group substances reflects a highly-branched structure with a portion made up either of carbohydrate residues resistant to periodate or of amino acids in peptide linkage or both. Such a highly-branched structure with a periodate-resistant region is rendered more likely by the behavior of the polyalcohols to acid. A linear polysaccharide, after about half of its sugar residues had been attacked by periodate, would be expected to become mostly dialyzable after reduction and exposure to acid if the periodate-sensitive residues were randomly dispersed. This does not happen. After exposure of the polyalcohols to acid, there are substantial amounts of non-dialyzable hexosamine and galactose, in addition to amino acids.

The high reducing sugar values of the five blood group substances before hydrolysis are apparently not a reflection of free reducing ends in the molecule. Borohydride reduction does not lower these values appreciably (Table I). They could be caused by the splitting of some alkali-labile bonds under the conditions of the reducing sugar assay. On the other hand, the lowering of the PI values by borohydride and by periodate treatment could be explained by the presence of some free reducing ends.

It has been previously established[30] that on mild acid hydrolysis and dialysis the glucosamine:galactosamine ratio in the dialyzate was 2 to 4 for blood group A subtance, 13 to 14 for O(H) substance and only glucosamine was split off from human B substance. From these ratios it can be seen that relatively more galactosamine was split off from A, less from O(H) and no galactosamine from blood group B substance. With the blood group A substances from both human and hog sources a greater percentage of the galactosamine was destroyed by periodate than with the hog mucin preparation (A + O(H)) and very little of the galactosamine was destroyed in the hog O(H) and human B substances. Therefore, for galactosamine there appears to be a rough correlation between dialyzability on mild acid hydrolysis and periodate sensitivity on the one hand and non-dialyzability (acid stability) and periodate resistance on the other.

Except for hog 39C(A), the amount of formic acid liberated on exposure to periodate is just slightly less than the amount of fucose destroyed. Since terminal non-reducing fucose is the only form of fucose which could liberate formic acid, this means that, if no acid is produced by oxidation of galactose, most of the fucose could be terminal and non-reducing. However some β-linked terminal galactose is known to be present since blood group substances cross react with type XIV anti-pneumococcal sera[31,32] before but not after treatment with *Cl. tertium* enzymes[33] which split off about 1 to 2% of the blood group substances as free galactose.

In addition, coffee bean α-galactosidase split off about 5% of Beach (B) as free galactose.[34] Thus an amount of fucose, equivalent to the terminal galactose, could then be non-terminal.

Although almost all of the fucose is periodate sensitive in all the preparations studied, fucosyl-(1→3)-fucose was isolated[19] by mild acid hydrolysis from blood group B substance (Beach). The amount isolated, 7 mg., represented only 0.4% of the dialyzable components and only 0.06% of the original blood group substance before hydrolysis. This amount of material is not determinable in the intact polymer by the analytical methods available.

(30) S. Leskowitz and E. A. Kabat, *J. Am. Chem. Soc.*, **76**, 5060 (1954).

(31) E. A. Kabat, A. Bendich, A. E. Bezer and V. Knaub, *J. Exptl. Med.*, **87**, 295 (1948).

(32) P. Z. Allen and E. A. Kabat, *J. Immunol.*, **82**, 358 (1959).

(33) C. Howe, G. Schiffman, A. E. Bezer and E. A. Kabat, *J. Am. Chem. Soc.*, **80**, 6656 (1958).

(34) M. L. Zarnitz and E. A. Kabat, *J. Am. Chem. Soc.*, **82**, 3953 (1960).

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE, RENSSELAER, N. Y.]

Some Reactions of 2-Hydroxytestosterone and its Diacetate. II

BY ROBERT L. CLARKE

RECEIVED SEPTEMBER 1, 1961

The rearrangement of 2α-hydroxytestosterone (Ic) and its diacetate Ib to 2-methoxy-4-methyl-1,3,5(10)-estratrien-17β-ol (IIIa) is described. The structure of IIIa was proved by degradation to 4-methyl-1,3,5(10)-estratrien-17β-ol (IVb), by synthesis from 17β-hydroxy-2-methoxy-1,4-androstadien-3-one (V) and by n.m.r. characteristics. A mechanism for the rearrangement is suggested.

The rearrangement of 2β-hydroxytestosterone diacetate (Ia) by means of *p*-toluenesulfonic acid (tosyl acid) in boiling methanol to form 17β-hydroxyandrostane-3,6-dione (II) (51% yield) has been described recently.[1] The present paper describes the rearrangement of 2α-hydroxytestosterone (Ic) and its diacetate Ib under the same conditions to 2-methoxy-4-methyl-1,3,5(10)-estratrien-17β-ol (IIIa), m.p. 114.5–116°, in 24 and 11% yields, respectively. A 6% yield of the dione II was also isolated from the rearrangement of Ic.

