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5-METHYLDOISYNOLIC ACID AND 1-METHYLESTRONE

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In 1940, Inhoffen (1) reported that 1-methylestradiol (I), prepared by the dienone-phenol rearrangement of 1,4-androstadien-17-ol-3-one (2) was estrogenically inactive in doses up to 1 mg. in rats, *i.e.* nearly ten thousand times the threshold dose of the female sex hormone estradiol (II). In view of the rather large number of diverse compounds which exhibit estrogenic activity, it is rather surprising that the introduction of a methyl group into the aromatic ring of estradiol should abolish completely the biological activity. Inhoffen offered this explanation: "Without doubt, the physiological inactivity is connected with the diminished solubility in alkali, and the latter is evidently a result of the 1-methyl group." In connection with a related problem, we have improved the synthesis of 1-methylestradiol (3) and have been able to substantiate fully Inhoffen's report regarding the loss in physiological activity. However, his explanation of this phenomenon seems to us to be over-simplified, particularly since the alkali-soluble 5-methyldoisynolic acid, to be discussed below, is also devoid of estrogenic potency.

It is an experimental fact that 1-methylphenols of the steroid series behave like pseudo-phenols in that they are insoluble in aqueous alkali, but it is difficult to understand how this alkali-insolubility *per se* should have physiological significance in the intact animal. While the mode of action of the estrogens in the body is as yet not understood, a more probable explanation for the inactivity of 1-methylestradiol appears to us to be a steric effect of the 1-methyl group and/or the low acidity of the phenolic group of 1-methylestradiol interfering with an essential metabolic step, such as an enzyme-coenzyme relationship, which thus is intimately connected with the nature of ring A. It seemed to us of interest to investigate the generality of this phenomenon since it might have some bearing on the biochemical function of the estrogens.

Doisy and co-workers (4) and later Heer and Miescher (5) have demonstrated that estradiol (II) could be converted by alkali fusion to an estrogenically highly potent acid (IV), recently termed doisynolic acid. By applying the same method to 1-methylestradiol (I), we have isolated an alkali-soluble monocarboxylic acid, still possessing the typical ultraviolet absorption spectrum of a phenol and which by analogy to the work of Heer and Miescher (5) is considered to be 5-methyldoisynolic acid (III). This acid proved to be inactive[1] in rats when injected in nearly one thousand times the active dose of doisynolic acid (6). This would in

[1] "Inactivity" in this paper refers to a lack of response in the vaginal smear test in rats (administered in oil solution), so as to be comparable to Inhoffen's results (1, 2) with 1-methylestradiol.

dicate that also in the doisynolic acid series the nature of ring A is an important factor for estrogenic activity. In addition, we have prepared 1-methylestrone (Va) by a method to be discussed below and have found this substance to be inactive in 0.5-mg. doses (higher levels have not been tested since estrone is active in 0.001-mg. doses). The theoretical implications are not clear at present, but it should be noted that in any future hypothesis on the mode of action of the estrogens, the unusual effect of methyl substitution in the aromatic ring of estrone, estradiol, and doisynolic acid will have to be considered.[2]

In their report on the synthesis of 1-methylestradiol (I), Inhoffen and Zuehlsdorff (2) in a footnote mentioned that they had prepared 1-methylestrone (Va) by the usual method [methyl migration in acetic anhydride-sulfuric acid solution, subsequently termed (7) the "dienone-phenol rearrangement"] from impure 1,4-androstadiene-3,17-dione (IX) which in turn had been obtained from impure 2,4-dibromoandrostane-3,17-dione (VIII). Except for the melting point, no details as to yield, analysis, biological activity etc. were reported.

To prepare 1-methylestrone (Va) by the dienone-phenol rearrangement, it was necessary to synthesize 1,4-androstadiene-3,17-dione (IX). Two obvious syntheses were available. One involves Oppenauer oxidation of the corresponding hydroxy compound, 1,4-androstadien-17-ol-3-one, which subsequently has been carried out successfully by Inhoffen and co-workers (8). However, at least eight separate steps from dehydroisoandrosterone acetate are necessary to prepare the starting material for the oxidation (2, 3). A much shorter synthesis from dehydroisoandrosterone acetate is outlined in the accompanying flowsheet and involves the dibromination of androstane-3,17-dione (VI). This synthesis was attempted already in 1937 (9), but neither pure nor crystalline products were isolated (1).

