[Contribution from the Chemical Research Division of Schering Corporation]

SYNTHESIS OF ESTRONE FROM ANDROSTADIENEDIONE

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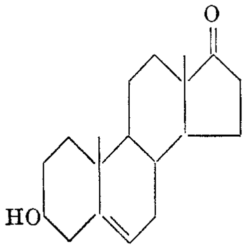
Inhoffen (1) was the first to convert the A-ring of the sterol skeleton into an aromatic structure. He developed methods (2, 3, 4, 5, 6, 7, 8) for obtaining the quinonoid structure II from a steroid I, and showed that it can be converted by pyrolysis or by rearrangement under the influence of sulfuric acid into the aromatic structure III.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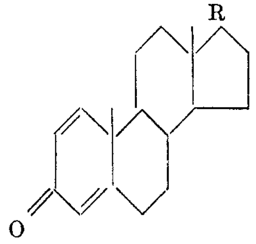
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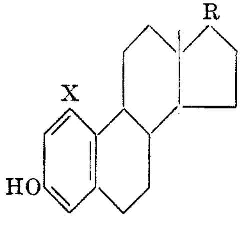
III

$X = H, CH_3$

$R = O, \left\langle{}^{H}_{OH}\right., \left\langle{}^{H}_{C_8H_{17}}\right.$

By appropriate choice of the starting material it should be possible to obtain either estrone, ($X = H, R = O$), or estradiol $\left(X = H, R = \left\langle{}^{H}_{OH}\right.\right)$ It is therefore significant that the preparation of estrone is not described in either the scientific or patent literature on the aromatization process.[2]

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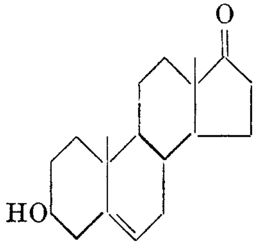
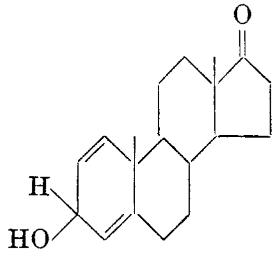
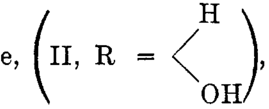
[2] Considerable amounts of estrone are said to have been made on a commercial scale by a process outlined in a report (8) by Allied investigators of German industry. This report is obviously incorrect in some of its statements. For example, it is stated that "dehydroisoandrosterone (I) is monobrominated and hydrogen bromide removed to yield $\Delta^{1,4}$-androstadiene-ol-3-one-17 (XIII)".

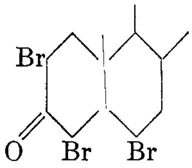

I


XIII

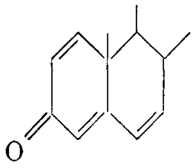
The conversion of dehydroepiandrosterone[3] (I) into estradiol through $\Delta^{1,4}$-androstadien-17-ol-3-one,  $\left(\text{II, R} = \overset{\text{H}}{\underset{\text{OH}}{<}}\right)$, is reported by Inhoffen and Zuehlsdorff (7) and their findings have been confirmed by Wilds and Djerassi (14). From $\Delta^{1,4}$-androstadiene-3,17-dione, (II, R = O), Inhoffen (1) obtained instead of estrone a new compound which he characterised as an isoequilin by its analysis and its absorption in the ultraviolet region. The experiments reported in this paper, on the contrary, gave a good yield of estrone from this same starting material.

When the experiment described by Inhoffen (15) was repeated with only two deviations from his procedure no isoequilin was obtained, but instead a mixture of estrone and 1-methylestrone. The differences were that purified $\Delta^{1,4}$-androstadiene-3,17-dione was used as a starting material instead of the crude bromine-containing preparation used by Inhoffen, and the total crude phenolic fraction was benzoylated and submitted to a chromatographic separation instead of relying on crystallization alone for purification of the reaction product. Inhoffen's isoequilin may have been derived from one or the other of the impurities in his starting material.