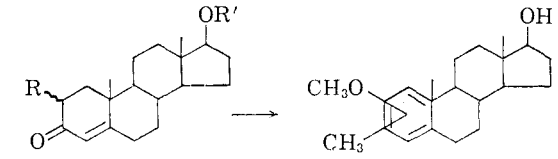
It was initially believed that the methoxyaromatic product (called III) from the rearrangement was the result of dehydration of Ic to produce a 1,4-dien-3-one which underwent a dieneone–phenol type of rearrangement[2] followed by etherification. The expected products, 1-methoxy-4-methyl-1,3,5-(10)-estratrien-17β-ol[3] and possibly 3-methoxy-1-methyl-1,3,5(10)-estratrien-17β-ol,[4] were synthe-

(1) R. L. Clarke, *J. Am. Chem. Soc.*, **82**, 4629 (1960).

(2) *Cf.* C. Djerassi, G. Rosenkranz, J. Romo, J. Pataki and St. Kaufmann, *ibid.*, **72**, 4540 (1950).

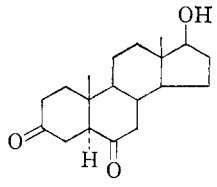
(3) R. M. Dodson and R. D. Muir, *ibid.*, **80**, 5004 (1958).

(4) V. Petrow and I. A. Stuart-Webb, British Patent 807,225, Jan. 14, 1959.



Ia, R = β-OAc, R′ = Ac
b, R = α-OAc, R′ = Ac
c, R = α-OH, R′ = H

IIIa, 2-OCH_3, 4-CH_3
b, 2-OCH_3, 3-CH_3
c, 2-OCH_3, 1-CH_3
d, 3-OCH_3, 2-CH_3
e, 3-OCH_3, 4-CH_3
f, 4-OCH_3, 1-CH_3



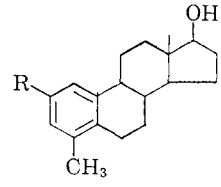
II

sized. Although they melted at 112.5–115.5° and 118–120°, respectively, each was different from the rearrangement product as evidenced by mixture melting point and infrared spectral comparison.

The ultraviolet spectrum of III [λ_{max}^{EtOH} 278 mμ (ε 2180), 285 mμ (ε 2150)] appeared to preclude the presence of two substituents *ortho* to the methoxyl group and to require the presence of a *p*-substituent.[5]

With the assumption that the C-10-methyl group was still attached to the A-ring, the above information narrowed the choices for the methoxyaromatic structure to six, *i.e.*, IIIa through IIIf. Attempts to gain further information by exhaustive oxidation (alkaline permanganate) of III to the corresponding known anisoletricarboxylic acids failed.[6]

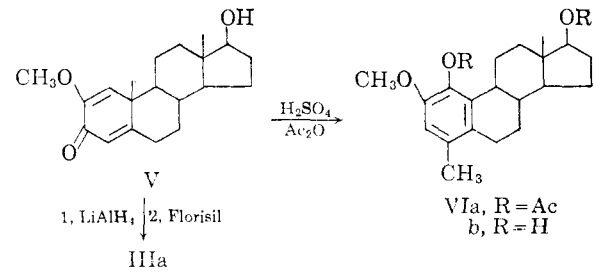
Cleavage of the methoxyl group of III with pyridine hydrochloride furnished a phenolic product, m.p. 257–259° (70% yield), shown below to be 4-methyl-1,3,5(10)-estratriene-2,17β-diol (IVa).[7] The phenolic group was then removed by sodium–am-



IVa, R = OH
b, R = H

monia reduction of the phosphate ester[8] furnishing 4-methyl-1,3,5(10)-estratrien-17β-ol (IVb).[9] This IVb proved to be identical with a sample of IVb prepared by the dienol–benzene rearrangement[9] of 17β-hydroxy-1,4-androstadien-3-one as evidenced by mixture melting point and infrared and ultraviolet spectral comparison. The presence of a C-4 methyl group eliminated structures IIIb, c, d and f.

Of structures IIIa and IIIe, the former was favored on mechanistic grounds. One attempt to prepare IIIa involved a dienone–phenol rearrangement[2] of 17β-hydroxy-2-methoxy-1,4-androstadien-3-one[10](V) to form 2-methoxy-4-methyl-1,3,5(10)-estratriene-1,17β-diol diacetate[11](VIa), m.p. 135–137°, followed by hydrolysis to the diol VIb. Attempts to remove the hindered phenolic hydroxyl group by the Kenner–Williams technique[8] were unsuccessful, probably due to failure of phosphate ester formation. Only starting material was recovered (82% crude and 54% purified).