As was stated at that time, the main difficulty was encountered in isolating a homogeneous dibromo derivative and dehydrobrominating the latter. Continuing our recent study of the bromination of 3-keto *allo*steroids, in which we employed extensively polarimetric procedures (10, 11), we have applied successfully those methods to the dibromination of the diketone VI.

In the dibromination of 3-keto *allo*steroids which possess no other groups reactive towards bromine, it has been shown (10) that the primary product was always the 2,2-dibromo derivative, which could be rearranged, either separately or *in situ* to the 2,4 isomer (*cf.* 14). In the case of androstane-3,17-dione (VI) however, the following dibromo derivatives are theoretically possible: 2,2; 2,4; 2,16; 16,16. Since it has been demonstrated (12) that the monobromination of VI results in preferential attack of C-2, only the first three dibromo compounds

[2] It is of interest to note that 3,4-bis(4-hydroxy-2,5-dimethylphenyl)hexane and the corresponding hexadiene derivative (Niederl, Weiss, and Van Meter, Abstracts p. 28K, A.C.S. Meeting, New York City, Sept. 1947) are soluble in 5% sodium hydroxide solution and are fully active in 5γ doses (J. B. Niederl, private communication). These compounds appear to be the closest analogs to 1-methylestradiol among the synthetic estrogens, but it is open to question whether on the basis of the superficial structural resemblance [see Koch, *Nature*, **161**, 309 (1948)] one can state that the estrogenic effect persisted because the synthetic phenols were sufficiently acidic.

mentioned above should be encountered. Dannenberg (13) in a study of the dibromination of androstane-3,17-dione considered only the possibility of 2,4 and 2,16 isomers, since at that time 2,2-dibromo derivatives had not been described as yet. Of the products isolated, the structure of the 2,16-dibromo derivative was proved by an independent and unequivocal method of synthesis, and thereby was noted the considerably lower reactivity of C-16 towards bromine as compared to the *alpha* positions in ring A (C-2 and C-4). A second dibromo compound of nearly the same melting point and rotation as the 2,16 isomer was obtained, but it gave a definite depression in a mixed melting point determination,

