtained from the reaction in acid medium of triphenylcarbinol on 4-bromo-*o*-cresol VIII and 6-bromo-*o*-cresol VII. The latter product I agreed with the substance obtained by mono-bromination of Schorigin's cryptophenol. Methylation of product I gave a substance agreeing with the material prepared in a different series of steps by Boyd and Hardy[4] and postulated to have structure VI. Thus from these two reaction cycles the evidence places the triphenylmethyl group in the para position in the simple cryptophenol, as shown in structure III.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. LXXXII. Estrane Derivatives

BY RUSSELL E. MARKER AND EWALD ROHRMANN

Although the catalytic hydrogenation of estrone has been studied by a number of investigators,[1–5] the only reduction products which have been studied to any extent are the isomeric estradiols and an estranediol-3,17(α). This latter product is of considerable interest inasmuch as it is undoubtedly identical with one of the estranediols isolated from human non-pregnancy urine.[6,7] No information has been presented concerning the configurations at C-5 and at C-3 of this substance. The problem concerning the isomeric reduction products of estrone is complicated by the fact that the C-10 position becomes an asymmetric center during the course of the reduction. Thus the reduction of α-estradiol theoretically could give rise to eight isomeric estranediols. The fact that an isomeric estranediol, m. p. 242°, was isolated from human non-pregnancy urine[6,7] indicates that additional isomers exist. This particular estranediol-3,17 has not as yet been encountered in the *in vitro* reduction of estrone.

The fact that the catalytic hydrogenation of estrone in acidic medium results in the formation of mono-hydroxyestranes is of interest and in this respect it would appear to be analogous to equilenin, which readily yields a monohydroxy compound on reduction under similar conditions.[8,9,10] Dirscherl[4] has reported the isolation of two estranols from the reduction products of estrone in acidic ethanol. Butenandt[1] reported that in the hydrogenation of estrone acetate in neutral ethanol with platinum oxide catalyst the carbonyl group is reduced to a methylene group, the aromatic ring reduced and the acetate residue re-

(1) Butenandt, *Z. physiol. Chem.*, **191**, 140 (1930).
(2) Butenandt, Stormer and Westphal, *ibid.*, **208**, 149 (1932).
(3) Butenandt and Westphal, *ibid.*, **223**, 147 (1934).
(4) Dirscherl, *ibid.*, **239**, 53 (1936).
(5) Marker and Rohrmann, THIS JOURNAL, **60**, 2927 (1938).
(6) Marker, Rohrmann, Wittle and Lawson, *ibid.*, **60**, 1512 (1938).
(7) Marker, Rohrmann, Lawson and Wittle, *ibid.*, **60**, 1901 (1938).
(8) Marker, Kamm, Oakwood and Tendick, *ibid.*, **59**, 768 (1937).
(9) Ruzicka, Muller and Morgeli, *Helv. Chim. Acta*, **21**, 1394 (1938).
(10) Marker and Rohrmann, THIS JOURNAL, **61**, 3314 (1939).

moved to yield an estranol-3. This product was reported to be identical with the estranol obtained by the hydrogenation of 17-desoxyestrone in acidic ethanol[3] but unfortunately no direct comparison of the two products was reported in their experimental work.

In our experience the reduction of estrone in neutral ethanol under conditions apparently more drastic than used by Butenandt[1] gives rise to α-estradiol in over 90% yields and no evidence of the reduction of the aromatic ring was observed. The removal of the acetate residue by catalytic hydrogenation in neutral ethanol as observed by Butenandt is most probably due to the presence of a trace of alkali in the catalyst, a possibility demonstrated by the experiments of Miescher and Scholz.[11] In this Laboratory we have experienced no difficulty in hydrogenating estrone esters in ethanol solution with Adams catalyst to give the mono-esters of α-estradiol.[12]

That the predominant estranol obtained from the reduction of estrone in acidic ethanol is an estranol-17 seems most likely especially since the analogous reduction of equilenin gives high yields of estratriene-5,7,9-ol-17(α). By carrying out the reduction of the 17-mono acetate of α-estradiol with Adams catalyst in acetic acid, we have obtained an estranol apparently identical with that obtained by the catalytic hydrogenation of estrone in acidic ethanol. Inasmuch as the reduction of an acetoxy group at C-17 to a methylene group under the conditions of the hydrogenation is hardly probable, it would appear that the product is an estranol-17(α).