V

1, $LiAlH_4$ | 2, Florisil

IIIa

VIa, R = Ac
b, R = H

The dienone V was converted to IIIa by the dienol–benzene rearrangement.[9] When the product of the reduction step was treated with hydrochloric acid to effect the rearrangement, no IIIa was isolated, possibly due to enol ether hydrolysis. However, when the reduction product was chromatographed on Florisil, a normal rearrangement occurred in 61% yield.[12] It would be extremely difficult to visualize the formation of structure IIIe from this reaction, whereas IIIa is the expected product.

Additional proof was furnished by the n.m.r. spectrum[13] of this methoxy-aromatic compound.

(5) A. Buraway and J. T. Chamberlain, *J. Chem. Soc.*, 2310 (1952), reported a series of methylated anisoles wherein those compounds with two *ortho* substituents showed λ_{max}^{EtOH} 265–271 mμ (ε 300–600) and occasionally a second peak at 277–278 mμ (ε 500–575). Those compounds with a single *o*-methyl or *m*-methyl or two *m*-methyl groups showed λ_{max}^{EtOH} 271–272 mμ (ε 1700) and 277–280 mμ (ε 1650–1725). *p*-Methylanisole, however, showed λ_{max}^{EtOH} 278 mμ (ε 2100) and 285 mμ (ε 1800).

(6) Similar difficulty with the oxidation of 3-methoxy-1-methyl-10-nor-1,3,5(10)-cholestatriene was encountered by A. L. Wilds and C. Djerassi, *J. Am. Chem. Soc.*, **68**, 1712 (1946).

(7) Recently reported by H. Dannenberg, D. Dannenberg von Dresler and T. Köhler, *Chem. Ber.*, **93**, 1989 (1960), from 2-amino-4-methyl-1,3,5(10)-estratrien-17-one by treatment with nitrous acid followed by reduction at C-17. These authors also accomplished the presently reported cleavage of IIIa to IVa. For details, see footnote 12.

(8) W. G. Kenner and N. R. Williams, *J. Chem. Soc.*, 522 (1955).

(9) N. L. Gentles, J. B. Moss, H. L. Herzog and E. B. Hershberg, *J. Am. Chem. Soc.*, **80**, 3702 (1958).

(10) J. S. Baran, *ibid.*, **80**, 1687 (1958).

(11) The evidence for assignment of structure VIa to the rearrangement product is presumptive and based on the fact that the presence of a methyl or a chlorien atom at C-2 [*cf.* D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 788 (1959)] or a bromine atom at C-2 [*cf.* C. Djerassi and C. R. Scholz, *J. Am. Chem. Soc.*, **70**, 1911 (1948)] does not affect the normal course of the reaction.

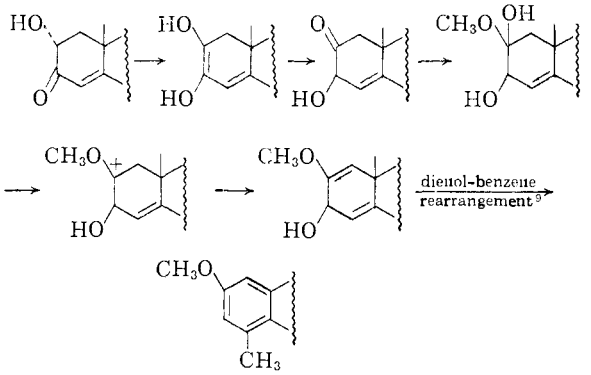
(12) H. Dannenberg, *et al.* (see footnote 7 for ref.), have reported this reaction wherein they effected the rearrangement with hydrochloric acid instead of Florisil. The methoxyaromatic product IIIa was isolated in very low yield, melted at 63–64° (*vs.* 114.5–116° reported here) and gave poor analytical values. Their reported melting point for the acetate of IIIa (104°) does correspond to the melting point of the IIIa acetate reported here (105–106°). No optical rotations were given for comparison but the ultraviolet absorption values are in agreement.

Cleavage of the methoxyl group of IIIa (using an oily fraction) was also reported by Dannenberg, *et al.*, to give a small amount of 4-methyl-1,3,5(10)-estratrien-2,17β-diol (IVa) of m.p. 249–250° (uncor.), λ_{max}^{EtOH} 281 mμ (ε 2210) which corresponds with the m.p. of 257–259° (cor.), λ_{max}^{EtOH} 281 mμ (ε 2100) and 286 mμ (ε 2100), reported here for that compound.

(13) The spectrum was recorded on a 20% solution of the compound in carbon disulfide in a spectrometer operated at 40 Mc. by Dr. W. S. Johnson and Mr. K. Williamson to whom we extend our appreciation.