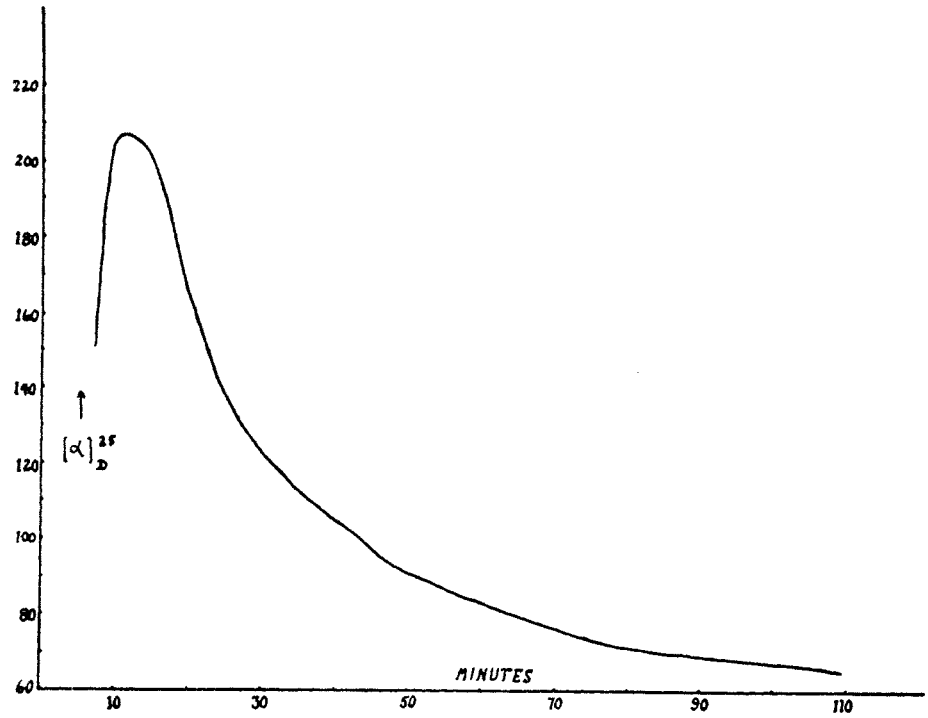


FIG. 1. POLARIMETRIC INVESTIGATION OF THE DIBROMINATION OF ANDROSTANE-3,17-DIONE (VI).

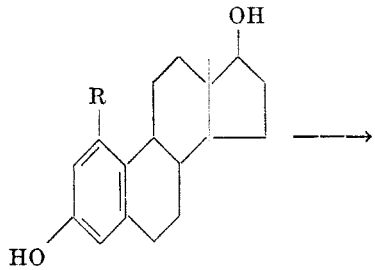
and was believed to be the 2,4 isomer. The structure of the latter could not be proved by dehydrobromination since the use of collidine had as yet not been introduced; in addition the presence of tribromo and possibly also other derivatives was noted.

In view of the rapid formation of the 2,2-dibromo compounds (10) in contrast to the relatively sluggish bromination of the 17-ketones (13), the structure VII suggested itself for the primary product. When the dibromination of VI was investigated in the polarimeter, the typical curve (Fig. 1) was observed showing an early maximum in rotation indicative of the formation of the 2,2 isomer. The end product (after complete rearrangement) showed a rotation of +40°, in ex-

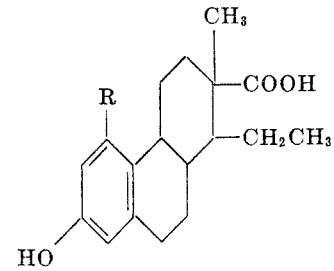
cellent agreement with the value reported by Dannenberg (13). Furthermore, on applying the method of molecular rotation differences, a $\Delta[M]_D$ value of $-124°$ is obtained, which falls well within the experimental limit of the observed $\Delta[M]_D$ value of $-136°$ reported for the 2,4-dibromo-3-keto *allo*steroids (11). Since Dannenberg's (13) 2,16 isomer showed the same rotation and nearly identical decomposition point, additional chemical evidence was necessary to prove the structure of the above compound as VIII. This was accomplished by dehydrobromination with collidine, yielding the desired 1,4-androstadiene-3,17-dione (IX). In agreement with earlier work on related 2,4-dibromo ketones (10, 14), it was also possible to dehydrobrominate VIII selectively by short treatment with collidine affording the monobromo derivative XI, which exhibited the typical absorption spectrum of a Δ^4-3-keto steroid (maximum at 243 mu). Its structure was confirmed further by debromination to Δ^4-androstene-3,17-dione (XII).

Attempts to isolate the pure 2,2-dibromo isomer (VII) were not completely successful. Judging from the results obtained in the polarimetric study of the dibromination (Fig. 1), the highest rotation ($[\alpha]_D$ $+207°$) corresponds to a $\Delta[M]_D$ value of $-623°$, but when the solution was diluted at the time it reached this maximum rotation and the precipitate isolated, it showed only a rotation of $+158°$ ($\Delta[M]_D$ $+403°$), which was somewhat beyond the experimental limit for the observed $\Delta[M]_D$ value of $+459°$ for 2,2-dibromo ketones (11); the lower value is due to the presence of small amounts of tribromo and probably also 2,4-dibromo compounds present as impurities. No obvious explanation is evident for the abnormally high rotation of the initial reaction mixture; nevertheless there is no doubt that it contained predominantly the 2,2-dibromo isomer as proved by the formation of the 2,4 derivative VIII in high yield on rearrangement and by dehydrobromination to the Δ^1-2-bromo derivative X with its typical maximum at 256 mu (10). It is quite clear that the difficulties encountered by the previous investigators (1, 13) in obtaining the desired 2,4-dibromo derivative VIII in a pure state lay in the fact that they diluted the reaction mixture at the point of decolorization and thus had to separate a mixture of 2,2 and 2,4 isomers. The properties of the by-product mentioned by Dannenberg (13) resemble those of the 2,2-dibromo compound VII, although no rotation was reported. By the method described in the experimental section, the desired dibromo compound VIII can be obtained directly from VI in about 90–95% yield in satisfactory purity for the dehydrobromination.