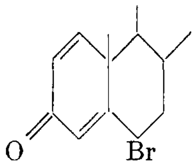
Djerassi and Scholz (18) have found that tribromides are formed in the dibromination of androstan-3,17-dione. Thus, 2,4,6-tribromoandrostan-3,17-dione, (IV), one possible isomer, would lead to a triene, (V), or to a monobromodiene, (VI), upon dehydrobromination, and either of these might form isoequilin upon aromatization.



IV



V



VI

$\Delta^{1,4}$-Androstadiene-3,17-dione, the starting material for the estrone preparation, was made by Inhoffen, Zuehlsdorff, and Huang-Minlon (5) by the Oppenauer oxidation of $\Delta^{1,4}$-androstadiene-17-ol-3-one, and they reported a melting point of 139–140°. The substance with a melting point of 168° assigned the same structure by Fujii and Matsukawa (16) has been found by repetition of

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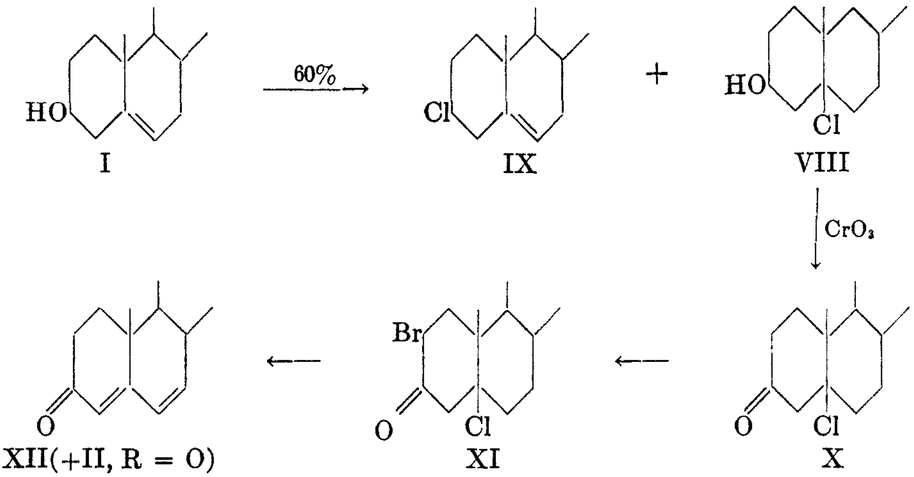
This unlikely monobromination reaction has not been described elsewhere in the chemical literature. [Compare, however, (10) page 77, paragraphs 4 and 5 which may be the source of the above mentioned report]. In neither of his two reviews on the subject (11, 12) does Inhoffen mention the use of this dieneolone to obtain estrone. Compound XIII is described (13) in a U. S. patent, granted to Schoeller, Serini, and Inhoffen. In his second review, Inhoffen reported that estrone was obtained as a by-product in the preparation of estradiol, without, however, giving any experimental details. Compare also Ref. (7), footnote 5, page 1914.

[3] We are here following the new nomenclature adopted by Professor and Mrs. Fieser in their monograph (23).

their experiments to be a mixture of dienediones containing only about half of the desired isomer.

When hydrogen chloride was added to the double bond of dehydroepiandrosterone, (I), only about 60% of the desired addition product 5-chloroandrostan-3-ol-17-one, (VIII), was obtained. From the mother liquors were isolated both unchanged starting material and 3-chloro-Δ^5-androsten-17-one (IX). Upon chromic acid oxidation, VIII was converted into 5-chloroandrostan-3,17-dione, (X), which was unstable when heated in solution. The bromination of X introduced one bromine atom and gave an equally unstable chlorobromandrostan-3,17-dione whose probable structure is XI. Dehydrohalogenation of this compound with collidine eliminated both the chlorine and the bromine and gave a mixture of $\Delta^{1,4}$- and $\Delta^{4,6}$-androstadiene-3,17-diones (II, R = O and XII), which could not be separated by crystallization. The ultraviolet spectrum of this mixture showed maxima at wavelengths characteristic for the two unsaturated ketones, and from the extinction coefficients it was estimated that each component formed about half of the mixture.