The spectrum showed a quartet of bands in the aromatic proton region (−252 c.p.s. with reference to tetramethylsilane) with the center two bands more intense than the outer two (ratio 1.3/2.0/2.1/1.0) and a coupling constant of 2. It has been shown[14] that the coupling constant for *meta*-oriented protons as present in IIIa lies in the 1.2–2.7 c.p.s. range. The alternate structure IIIe with its *ortho*-related aromatic protons should have shown a coupling constant of about 8.[14]

The mechanism for the formation of the methoxyaromatic compound IIIa from Ib and Ic is somewhat obscure. A 1,4-dien-3-one intermediate is discounted both on the basis of the fact that this system should lead to the wrong product and that such a system is stable to the reaction conditions present. For example, 17β-hydroxy-1,4-androstadien-3-one was unaffected by refluxing it with methanol in the presence of tosyl acid for 15 hours. The methoxyl group is not formed as a last stage in the rearrangement, *i.e.*, from 4-methyl-1,3,5(10)-estratriene-2,17β-diol (IVa), for the reaction conditions are not suitable. For example, estrone was recovered unchanged from this rearrangement environment. One possible reaction course is shown below. Perhaps the direction which the rearrangement of compound I takes is related to the direction of enolization, *i.e.*, if the 2-substituent is β-oriented enolization gives the 4,6-diene and the final product II,[1] whereas if it is α-oriented enolization gives predominantly a 2,4-diene and a methoxyaromatic product is formed. So many by-products of unknown nature were present that such generalizations are hazardous.



As in the rearrangement of the 2β-epimer,[1] the rate of rearrangement of Ic is dependent upon the concentration of tosyl acid. A solution of Ic with 1/80 of its weight of tosyl acid in methanol at reflux gave a 5% yield of IIIa, a 1.2% yield of dione II and 68% crude recovered starting material (41% when purified). Use of 1/8 as much tosyl acid as Ic gave a 24% yield of IIIa, a 6% yield of dione II,[15] and no starting material was isolated. Use of equal weights of Ic and tosyl acid gave a 36% yield of IIIa which melted somewhat low (110–114°) and was difficult to purify further.

(14) H. S. Gutowsky, C. H. Holm, A. Saika and G. A. Williams, *J. Am. Chem. Soc.*, **79**, 4596 (1957).

(15) This product may have resulted from epimerization of the 2-substituent in the starting material to the β-configuration under the reaction conditions followed by 2 → 6-rearrangement. It is not believed to have arisen from the β-epimer as an impurity in the starting material.

Compound IIIa formed an acetate of m.p. 105–106°. Oxidation of compound IIIa with chromic acid gave 2-methoxy-4-methyl-1,3,5(10)-estratrien-17-one, m.p. 136–137°.

2,17β-Dihydroxy-1,4-androstadien-3-one diacetate was rearranged by sulfuric acid in acetic anhydride to form 4-methyl-1,3,5(10)-estratriene-1,2,17β-triol triacetate. The assignment of structure to the rearrangement product was based on analogy with the formation of VIa from V. Hydrolysis of this triacetate gave the corresponding triol.

Experimental[16]

Rearrangement of 2α-Hydroxytestosterone.—A mixture of 21.3 g. (0.07 mole) of 2α-hydroxytestosterone, m.p. 165–168°, 2.7 g. of anhydrous *p*-toluenesulfonic acid and 350 ml. of methanol was refluxed for 15 hr. The solvent was removed and the residue dissolved in 35 ml. of methylene dichloride. This solution was diluted with 400 ml. of ether, washed with 2 *N* sodium hydroxide, then with saturated salt solution and dried over potassium carbonate. The solvent was removed and the oily residue chromatographed on 400 g. of silica gel in 1.5:3:5.5 methylene dichloride–ether–pentane. Elution of the column with 3:7 ether–pentane quickly removed **2-methoxy-4-methyl-1,3,5(10)-estratrien-17β-ol** (IIIa) which, after two recrystallizations from hexane, amounted to 4.93 g. (24% yield), m.p. 114.5–116°, $[\alpha]^{25}D$ +123° (1% in $CHCl_3$), λ_{max}^{EtOH} 285 mμ (ε 2150) and 278 mμ (ε 2180) with a shoulder at 222 mμ (ε 9450).

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 80.2; H, 9.6.

Elution of the column with 100% ether afforded 1.3 g. (6%) of 17β-hydroxyandrostane-3,5-dione (II), m.p. 235–240°, which was identified by mixture melting point and infrared spectral comparison with an authentic sample.[1]

Rearrangement of 2α-hydroxytestosterone diacetate was carried out under conditions identical with those for the rearrangement of 2α-hydroxytestosterone and with the same molar proportions of reactants. The product, isolated in 11% yield, melted at 114–115° and showed no depression in melting point upon admixture with the above rearrangement product. The infrared spectra of the two samples were identical.