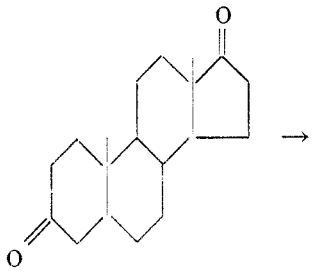
The dienone-phenol rearrangement of the dienone IX to yield the desired 1-methylestrone (Va) was attempted first in acetic anhydride solution containing sulfuric acid, a method which has been successful in a number of dienones with varying substituents at C-17. However, in the first runs none of the desired material was isolated, and it was noted that the entire product of the reaction was water-soluble. Windaus and co-workers (17, 18) have shown that steroid ketones such as cholestenone or coprostanone are readily sulfonated at room temperature with sulfuric acid in acetic anhydride solution, conditions which are nearly identical with those of the dienone-phenol rearrangement. It was, therefore, suspected that sulfonation had occurred at C-16, since the dienone IX differs



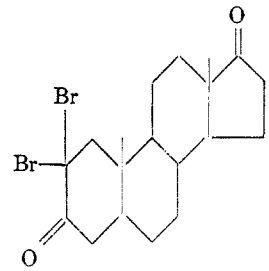
I R = CH_3
II R = H



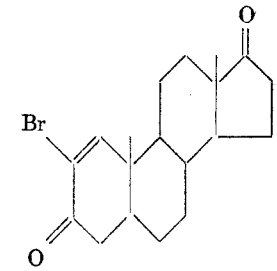
III R = CH_3
IV R = H



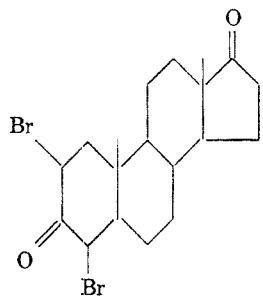
VI



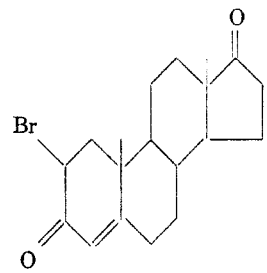
VII



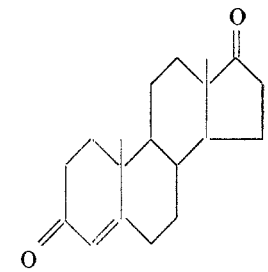
X



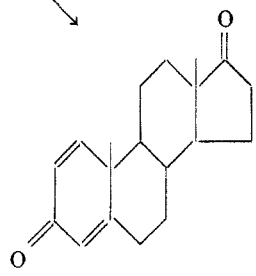
VIII



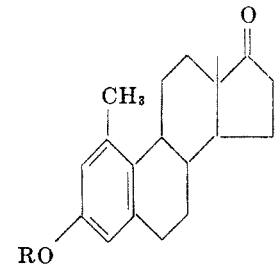
XI



XII



IX



Va R = H
Vb R = CH_3

only in a C-17 carbonyl group from the other steroid dienones which can be rearranged under those conditions without sulfonation (2, 3, 10, 15, 16). For instance, the corresponding compound with a C-17 hydroxyl group, on treatment with 1.5 moles of sulfuric acid, gave 71% of the corresponding phenol (3) while in the present case under the same conditions *none* of the phenol was isolated. The ease of sulfonation of 17-keto steroids was demonstrated when it was found possible to sulfonate estrone, isoandrosterone acetate etc., with one mole of sulfuric acid in acetic anhydride, sulfonation occurring *alpha* to the ketone group. These sulfonation studies as well as the isolation of 1-methylestrone-16-sulfonic acid from the rearrangement will be described in a forthcoming publication in this journal.