I IX VIII

XII(+II, R = O) XI X

A quantity of $\Delta^{1,4}$-androstadiene-3,17-dione was prepared by the method first outlined by Inhoffen (1, 17) and described in greater detail by Djerassi and Scholz (18).

Several methods have been used to carry out the aromatization reaction such as heating the androstadienedione in a carbon dioxide atmosphere (15), heating in an evacuated tube with or without solvent (7, 19), and continuous flow through a heated tube in the presence of a solvent with and without a catalyst (10, 17). Both cyclohexane (17) and tetralin (10, p. 79) have been used as carrier-solvents. In the experiments reported here the $\Delta^{1,4}$-androstadienedione was dissolved in mineral oil and the contact time in the furnace was adjusted to the optimum value by changes in the concentration of this solution. Estrone was obtained in yields of 15–20 per cent by carrying out the aromatization in an electrically-heated glass tube filled with glass beads.

The standards of purity for estrone prescribed by the United States Pharmacopeia are based upon material obtained from natural sources. Estrone obtained from equine urine is accompanied by varying amounts of equilin $[\alpha]_D$ $+308°$, and equilenin $[\alpha]_D$ $+87°$, both of which are difficult to eliminate from the finished product. Substantial amounts of these closely related estrogens may be present in commercial estrone and the product will still meet the U.S.P. specifications for optical rotation, since the high rotation of the former will offset the low rotation of the latter. In order to determine the physical constants of estrone free from these impurities, a sample of the synthetic material was crystallized to constant rotation. The melting point was still broad due to the polymorphism of estrone (22).

ACKNOWLEDGEMENT

We are glad to acknowledge the skillful assistance of Miss Jean Scholler and Mr. John Mentha. For microanalyses, optical rotations, and the measurement of absorption spectra we are indebted to Mr. Edwin Conner, Miss Betty Blasko, and Mrs. Alice Barrella of the Micro Analytical Department of this laboratory.

EXPERIMENTAL[4]

Addition of hydrogen chloride to dehydroepiandrosterone. 5-Chloroandrostan-3-ol-17-one was prepared by dissolving 12 g. of dehydroepiandrosterone in chloroform and saturating the solution with hydrogen chloride while cooling in a Dry Ice-acetone bath. Upon standing 48 hours at 25°, a crystalline solid separated. When collected, washed with chloroform saturated with hydrogen chloride, and dried *in vacuo* over barium oxide, it weighed 6.9 g. A second crop of 1.45 g. was collected after the mother liquor had stood at room temperature for another 48-hour period (total 8.3 g., 60%). The crude product thus obtained from the solution was a loose solvate with chloroform and possibly with hydrogen chloride (1.65 g. lost 0.45 g. upon 5-hours drying in a vacuum). Recrystallization of 6.9 g. of crude chloro compound from chloroform-hexane resulted in some initial loss of hydrogen chloride and gave two crops totaling 5.5 g., m.p. 170–172.5°. A sample recrystallized several times from ether melted at 171.5–172.5° dec. $[\alpha]_D$ $+62.4°$. Fujii and Matsukawa (16) report the melting point 160° with decomposition, while Ruzicka, Fischer, and Megu (20) report 156–157°:

Anal. Calc'd for $C_{19}H_{29}ClO_2$: Cl, 10.9. Found: Cl, 11.1.

The material in the chloroform mother liquor was chromatographed on alumina (Brockmann) and gave two principal fractions upon elution with successive portions of petroleum ether, ether, ether-benzene (1:1), and benzene. The ether extract gave a product m.p. 135–145° which after three crystallizations from acetone melted at 155.5–156.5°, $[\alpha]_D$ $+13.5°$.

Anal. Calc'd for $C_{19}H_{27}ClO$: C, 74.36; H, 8.87; Cl, 11.56.
Found: C, 74.72; H, 8.89; Cl, 11.18.

Dr. Oliveto of this laboratory compared this compound by mixture melting point with 3-chloro-Δ^5-androsten-17-one prepared by the action of phosphorus pentachloride on dehydroepiandrosterone and found the two substances to be identical.