Further evidence that the hydroxyl group at C-3 is removed in the reduction is shown by the work of Butenandt and Westphal[3] on the catalytic hydrogenation of estriol in acidic medium. This reduction yielded two isomeric diols which upon dehydration with potassium bisulfate yielded ketonic compounds. This indicates a vicinal arrangement of the hydroxyl groups, which would be possible only in the C-17,C-16 positions.

The fact that estranediol-3,17(α) may be regarded as a *nor*-androstanediol or a *nor-etio*-cholanediol makes the substance of considerable interest because of its possible relationship to the androgenic hormones. Estranediol-3,17(α) on mild oxidation with chromic anhydride yields an estranedione-3,17 which we have now found to exist in two interconvertible polymorphic crystal forms, m. p. 146° and m. p. 180°. Estranedione readily reacts with bromine in acetic acid to yield a nicely crystalline bromo-estranedione. The removal of hydrogen bromide from this product with boiling pyridine proceeded smoothly to yield an estrenedione (*nor*-androstenedione). While the position of the ethylenic linkage in this substance is not proved, it appears probable that it is in the C-4,5 position, especially since the bromo compound behaves as a substance of coprostane configuration at C-5 in its reaction with pyridine.

An attempt to prepare crystalline *nor*-testosterone was unsuccessful. An estranol-17-one-3 was prepared by the reduction of the 17-monoacetate of α-estradiol and subsequent oxidation with chromic anhydride and hydrolysis with ethanolic alkali. The resulting ketone readily reacted with bromine to liberate hydrogen bromide but no crystalline bromide was obtained. Likewise, reaction with pyridine gave a non-crystalline product.

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Experimental Part

Estranediol-3,17(α), m. p. 205–206°, was prepared by the catalytic hydrogenation of estrone in acidic ethanol as described by Dirscherl.[4]

Estranedione.—This was prepared by the chromic anhydride oxidation of estranediol as described previously by us.[7] The product was crystallized from dilute acetone and dilute methanol to give a product of m. p. 176–178°.

The mother liquors remaining from the reduction of estrone after removal of part of the estranediol were evaporated and the residual sirup taken up in acetic acid and oxidized with chromic anhydride at room temperature for two hours. The crude oily oxidation product was sublimed in high vacuum. The first fraction sublimed at 80–90° and evidently consisted of mono-ketones which could not be crystallized. The higher fraction subliming at 125–140° consisted of estranedione which was crystallized from dilute acetone to give a product, m. p. 144–146°.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.8; H, 9.6. Found: C, 78.9; H, 9.6.

Upon another crystallization from ether–pentane white needles, m. p. 179–180°, were obtained. The mixture, with the lower melting form, melted at 160–178°. In another case the higher melting form was observed to revert to the lower form, m. p. 144–146.5°, on recrystallization from dilute acetone.

Estranol-17(α) from Estrone.—The material subliming at 80–90° obtained above was dissolved in a mixture of 300 cc. of absolute ethanol and 3 cc. of concentrated hydro-

(11) Miescher and Scholz, *Helv. Chim. Acta*, **20**, 263 (1937).
(12) Marker and Rohrmann, THIS JOURNAL, **61**, 1922 (1939).

chloric acid. The solution was shaken with Adams catalyst at two atmospheres hydrogen pressure at 25° for five hours. The reduction product was crystallized from aqueous methanol as white needles, m. p. 105–107°. This gave no depression with a sample of m. p. 106–108°, prepared by the direct catalytic hydrogenation of estrone.

Anal. Calcd. for $C_{18}H_{30}O$: C, 82.4; H, 11.5. Found: C, 82.2; H, 11.5.

An attempt to obtain a crystalline ketone on oxidation with chromic anhydride was unsuccessful.