The rearrangement could be carried out in 80% yield by using *p*-toluenesulfonic acid; by limiting the amount of sulfuric acid considerably it was also possible to isolate 1-methylestrone (Va) although in lower yield. The reduction of the keto group of Va with lithium aluminum hydride (20) afforded 88% of 1-methylestradiol (I), which represents a considerable simplification of the earlier synthesis involving 1,4-androstadien-17-ol-3-one (2, 3).

Acknowledgment. The authors would like to express their gratitude to Jean Rogers and Helen Dudek for their skillful assistance. Elizabeth Ryan was responsible for most of the rotations and absorption spectra, and Greta Holmquist carried out all of the biological assays.

EXPERIMENTAL[3]

5-Methyldoisynolic acid (III). The procedure described below was adapted from the one of Heer and Miescher (5) for the fusion of estradiol.

A mixture of 0.5 g. of 1-methylestradiol (2, 3), 25 g. of potassium hydroxide pellets, and 4 cc. of water was fused in an open crucible with occasional stirring for thirty minutes in a metal-bath maintained at 350–370°, a slow current of nitrogen being passed over the surface of the reaction mixture. The cooled melt was taken up in water, acidified, extracted with ether, and the organic layer was extracted several times with 5% potassium hydroxide solution. The combined basic solutions were acidified with concentrated hydrochloric acid and the product was extracted with ether. After washing with a few cc. of sodium bicarbonate solution to remove colored impurities, the ether solution was washed with water, dried, and evaporated. The residue crystallized on trituration with hexane to yield 0.23 g. (43%) of light tan crystals ranging in m.p. (in two separate experiments) from 144–148° to 149°–155°; (Found: C, 75.66; H, 8.56). After several recrystallizations from a mixture of hexane and acetone, 5-methyldoisynolic acid (III) crystallized as colorless, minute octahedra with m.p. 154–156° (cloudy, clearing at 162°), $[\alpha]_D^{25}$ +161°. The ultraviolet absorption spectrum was practically identical with that of doisynolic acid (5), maximum at 285 mu, log E 3.15, minimum at 249.5 mu, log E 2.13.

Anal. Calc'd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.66; neutral equiv., 302.
Fonnd: 75.36; H, 8.81; neutral equiv., 299.

Dibromination of androstane-3,17-dione. The polarimetric study was carried out exactly

[3] All melting points below 220° are corrected. Rotations were determined on 5–10 mg. of sample in 1.2 cc. of chloroform in a 1 dcm. tube of 1 cc. capacity. Absorption spectra measurements were carried out in 95% ethanol solution. The microanalyses were carried out by Mr. Joseph F. Alicino, Metuchen, N. J. and Mr. George L. Stragand, Microchemical Laboratory, University of Pittsburgh.

as described in our earlier paper (10) using 144 mg. of androstane-3,17-dione (VI), 15.00 cc. of Baker C.P. glacial acetic acid and 2.50 cc. of standard bromine-acetic acid solution (1.6 g. in 25 cc.). The results are shown in Fig. 1 and demonstrate clearly the intermediate formation of a 2,2-dibromo derivative.

(a) *Isolation of 2,2-dibromoandrostane-3,17-dione* (VII). The reaction was carried out in a polarimeter tube, but the solution was poured immediately into water when the rotation had reached its highest value ($[\alpha]_D^{25}$ +207°). After cooling in ice, the crystals were filtered, washed thoroughly with water, and dried; yield 90%, m.p. 135–170° (dec.), $[\alpha]_D^{25}$ +144.3° (chloroform), (Found: Br, 37.72). Recrystallization from ethanol gave crystals of m.p. 133–135° (dec.), $[\alpha]_D^{25}$ +147.9°.[4] In another run, where the product was precipitated only partially with water so as to obtain two fractions, the first crop had m.p. 179–183° (dec.) $[\alpha]_D^{25}$ +153°, and the second crop showed m.p. 124–178° (dec.) $[\alpha]_D^{25}$ +84°. Recrystallization of the first fraction from ethanol gave crystals with the following properties: m.p. 148–150° (dec.), $[\alpha]_D^{25}$ +157.9° (chloroform).