The ether-benzene extract gave dehydroepiandrosterone, m.p. 145.5–147.5° identified by mixture melting point with authentic material.

Oxidation of 5-chloroandrostan-3-ol-17-one to 5-chloroandrostan-3,17-dione. A solution of 2.38 g. of 5-chloroandrostan-3-ol-17-one was prepared by warming with 15 ml. of ethylene

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[4] All melting points were determined on Anschütz thermometers using total thread immersion. Unless otherwise noted the rotations were determined in dioxane solution with a 1-dcm., 1-ml. capacity tube with 25.0° thermostatically controlled water flowing through the jacket of the tube. The probable precision is approximately ±1° unless specified otherwise.

chloride to 40–50°, then cooling to room temperature and diluting with 20 ml. of acetic acid. To this was added dropwise and with shaking over a 30-min. period a solution of 0.54 g. of chromic acid dissolved in 1 ml. of water and diluted with 30 ml. of acetic acid. The deep reddish-purple solution stood for 2.5 hours and to it was added slowly and with shaking 25 ml. of water. The ethylene chloride was removed at the water pump without applying heat and crystals of the ketone separated. More water was added slowly until, when a total of 50 ml. had been added, most of the ketone had crystallized. After drying at room temperature there was obtained 2.19 g. (92%) of 5-chloroandrostanedione. Apparently unnoticed by Fujii and Matsukawa (16), the compound melted with decomposition considerably below the melting point they reported. When immersed in a rapidly heated melting point bath (10°/min.) it melted with evolution of gas at 102–104° (inserted at 98°) then solidified and remelted at 155–166°.

The decomposition was very rapid and the upper melting point in the case of purified material approached that of Δ^4-androstene-3,17-dione (m.p. 173°). The initial decomposition point was dependent upon the temperature at immersion. For example, when the sample was immersed at 90°, it melted at 99–100°, while upon immersion at 110° it melted at 112°. A small portion was recrystallized by dissolving it in a minimum volume of chloroform at room temperature, adding pentane, and cooling in the refrigerator. It crystallized in clusters of flat needles which melted with gas evolution at 99–102°, solidified and then remelted at 160–167°. Fujii and Matsukawa (16) give the melting point 179° with decomposition. The chloroketone was extremely unstable and decomposed readily in warm solutions. Even at room temperature a chloroform solution instantly evolved hydrogen chloride upon treatment with Darco decolorizing charcoal.

Anal. Calc'd for $C_{19}H_{27}ClO_2$: Cl, 10.98. Found: Cl, 10.68, 10.85.

Bromination of 5-chloroandrostane-3,17-dione and dehydrohalogenation of the product. To a solution of 0.83 g. of chloroketone dissolved in 10 ml. of chloroform was added dropwise 0.44 g. of bromine dissolved in 15 ml. of chloroform. After a short induction period the bromine color was instantaneously discharged. The chloroform solution was concentrated to a small volume and 3 ml. of 2,4,6-collidine was added. All of the chloroform was distilled and the collidine solution was refluxed for 1 hr. The solution was cooled, diluted with ether, and extracted with dilute sulfuric acid and with sodium carbonate solution. Evaporation of the dried ethereal solution left a crystalline residue which after four recrystallizations from acetone-ligroin and from ether gave pale yellow prisms which melted at 161–163°. A solution of 2.106 mg. of this product dissolved in 100 cc. of isoöctane showed two absorption maxima in the ultraviolet region. One at 231 mμ, ϵ = 8700, was at the same wavelength as that of $\Delta^{1,4}$-androstadiene-3,17-dione, while the other at 269 mμ, ϵ = 10,300, coincided with that of $\Delta^{4,6}$-androstadiene-3,17-dione. From these data it would appear that each was present in approximately equimolecular amounts since the molar extinction coefficients, ϵ, are 15,600 and 26,200 respectively.