3-Methoxy-1-methyl-1,3,5(10)-estratrien-17β-ol.[4]—A mixture of 1.86 g. of 1-methylestradiol,[3] 25 ml. of absolute ethanol, 0.83 ml. of dimethyl sulfate and 0.7 g. of sodium methoxide was refluxed for 2 hr., cooled and poured into 300 ml. of water. The ethanol was removed by warming the mixture *in vacuo* and the resulting aqueous mixture was extracted with ether. The ether extract was washed with dilute sodium hydroxide solution and dried over sodium sulfate. Removal of the ether gave an oily residue which was chromatographed on 100 g. of silica gel in 3:7 ether–pentane. The 0.85 g. of desired methyl ether obtained was recrystallized from 6 ml. of hexane to give 0.75 g. of white needles, m.p. 118–120°, $[\alpha]^{25}D$ +154° (1% in $CHCl_3$), λ_{max}^{EtOH} 280 mμ (ε 1600) and 288 mμ (ε 1600) with a shoulder at 222 mμ (ε 9600). This material melted at 84–103° upon admixture with IIIa of m.p. 114.5–116°.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39; OCH_3, 10.33. Found: C, 79.8; H, 9.6; OCH_3, 10.5.

4-Methyl-1,3,5(10)-estratriene-2,17β-diol (IVa).—An intimate mixture of 2.0 g. of IIIa, m.p. 114.5–116°, and 16 g. of pyridine hydrochloride was heated at 165° for 5 hr., cooled and treated with 200 ml. of water. The insoluble solid was collected (1.9 g.) and chromatographed on 100 g. of silica gel. Development of the column with 7:3 ether–pentane and finally with pure ether gave compound IVa which, after two recrystallizations from acetonitrile, melted at 257–259° (1.34 g., 70% yield), $[\alpha]^{25}D$ +50.1° (1% in pyridine), λ_{max}^{EtOH} 281 mμ (ε 2100), 286 mμ (ε 2100), 220 mμ shoulder (ε 7900). The melting point was not raised by two further recrystallizations.

Anal. Calcd. for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.6; H, 9.1.

(16) All melting points are corrected. The silica gel used for chromatography was 100–200 mesh obtained from the Davison Co., Baltimore, Md.

4-Methyl-1,3,5(10)-estratriene-2,17β-diol 2-Diethylphosphate.—A partial solution of 1.04 g. of 4-methyl-1,3,5(10)-estratriene-2,17β-diol, m.p. 248–255°, in 10 ml. of carbon tetrachloride and 10 ml. of pure dioxane was treated with 0.54 ml. of diethyl phosphite, b.p. 67.5–68.5° (6 mm.), and 0.57 ml. of triethylamine and the mixture was shaken for 16 hr. at room temperature. The steroid dissolved and triethylamine hydrochloride precipitated. The solvent was removed by warming *in vacuo* and the residue was partitioned between water and ether. The ether layer was separated, washed once with 2 *N* hydrochloric acid, three times with 2 *N* sodium hydroxide, once with saturated salt, and dried over potassium carbonate. Removal of the solvent gave the desired ester as an oil which was used without further purification.

4-Methyl-1,3,5(10)-estratrien-17β-ol[9] **(IVb).**—The oily phosphate ester described immediately above was dissolved in 40 ml. of tetrahydrofuran and 60 ml. of liquid ammonia was added. Addition of 0.25 g. of sodium with stirring resulted in the formation of a permanent blue color within 2 min. The solution was stirred for 5 min., 2 ml. of absolute ethanol was added and the ammonia was allowed to evaporate from the now colorless solution. Water (20 ml.) was added and the tetrahydrofuran was removed by warming *in vacuo*. The aqueous suspension remaining was extracted twice with ether and the ether extracts were washed twice with saturated salt solution and dried over potassium carbonate. Evaporation of the ether gave an oil which was dissolved in 5% ether–95% pentane and put on 60 g. of silica gel. Elution with this same solvent mixture followed by 10% ether–90% pentane afforded the desired product. One recrystallization from methanol gave 0.35 g. (36% yield) of needles which were opaque after drying for 5 hr. at 55° (10 mm.) (apparent loss of solvent), m.p. 110–113°. Two further recrystallizations from methanol and drying gave a sample, m.p. 114–115.5°, $[\alpha]^{25}D$ +59° (1% in dioxane), the melting point of which was undepressed upon admixture with a sample described immediately below. The infrared spectra of the two materals were identical.