Anal. Calc'd for $C_{19}H_{26}Br_2O_2$: C, 51.14; H, 5.87; Br, 35.82.
Found: C, 49.67; H, 5.63; Br, 37.63.

The significance of the above rotation values in terms of molecular rotation differences is given in the discussion. It is clear that the material consists to a large extent of the 2,2-dibromo isomer, contaminated by some tribromo and possibly also 2,4-dibromo derivative. The mixture[5] does not seem to be amenable to complete separation by crystallization, but the presence of the 2,2 isomer was demonstrated by dehydrobromination to the Δ^1-2-bromo compound X, and by the high yield obtained in the direct preparation of the 2,4-dibromo compound [see (b)] in which the 2,2 isomer is an intermediate (10).

(b) *Isolation of 2,4-dibromoandrostane-3,17-dione* (VIII). This compound has already been prepared in unspecified yield by Dannenberg (13) by dibromination of VI in acetic acid and immediate precipitation with water at the point of decolorization. Although not realized at the time, such a procedure always results in mixtures contaminated by varying amounts of 2,2-dibromo derivative (10). Taking into account the intermediate formation of this isomer and the results of the polarimetric measurements, the following method was developed and has given excellent yields.

A solution of 1 g. of androstane-3,17-dione in 10 cc. of C.P. glacial acetic acid (water content not above 35 mg./10 cc., see ref. 10) was treated at room temperature[6] with 0.2 cc. of 4 *N* hydrogen bromide-acetic acid solution followed by 17.4 cc. of standard bromine-acetic acid solution. After decolorization, which was almost instantaneous, the solution was warmed to about 50° and stoppered. Crystals of the 2,4-dibromo compound VIII appeared within a few minutes, particularly when seed crystals were added, and after standing at room temperature (25°) for three and one-half hours, the solution was cooled for one-half hour, the crystals collected and washed well. The yield of 2,4 isomer was 68–71% of material with $[\alpha]_D^{25}$ +38° to 44°. The decomposition point varied between 182° and 187°, but this material was satisfactory for the next step. Dilution of the filtrate gave an additional 22–30% of material of m.p. 179° (dec.) which was satisfactory for the dehydrobromination step if the

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[4] It was found that the rotation of the 2,2-dibromo compound was nearly the same in acetic acid as in chloroform and that it did not change on standing. This observation excludes, therefore, the possibility that a change in solvents was responsible for the difference of the two rotations observed ($[\alpha]_D^{25}$ +207° in the polarimeter as compared to +150° to 158° of the sample isolated).

[5] Such a mixture was encountered already by Dannenberg (13) although he did not realize the presence of the 2,2-dibromo compound.

[6] This is in contrast to the dibromination of androstan-17-ol-3-one 17-hexahydrobenzoate (10), where the solution was warmed first so as to catalyze both the bromination and rearrangement. In the present case, advantage is taken of the lowered reactivity of the C-17 carbonyl group and the bromination is carried out at room temperature to avoid as much as possible reaction at C-16, and the solution is warmed only at the point of decolorization to facilitate the rearrangement of the 2,2 to the 2,4 isomer.

androstanedione used was of good grade (m.p. 132–133°). Otherwise, this crop had to be recrystallized.

After several recrystallizations from chloroform-ethanol, the analytical sample had m.p. 209–210° (dec.) when immersed into the bath at 200°, $[\alpha]_D^{25}$ +39.8°. Dannenberg reported m.p. 223–225° (dec. uncorr.), $[\alpha]_D^{25}$ +41.5°. In our experience, the decomposition point was not a very reliable criterion.