Abnormal dehydrobromination of 2,4-dibromoandrostan-3,17-dione in the presence of sodium iodide and butanol. At one time it was believed that the dehydrobromination of 2,4-dibromoandrostandione with γ-collidine could be aided by the addition of sodium iodide and butanol in order to first effect an exchange of the bromine atoms by iodine. The product obtained from this reaction was a mixture from which only androstan-3,17-dione and Δ^4-androsten-3,17-dione were isolated. A similar replacement of bromine by hydrogen has been observed by Schwenk and Whitman (21) but it appears that the sodium iodide increases the reducing effect to a considerable degree.

To a hot solution of 4 g. of sodium iodide in 15 ml. of 2,4,6-collidine and 1.5 ml. of butanol was added 3 g. of purified dibromoandrostandione (m.p. 194–200° dec., inserted at 190° and heated 4°/min.). The temperature of the solution was held at 130° for one hour whereupon collidine hydrobromide separated. After cooling and adding ether the collidine was extracted with dilute sulfuric acid and the neutral ethereal solution was dried over sodium sulfate and evaporated to dryness. A dark brown resin (1.8 to 2 g.) remained which usually crystallized upon short standing. Upon recrystallization from ether there was obtained a yellow crystalline product melting at 156–168°. The melting point of this material was sharply depressed upon admixture with $\Delta^{1,4}$-androstadiene-3,17-dione. Its absorption in the ultraviolet in isoöctane solution showed a strong peak at 230–232 mμ characteristic of $\Delta^{1,4}$-androstadiene-3,17-dione or of Δ^{4}-androstene-3,17-dione and a weak band at 269–273 mμ.

The products from several such runs totaling 8.15 g. were combined and chromatographed upon alumina using (A) petroleum ether; (B) petroleum ether-benzene (75/25); (C) petroleum ether-benzene (50/50); (D) petroleum ether-benzene (25/75); (E) benzene; and (F) benzene-ether (75/25).

The product split into two principal fractions, A and CD. From a 1.5-g. portion of (2.74 g.) fraction A, there was obtained after three crystallizations from ether 0.71 g. of colorless flat blades of androstan-3,17-dione, m.p. 133.3–133.9°.

Anal. Calc'd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78.
Found: C, 78.97; H, 10.01.

Mixture melting point with authentic material was unchanged. Fractions C and D (1.07 g.) were combined and recrystallized from ether (Darco) and gave 0.49 g. of yellow prisms. After three more recrystallizations from ether there were obtained cream-colored prisms of androstene-3,17-dione, m.p. 170.0–171.4°, unchanged upon admixture with authentic material.

Anal. Calc'd for $C_{19}H_{26}O_2$: C, 79.61; H, 9.09.
Found: C, 79.39; H, 9.23.

Pyrolysis of $\Delta^{1,4}$-androstadiene-3,17-dione by the procedure of Inhoffen (15). Two 5-g. portions of androstadienedione, m.p. 138–140° were separately heated in a flask immersed in a molten metal-bath. Carbon dioxide gas was passed through the flask during the pyrolysis and the gaseous products of the thermal cracking were collected over 50% potassium hydroxide solution. At 300–310°, the temperature used by Inhoffen, the decomposition was very slow. With increasing temperature it accelerated until at 340–350° it was complete in 15–20 min. Each portion produced about 85 cc. of gas.

The resinous product remaining in the flask from each of the two pyrolyses was dissolved in a small volume of acetone and then extracted with ether. This reprecipitated much of the resin. After three such treatments with acetone followed by ether extraction the ether solutions were combined and exhaustively extracted with 5% sodium hydroxide solution until upon acidification of the last alkaline extract with dilute hydrochloric acid no further precipitate of acidic material was obtained.