4-Methyl-1,3,5(10)-estratrien-17β-ol[9] **(IVb) from 17β-hydroxy-1,4-androstadien-3-one.**—To a solution of 1.5 g. of lithium aluminum hydride in 50 ml. of ether was added dropwise with stirring at room temperature a solution of 1.0 g. of 17β-hydroxy-1,4-androstadien-3-one, m.p. 169–171.5°, in 100 ml. of ether over a period of 30 min. The mixture was then refluxed with stirring for 2 hr., 10 ml. of water was added dropwise and the now granular inorganic salts were removed by filtration. The filtrate was washed twice with saturated salt solution and dried over sodium sulfate. Removal of the solvent gave a solid residue which was chromatographed on 70 g. of Florisil in 1:1:3 ether–methylene dichloride–pentane. The product was recrystallized four times from methanol and dried for 6 hr. at 78° (10 mm.). The resulting opaque needles melted at 114.5–116° (0.30 g., 32% yield), $[\alpha]^{25}D$ +60.5° (1% in dioxane) [reported[9] m.p. 113–114°, $[\alpha]^{25}D$ +64° (dioxane)].

Anal. Calcd. for $C_{19}H_{26}O$: C, 84.39; H, 9.69. Found: C, 84.1; H, 9.8.

2-Methoxy-4-methyl-1,3,5(10)-estratriene-1,17β-diol Diacetate (VIa).—A suspension of 2.23 g. of the enol methyl ether V,[10] m.p. 216–220°, in 50 ml. of acetic anhydride was treated with 0.5 g. of concentrated sulfuric acid. The suspension was shaken for 10 min. to effect solution and the solution allowed to stand at room temperature for 3.5 hr. The solution was poured into 1 l. of water and the product extracted with three portions of methylene chloride. The extracts were washed with saturated sodium bicarbonate and water, dried over potassium carbonate and concentrated *in vacuo* to a residue. The residue was chromatographed on 60 g. of silica gel in 1:4 ether–pentane; this solvent mixture rather quickly eluting the desired product. This product was recrystallized from 4 ml. of methanol to give 1.56 g. of white, massive prisms, m.p. 130–136.5°. Two further recrystallizations gave 1.1 g. (49% yield) of m.p. 135–137°, $[\alpha]^{25}D$ +104.4° (1% in $CHCl_3$), unchanged by further recrystallization.

Anal. Calcd. for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05; OCH_3, 7.75. Found: C, 72.3; H, 8.1; OCH_3, 7.9.

2-Methoxy-4-methyl-1,3,5(10)-estratriene-1,17β-diol (VIb).—The diacetate VIa (5.8 g.), m.p. 134.5–137°, was refluxed with a mixture of 2.9 g. of potassium hydroxide, 8 ml. of water and 75 ml. of methanol for 1.5 hr. The solution was cooled, treated with 2 ml. of glacial acetic acid and concentrated to a residue *in vacuo*. The residue was partitioned between ether and water, the layers separated, and the ether layer washed with saturated sodium bicarbonate solution, then with saturated salt solution and dried over sodium sulfate. Removal of the ether gave a solid residue which was recrystallized once from ethyl acetate to furnish 3.35 g. (73% yield) of nearly white solid, m.p. 174.5–176°, $[\alpha]^{25}D$ +165.0° (1% in $CHCl_3$), λ_{max}^{EtOH} 288 mμ (ε 2600). Further recrystallization failed to change the melting point significantly.

Anal. Calcd. for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.7; H, 8.7.

2-Methoxy-4-methyl-1,3,5(10)-estratrien-17β-ol (IIIa) from 17β-Hydroxy-2-methoxy-1,4-androstadien-3-one (V).—To a stirred solution of 2.0 g. of lithium aluminum hydride in 100 ml. of tetrahydrofuran was added in 10 min. a solution of 1.5 g. of 17β-hydroxy-2-methoxy-1,4-androstadien-3-one, m.p. 215–218.5°, in 85 ml. of tetrahydrofuran. The mixture was refluxed for 1 hour, cooled, treated with 5 ml. of water and filtered. Solvent was removed from the filtrate *in vacuo* and the residual oil was chromatographed on 100 g. of Florisil in 3:7 ether–pentane. The desired methoxyaromatic product came off the column first and was recrystallized once from hexane to give 0.87 g. (61% yield) of needles, m.p. 113–114.5°. This material showed no depression in melting point upon admixture with a sample of compound IIIa, m.p. 113.5–115°, prepared by acid rearrangement of Ic and the infrared spectra of the two samples were identical.