Anal. Calc'd for $C_{19}H_{26}Br_2O_2$: C, 51.14; H, 5.87; Br, 35.82.
Found: C, 51.23; H, 5.77; Br, 35.39.

Δ^1-2-Bromoandrostene-3,17-dione (X). To demonstrate the presence of the 2,2-dibromo structure in the dibromo derivative of $[\alpha]_D^{25}$ +157.9° obtained above (a), 0.25 g. of the compound was refluxed with 1 cc. of collidine for ten minutes. The collidine hydrobromide weighed 151 mg. and corresponded to 1.34 moles of hydrogen bromide. The collidine solution was worked up in the usual manner, yielding an oil which on crystallization from hexane gave 0.12 g. (59%) of crystals melting at 142–160° (Found: Br, 20.57) and showed a single maximum at 255 mu, characteristic for Δ^1-2-bromo-3-keto steroids (10). Complete purification could be accomplished only by chromatographing and entailed considerable loss of material. The analytical sample crystallized from hexane-acetone as colorless, prismatic needles of m.p. 175–177°, $[\alpha]_D^{25}$ +84.9°. The ultraviolet absorption spectrum exhibited a maximum at 256 mu, log E 3.84 and a minimum at 215 mu, log E 3.30.

Anal. Calc'd for $C_{19}H_{25}BrO_2$: C, 62.47; H, 6.90; Br, 21.88.
Found: C, 62.40; H, 6.92; Br, 21.68.

1,4-Androstadiene-3,17-dione (IX). When 1 g. of the 2,4-dibromo derivative (unrecrystallized) was refluxed with 4 cc. of collidine for one-half hour, 0.95 g. of collidine hydrobromide was formed. Since this was in excess of the theoretical amount (0.905 g.) for two moles of hydrogen bromide, it afforded further indication that small amounts of tribromo derivative are formed during the dibromination. The collidine filtrate was worked up as usual (including chromatography, see ref. 15) and afforded 54% of crude crystalline material of m.p. 104–126°, maximum at 244 mu, which could be used for the dienone-phenol rearrangement. The compound had a great tendency to oil out, but the analytical sample was obtained as large, colorless rectangular plates on careful cooling of a hexane-acetone solution; m.p. 140–141°, $[\alpha]_D^{25}$ +118.8°. Inhoffen and co-workers (8) prepared this compound in 56% yield by Oppenauer oxidation of 1,4-androstadien-17-ol-3-one and reported m.p. 139–140°, $[\alpha]_D^{24}$ +115.8° (chloroform). The present synthesis is superior in terms of availability of starting material, over-all yield, and number of steps.

Anal. Calc'd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51.
Found: C, 80.15; H, 8.36.

Δ^4-2-Bromoandrostene-3,17-dione (XI). Previous reports (10, 14) have shown that the bromine atom at C-4 of 2,4-dibromo-3-keto *allo*steroids can be removed selectively in the form of hydrogen bromide by short collidine treatment. This has been applied to 2,4-dibromoandrostane-3,17-dione (VIII) as additional proof of structure.

After refluxing 1.5 g. of VIII in 6 cc. of collidine for thirty seconds, the collidine hydrobromide was filtered (0.98 g., equivalent to 1.45 moles of hydrogen bromide), the collidine filtrate was diluted with ether, washed with acid, and the ether dried and evaporated. The nearly colorless residue was recrystallized several times from a mixture of hexane and acetone to give 39% of rosettes of thin needles with m.p. 167–168° (dec.), $[\alpha]_D^{25}$ +170°, maximum at 243 mu, log E 4.07.

Anal. Calc'd for $C_{19}H_{25}BrO_2$: C, 62.47; H, 6.90; Br, 21.88.
Found: C, 62.35; H, 6.77; Br, 22.58.