The acidic product which precipitated was allowed to stand for several hours to coagulate and then collected and dried. It weighed 2.5 g. and was dark brown and amorphous in appearance. This product was then benzoylated in 15 cc. of pyridine with 3 cc. of benzoyl chloride by warming to 70° for three hours. After pouring onto ice the mixture was allowed to remain overnight to decompose the benzoyl chloride, and the aqueous layer was decanted from the dark brown resin which was then washed with water by decantation. The resin was taken up in ether, extracted with sodium carbonate solution and the dried ethereal solution adsorbed upon a chromatographic column consisting of 150 g. of a mixture of magnesium silicate and Celite (2:1) topped with a layer of sand. Development of the column gave two principal fractions with ether. Upon evaporation of the first fraction a resinous residue remained which formed a cheeselike solid after standing overnight with a little ether. By triturating with ether, filtering and washing with ether, there was obtained 0.75 g. of white solid, m.p. 165–175°. As described below, this mixture was eventually separated into two products, *estrone benzoate,* and *1-methylestrone benzoate,* while the second principal fraction (0.3 g. of resin) upon sublimation gave only benzoic acid as an identifiable product.

Rechromatography of the first mixture did not effect a further separation and it was found that the mixture was better separated by fractional crystallization. The less soluble component, (0.26 g., m.p. 210–218.5°) identified as estrone benzoate gave after four recrystallizations from acetone 90 mg. of thick, colorless prisms, m.p. 218.5–222°, $[\alpha]_{546}$ + 131.4°, $[\alpha]_{589}$ + 111.3°, $[\alpha]_{643}$ + 80.6° (14.42 mg./ml.).

A mixture melting point with an authentic sample of estrone benzoate (m.p. 218.4–

222.5°) was unchanged. The rotation of this sample of estrone benzoate at the same three wavelengths and concentration was: $[\alpha]_{546}$ + 133.0°, $[\alpha]_{589}$ + 112.1°, $[\alpha]_{643}$ + 80.3° (14.38 mg./ml.).

From the mother liquors left after the crystallization of the estrone benzoate there was obtained 40 mg. of pearly white leaflets after two crystallizations from acetone and two from hexane-acetone. M.p. 236–238.5°, $[\alpha]_{546}$ + 213.8°, $[\alpha]_{589}$ + 180.3, and $[\alpha]_{643}$ + 142.0°, (5.940 mg./ml.).

In order to compare this compound with 1-methylestrone the latter was synthesized according to the directions of Djerassi and Scholz (18) by the rearrangement of $\Delta^{1,4}$-androstan-3,17-dione with concentrated sulfuric acid in acetic anhydride. It was obtained as white needles from methanol, m.p. 251–253°, $[\alpha]_{546}$ + 348.4°, $[\alpha]_{589}$ + 292.4°, $[\alpha]_{643}$ + 227.5°, (11.20 mg./ml.). The above authors report m.p. 249–251°, $[\alpha]_D$ +271.6°.

A 0.30-g. portion of 1-methylestrone was dissolved in 3 ml. of pyridine and warmed for $\frac{3}{4}$ hr. at 90° with 0.5 ml. of benzoyl chloride. After dilution with hot water this gave 0.40 g. of crude product, m.p. 233–237°. Thick prisms were obtained upon recrystallization from acetone but the melting point range remained broad and unchanged. Upon further recrystallization from hexane-acetone, characteristic glistening pearly leaflets of 1-methylestrone benzoate separated, similar to those obtained by chromatographic separation of the batch pyrolysis product of $\Delta^{1,4}$-androstadiene-3,17-dione; m.p. 237.5–238.7°. The rotation was: $[\alpha]_{546}$ + 212.3°, $[\alpha]_{589}$ + 180.1°, and $[\alpha]_{643}$ + 145.1° (8.453 mg./ml.).

Anal. Calc'd for $C_{26}H_{28}O_3$: C, 80.37; H, 7.26.

Found: (Sample sublimed under high vacuum): C, 80.27; H, 7.35.

The mixture melting point with the product obtained from the pyrolysis experiment described above was unchanged.