2-Methoxy-4-methyl-1,3,5(10)-estratrien-17β-ol Acetate.[12]—2-Methoxy-4-methyl-1,3,5(10)-estratrien-17β-ol (0.87 g.) was heated for 1.5 hr. with 2 ml. of acetic anhydride and 4 ml. of pyridine. The solution was cooled, poured into water and the precipitated solid was collected and air-dried. Two recrystallizations from methanol furnished 0.72 g. of white needles, m.p. 105–106°, $[\alpha]^{25}D$ +38.4° (1% in $CHCl_3$).

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83; OCH_3, 9.06. Found: C, 77.1; H, 8.8; OCH_3, 9.1.

2-Methoxy-4-methyl-1,3,5(10)-estratrien-17-one.—A solution of 1.51 g. of the trien-17β-ol IIIa, m.p. 114–115.5°, in 65 ml. of benzene was shaken for 15 min. with 6.5 ml. of chromic acid solution.[17] Ether was added, the layers were separated and the ether layer was washed with water, with saturated sodium bicarbonate solution and dried over sodium sulfate. Removal of the ether gave an oily residue which was chromatographed on 60 g. of silica gel in 1:4 ether–pentane. The desired ketone, which was eluted rapidly, was recrystallized twice from ether–pentane to give 0.7 g., m.p. 136–137° (unchanged upon further recrystallization), $[\alpha]^{25}D$ +112.7° (1% in $CHCl_3$), λ_{max}^{EtOH} 279 mμ (ε 2000) and 284 mμ (ε 2000) with a shoulder at 222 mμ (ε 8700).

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78; OCH_3, 10.40. Found: C, 80.8; H, 8.5; OCH_3, 10.4.

4-Methyl-1,3,5(10)-estratriene-1,2,17β-triol Triacetate.—Treatment of a suspension of 1.0 g. of 2,17β-dihydroxy-1,4-androstadien-3-one diacetate,[10] m.p. 207–209°, in 25 ml. of acetic anhydride with a solution of 0.5 g. of concentrated sulfuric acid in 5 ml. of acetic anhydride with stirring caused immediate solution of the steroid. After the solution had stood for 4.5 hr. at room temperature, it was poured into 400 ml. of water with stirring. The precipitated solid was filtered and air-dried to give 1.04 g., m.p. 170–174°. Two recrystallizations of the product from methanol furnished 0.96 g. (86% yield) of white plates, m.p. 176–177°, $[\alpha]^{25}D$ +94.4° (1% in $CHCl_3$), λ_{max}^{EtOH} 269 mμ (ε 530) and 276 mμ (ε 520), λ_{max}^{KBr} 5.63-(vs) and 5.76(s) μ.

Anal. Calcd. for $C_{25}H_{32}O_6$: C, 70.07; H, 7.53. Found: C, 70.2; H, 7.4.

4-Methyl-1,3,5(10)-estratriene-1,2,17β-triol.—To a suspension of 14.0 g. of 4-methyl-1,3,5(10)-estratriene-1,2,17β-triol triacetate, m.p. 175.5–178°, in 300 ml. of methanol was added a solution of 13.1 g. of potassium hydroxide

(17) Prepared from 84 g. of sodium dichromate dihydrate, 63 ml. of acetic acid, 114 ml. of concentrated sulfuric acid and 372 ml. of water.

(assay 85%) in 65 ml. of water. The system was flushed with nitrogen and the mixture was heated under reflux for 2 hours. The resulting solution was cooled, treated with 13 ml. of acetic acid and concentrated by warming *in vacuo*. Recrystallization of the residual solid from methanol four times afforded 4.8 g. (50% yield) of needles which melted with gas evolution when immersed at 150°, resolidified and then melted at 209–211°. The sample was dried at 110°-(10 mm.) for 8 hr. whereupon it melted at 210–212° without prior change; $[\alpha]^{25}D$ +167.6° (1% in $CHCl_3$).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67; neut. equiv., 302. Found: C, 75.5; H, 8.8; neut. equiv., 294.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF WISCONSIN, MADISON 6, WIS.]

Cyclitols and their Methyl Ethers. III. Catalytic Air Oxidation, the Hydrogenolysis of Inososes, and Some Pentol and Tetrol Methyl Ethers[1–3]

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L-Inositol, D-inositol and four inositol methyl ethers were oxidized by treatment, in solution, with air or oxygen and a platinum catalyst. In all cases, only axial hydroxyl groups were oxidized. Only monoketones (inososes) were obtained from the cyclitols with two axial hydroxyl groups (D- and L-inositol and their methyl ethers, pinitol and quebrachitol), and where the two axial hydroxyls were unlike (pinitol and quebrachitol), one of these was oxidized to the exclusion of the other. Catalytic oxidation is a useful method for the small-scale preparation of inososes, of which several new examples are described. The inososes related to D- and L-inositol, in which an axial hydroxyl is adjacent to the keto group, gave unexpectedly complex mixtures under the conditions normally used for the hydrogenolysis of keto groups in cyclitols. The mixtures consisted of the two inositols resulting from simple reduction, the deoxy compound (quercitol) resulting from loss of the oxo-oxygen, and the cyclohexanetetrol resulting from loss of both the axial hydroxyl and the oxo-oxygen. Two *O*-methylcyclohexane-1,2,3,4-tetrols and three *O*-methylquercitols, the first examples of monomethyl ethers in each of the respective series, were characterized in the course of the present work.