Debromination of Δ^4-2-bromoandrostene-3,17-dione (XI). Debromination was accomplished by treating 150 mg. of the unsaturated bromo derivative XI in 10 cc. of acetone with 6 cc. of chromous chloride solution (19) for two hours in a carbon dioxide atmosphere. After dilution with water and extraction with ether, there was obtained 70 mg. (57%) of bromine-free, colorless crystals of m.p. 168–170°, $[\alpha]_D^{27}$ +186.5°, which gave no depression in melting point on admixture with authentic Δ^4-androstene-3,17-dione (XII) (m.p. 170–171°).

1-Methylestrone (Va). (a) *With sulfuric acid.* A solution of 200 mg. of 1,4-androstadiene-3,17-dione (m.p. 138–140°) in 7 cc. of acetic anhydride was treated with one drop (25 mg.) of concentrated sulfuric acid and the light tan colored solution was allowed to stand at room temperature for five hours. Water was added to hydrolyze the acetic anhydride, the oily acetate was extracted with ether, washed with sodium hydroxide and water, and the ether was evaporated. The oil was refluxed for one hour with 500 mg. of potassium hydroxide and 10 cc. of methanol and acidified with 5% aqueous hydrochloric acid. The pale yellow crystals were filtered and dried; yield 80 mg. (40%), m.p. 235–242°, $[\alpha]_D^{25}$ +266°. Recrystallization from ethanol gave colorless needles with m.p. 249–251°, $[\alpha]_D^{25}$ +271.6°. The absorption spectrum was practically identical with that of 1-methylestradiol (2,16), maximum at 282.5 mu, log E 3.37, minimum at 249 mu, log E 2.15. Inhoffen and Zuehlsdorff (2) reported m.p. 247–249° for 1-methylestrone, but gave no details as to yield, analysis etc..

Anal. Calc'd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51.

Found: C, 80.29; H, 8.66.

(b) *With p-toluenesulfonic acid.* This catalyst has already been found useful in a similar rearrangement in the chrysene series (7). One-hundred milligrams of IX in 5 cc. of acetic anhydride was warmed for four and one-half hours on the steam-bath with 30 mg. of *p*-toluenesulfonic acid and then worked up as in (a), yielding 80 mg. (80%) of 1-methylestrone with m.p. 231–240°. One recrystallization sufficed to give pure material. When carried out at room temperature, the yield was reduced to 60 mg. of inferior product (m.p. 217–229°, $[\alpha]_D^{25}$ +233°).

1-Methylestrone methyl ether (Vb). The methylation was carried out in alcoholic solution as described for similar compounds (2,15) and the methyl ether was recrystallized from hexane; m.p. 117–118°, $[\alpha]_D^{25}$ +297°. As was to be expected the absorption spectrum was very similar to that of 1-methylestrone.

Anal. Calc'd for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78.

Found: C, 80.63; H, 8.86.

Reduction of 1-methylestrone (Va) *to 1-methylestradiol* (I). A solution of 0.5 g. of the ketone Va in 100 cc. of anhydrous ether was added over a period of ten minutes to a previously prepared solution (20) of excess lithium aluminum hydride (0.7–0.8 g.) in 40 cc. of ether, and the mixture was warmed for a few minutes. After decomposition with water and addition of acid, the ether layer was separated, washed, dried and evaporated, yielding 0.5 g. of crude material of m.p. 226–230°. Recrystallization from a mixture of hexane and acetone gave 0.44 g. (88%) of 1-methylestradiol with m.p. 233–236°, undepressed on admixture with an authentic specimen (3).

SUMMARY

1. The dibromination of androstane-3,17-dione has been shown to proceed through a 2,2-dibromo derivative VII to the 2,4 isomer VIII. A number of transformations involving these dibromo ketones are described and a satisfactory preparative method for 1,4-androstadiene-3,17-dione is given.

2. In contrast to the usual dienone-phenol rearrangements of steroid dienones in acetic anhydride-sulfuric acid solution, it was noted that such treatment results in considerable sulfonation (evidently at C-16) when applied to 1,4-androstadiene-3,17-dione.

3. The preparation of 1-methylestrone (by a modified dienone-phenol rearrangement) and of 5-methyldoisynolic acid is described. These compounds are inactive estrogenically and the significance of these findings is discussed briefly.

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