Pyrolysis of $\Delta^{1,4}$-androstadiene-3,17-dione to estrone. $\Delta^{1,4}$-androstadiene-3,17-dione was prepared in substantially the same way as described by Djerassi and Scholz (18) except that purified 2,4-dibromoandrostan-3,17-dione was used. Upon dehydrobromination with 2,4,6-collidine this gave crystalline $\Delta^{1,4}$-androstadiene-3,17-dione, m.p. 130–135° from an ether solution without need for chromatography. Repeated recrystallization from ether gave androstadienedione in the form of square prisms, m.p. 140.9–142.1°, $[\alpha]_D$ +103.4°. Inhoffen (5), m.p. 139–140°, $[\alpha]_D$ +115.8° (chloroform). Djerassi and Scholz (18), m.p. 140–141°, $[\alpha]_D$ +118.8° (chloroform). In isoöctane solution its molecular extinction coefficient, ϵ was 15,600 at 230–232 mμ.

A solution of 6 g. of $\Delta^{1,4}$-androstadiene-3,17-dione in 300 ml. of mineral oil (b.p. 310–405°) was added dropwise over a $\frac{1}{2}$ hour-period into a glass tube 1.25 in. in diameter and 12 in. long filled with glass beads and heated to 525–535° in an electric furnace. The vapor of the mineral oil condensed together with the estrone in the receiver. A small amount of low-boiling hydrocarbons which formed were condensed in a trap and the gaseous products were passed into an exhaust line. Upon dilution of the mineral oil with ether and extraction with 5% alkali there was obtained an aqueous solution of the crude acidic compounds. This solution was acidified with dilute hydrochloric acid and the precipitated estrone was collected, washed, and dried. There was obtained 3.2 g. of a yellow solid, m.p. 235–250°. After two recrystallizations from methanol or from acetone this gave 1.2 g. (21%) of colorless prisms m.p. 256–260°, $[\alpha]_D$ +160° to + 162°. A mixed melting point with U.S.P. Reference Standard material (m.p. 255–260°) was unchanged.

A sample of this estrone was recrystallized nine times alternating every three times between methanol and acetone as a solvent, whereupon the melting point determined by the capillary tube method rose to a constant figure of 257.8–260.6° (colorless to pale brown melt) from acetone and then dropped to about 257–260.6° upon shifting to methanol (Darco). This observation corresponds with the report on the crystalline modifications of estrone by Kofler and Hauschild (22) who found that crystallization from methanol gave only crystals of the rhombic metastable form with a hot-stage melting point of 256°. From acetone, however, we obtained the monoclinic-metastable crystalline platelets which we found melted somewhat higher. In any case, the melting point will be broad due to the equilibria between the above two crystalline forms and the stable rhombic form, and only the end-point of the melt will be sharp and unequivocal.

The rotation of the purified estrone at the sixth (acetone) and ninth (methanol) recrystallization stage was determined in dioxane solution at three different wavelengths using a monochromator and a sodium vapor lamp. The mean values of several determinations at from 20° to 25° are as follows:

$[\alpha]_{546}$ 199.6° ±1.6°; $[\alpha]_{589}$ 162.9° ±0.9°; $[\alpha]_D$ 163.5° ±0.7°; $[\alpha]_{643}$ 126.4° ±0.8°.

The synthetic estrone was indistinguishable from the natural product in biological activity. From it were prepared the benzoate, acetate, semicarbazone, and estradiol, which were likewise indistinguishable from similar derivatives of natural estrone. The product also showed the known color reactions of estrone.

SUMMARY

1. Repetition of the aromatization experiments of Inhoffen (15) by which he obtained "isoequilin" from $\Delta^{1,4}$-androstadiene-3,17-dione gave a mixture of estrone and 1-methylestrone.

2. In our hands the procedure of Fujii and Matsukawa for the preparation of $\Delta^{1,4}$-androstadiene-3,17-dione (16) gave a mixture of this and the corresponding $\Delta^{4,6}$ compound. Some of the intermediates in their synthesis differ in properties from those described in this paper.

3. In the case of 2,4-dibromoandrostan-3,17-dione, the addition of an iodide to the *s*-collidine dehydrobromination has been shown to give a mixture of reduction products.

4. A continuous-flow process is described for the formation of estrone by the aromatization of $\Delta^{1,4}$-androstadiene-3,17-dione in a furnace.

5. The physical constants of highly purified synthetic estrone have been determined.

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