Investigations of the catalytic oxidation of cyclitols were undertaken in our laboratory, and in that of S. J. Angyal at the University of New South Wales,[5] following the report by Heyns and Paulsen[6] that *myo*-inositol[7] (II) could be smoothly converted to *myo*-inosose-2 (*scyllo*-inosose, XXVIII) by this technique. In our work, we used procedures patterned after those described by Heyns[8,9]—agitation of an aqueous solution of the substance to be oxidized with air or oxygen, in the presence of a platinum catalyst, at temperatures up to 90°— and applied these to the optically active inositols (D and L) and to the readily available inositol methyl ethers. The results, together with those of a study of the hydrogenolysis reaction of inososes, are presented here. The establishment of the absolute configurations of the optically active *myo*-inositol monomethyl ethers, which was made possible by the availability of the catalytic oxidation procedure, is described in the accompanying paper.

Catalytic Oxidation.—In the catalytic conversion of *myo*-inositol to *myo*-inosose-2, oxidation takes place at the single axial hydroxyl which is present in the preferred chair conformation of the molecule,[10] and is essentially restricted to this hydroxyl. This result suggested that the catalytic oxidation of cyclitols might, like the well known oxidation by *Acetobacter suboxydans*,[10] be specific for axial hydroxyls. Inasmuch as experiment confirmed this suggestion, these hydroxyls will be the focus of the discussion which follows.

Most of the work with the optically active inositols was done with L-inositol (I), the more readily available of the two isomers. Oxidized solutions of this inositol treated with phenylhydrazine gave, in yields of 55–65%, an inosose phenylhydrazone, from which the free inosose was obtained by reaction with benzaldehyde in the usual way. The melting point of the phenylhydrazone, and the melting point and optical rotation of the inosose tentatively identified it as the *enantiomorph* VI of the known L-*myo*-inosose-1 [(+)-*vibo*-inosose], and this identification was confirmed by reducing the inosose to a mixture of L-inositol (I) and *myo*-inositol (II). Thus VI is a product of the oxidation of one of the two axial hydroxyls (positions 2 and 3, formula I)[10] of L-inositol, and, since these two hydroxyls are sterically equivalent, VI is the only monoketone which can be formed by the oxidation of one of them. The oxidation of D-inositol gave L-*myo*-inosose-1 as expected.

In (+)-pinitol (V) and quebrachitol (XIX), which are, respectively, 5-*O*-methyl-D-inositol and 1-*O*-methyl-L-inositol,[10] the axial hydroxyls (at positions 2 and 3, as in the parent compounds) are no longer sterically equivalent, because of their different relationships to the methyl groups. Each of these inositol methyl ethers could thus give rise to two different monoketones by oxidation at an axial hydroxyl. However, only one inosose was ob-

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(2) Paper II of this series: L. Anderson, Emily S. DeLuca, A. Bieder and G. G. Post, *J. Am. Chem. Soc.*, **79**, 1171 (1957).

(3) Part of this work was presented orally: L. Anderson and G. G. Post, *Abstracts 134th Natl. Meeting Am. Chem. Soc.*, 12D (1958).

(4) To whom requests for reprints should be sent.

(5) We are grateful to Prof. Angyal for his willingness to participate in a free exchange of information while this investigation was underway.

(6) K. Heyns and H. Paulsen, *Chem. Ber.*, **86**, 833 (1953).

(7) In this paper, cyclitols are named and numbered according to H. G. Fletcher, Jr., L. Anderson and H. A. Lardy, *J. Org. Chem.*, **16**, 1238 (1951). For inososes (pentahydroxycyclohexanones) and quercitols (pentahydroxycyclohexanes), the names suggested by S. J. Angyal, C. G. Macdonald and N. K. Matheson, *J. Chem. Soc.*, 686 (1952), are also given, in parentheses. The configurations of cyclohexane-1,2,3,4-tetrols are designated by the conventional "fractional" system. See also ref. 10.

(8) K. Heyns, *Ann.*, **558**, 177 (1947).

(9) K. Heyns and R. Heinemann, *ibid.*, **558**, 187 (1947).

(10) The literature relevant to this point is reviewed by S. J. Angyal and L. Anderson, *Adv. in Carbohydrate Chem.*, **14**, 135 (1959).