Bromoestranedione.—To a solution of 700 mg. of estranedione in 20 cc. of acetic acid acidified with two drops of 48% hydrobromic acid was slowly added 5.3 cc. of 0.5 *M* bromine in acetic acid. Water was added and the precipitated solid collected, washed and dried. The product was crystallized from ether to give white crystals, m. p. 170–172°.

Anal. Calcd. for $C_{18}H_{25}O_2Br$: C, 61.2; H, 7.1. Found: C, 61.0; H, 7.1.

Estrenedione.—A solution of 400 mg. of bromoestranedione in 5 cc. of dry pyridine was refluxed for nine hours. The solution was diluted with water and the precipitated solid taken up in ether and freed from pyridine by washing with dilute hydrochloric acid. The ether was removed and the residue sublimed in high vacuum at 130–140°. The sublimate was crystallized from pentane as white leaflets, m. p. 146–148°.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.5; H, 8.9. Found: C, 79.2, 79.4; H, 8.9, 8.9.

Hydrogenation of Estrone in Neutral Medium.—Estrone (m. p. 259°) (5 g.) was shaken in absolute ethanol (300 cc.) with Adams catalyst (0.5 g.) and hydrogen at 3 atm. pressure at room temperature for eighteen hours. The reduction product was crystallized from aqueous acetone to give α-estradiol (4.6 g.), m. p. 173–175°. The mother liquors upon being subjected to sublimation in high vacuum gave no evidence of the presence of substances other than the isomeric estradiols.

17-Mono-acetate of α-Estradiol.—This was prepared in almost theoretical yields by the hydrolysis of α-estradiol diacetate with methanolic potassium carbonate at 20° as described by Miescher and Scholz[11] for the preparation of the 17-mono-*n*-butyrate of α-estradiol. The product formed white crystals, m. p. 215–217°. Miescher and Scholz[11] prepared the compound by carrying out the partial hydrolysis with Adams catalyst in ethanol in the presence of alkali and in an atmosphere of carbon dioxide. They report a m. p. of 215–217.5°.

Reduction of 17-Mono-acetate of α-Estradiol.—A mixture of 4 g. of the 17-monoacetate of α-estradiol, 250 cc. of glacial acetic acid, 70 cc. of absolute ethanol and 800 mg. of Adams catalyst was shaken with hydrogen at 10 pounds pressure at room temperature for fourteen hours. The catalyst was filtered and the filtrate diluted with water. The milky mixture was shaken with ether and the ethereal layer washed well with water and the ether removed. The residual sirup was dissolved in 100 cc. of glacial acetic acid and to this solution was added a solution of 2 g. of chromic anhydride in 25 cc. of 80% acetic acid. After standing at room temperature for two hours the mixture was diluted with water and the precipitated solid taken up in ether. The ether was removed and the residual sirup hydrolyzed with ethanolic potassium hydroxide.

The ketonic fraction was separated by means of Girard's reagent. After sublimation in high vacuum at 120–130° the product was crystallized from ether–pentane and aqueous acetone as white needles, m. p. 102–104°.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 78.2; H, 10.2. Found: C, 78.0; H, 10.1.

The product readily absorbed a mole of bromine in acetic acid solution acidified with a trace of hydrobromic acid. Hydrogen bromide was liberated. The bromination product could not be obtained crystalline. Heating with pyridine gave a non-crystalline product.

The neutral fraction (non-ketonic) from the chromic anhydride oxidation was sublimed in high vacuum and the fraction subliming at 100° was collected. This was crystalized from aqueous methanol as white needles, m. p. 106–108°. This gave no depression with a sample of estranol, m. p. 106–108°, obtained in the direct catalytic hydrogenation of estrone in acidic medium.

Anal. Calcd. for $C_{18}H_{30}O$: C, 82.4; H, 11.5. Found: C, 82.3; H, 11.4.

Summary

Estrenedione has been prepared from estranedione-3,17.

The major monohydroxyestrane resulting from the reduction of estrone in acidic medium appears to be an estranol-17(α).

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