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THE PREPARATION OF A SERIES OF 3β-METHOXY-Δ⁵-STEROIDS[1]

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In 1949 Dr. H. C. Coggeshall and one of us submitted pregnanediol-3-glucuronide (sodium salt)[3] to clinical trial in rheumatoid arthritis. This was done with the view that the ameliorative action of steroids in the hypersensitivity diseases might be explained under the hypothesis that certain steroids, as glucuronides, function as carriers of "labile" glucuronic acid which may be biochemically donated to detoxify antigen-like or inflammation-producing substances. However, patients suffering from rheumatoid arthritis treated with sodium pregnanediol glucuronidate failed to give the clinical improvement elicited by cortisone. Reasoning that the glucuronide at C_3 of the steroid nucleus might not be utilizable in the predicated mechanism, we decided to block position C_3 on the steroid nucleus from metabolic change, with the hope of forcing glucuronide anabolism to the C_{20} portion of the molecule. For this, 20α-hydroxy-5-pregnen-3β-yl methyl ether (III) was at first chosen for clinical studies. This latter compound, however, was not easily synthesizable in yields sufficient for clinical study, and it was therefore decided to use the readily procurable pregnenolone methyl ether (I), which should, theoretically at least, serve in the human as a metabolic precursor of the desired pregnenediol methyl ether.[4] The authors have prepared 800 grams of pregnenolone methyl ether (1) for clinical experimentation in hypersensitivity disease.

20α-Hydroxy-5-pregnen-3β-yl methyl ether (III) was prepared in unsatisfying yield by the sodium-alcohol reduction of pregnenolone methyl ether (I). It is best obtained in this reaction by isolation as the acetate, followed by saponification. On the contrary, the C_{20} β-epimer in this group is readily obtained by the sodium borohydride reduction of pregnenolone methyl ether. The steric configuration of each of the C_{20} epimers was determined by conversion to the known 3,20-diacetate.

During the early course of this research our attention was drawn to the publication of Ishmael, Hellbaum, Kuhn, and Duffy (3) describing a beneficial effect of testosterone in rheumatoid arthritis. A personal communication with Dr. Ishmael brought out the desirability of having an androgen-like steroid which would possess the "anti-rheumatic" effect of testosterone without an undue amount of virilizing property. We therefore decided to prepare for Dr. Ishmael's clinical experimentation 17β-hydroxy-5-androsten-3β-yl methyl ether

[1] A portion of the experimentation described in this publication was done in the Department of Biochemistry of the Southwestern Medical School, Dallas, Texas.

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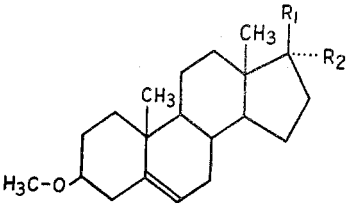
[3] Purchased from Ayerst, McKenna and Harrison, Ltd., Rouses Point, New York.

[4] None of our experimentation to date has served either to confirm or to deny the hypothesis of donation of glucuronic acid by steroids.

(VIII). Somewhat unexpectedly, however, this steroid is reported to possess to a striking degree the salt- and water-retaining effect often seen with pharmacodynamic doses of steroids.[5] We next prepared for the Ishmael group the previously known dehydroisoandrosterone methyl ether (4) (VI).[6]



(I) R_1 = $-\overset{\overset{O}{\|}}{C}-CH_3$; R_2 = H

(II) R_1 = $-\overset{\overset{H}{|}}{C}-CH_3$ (OAc); R_2 = H

(III) R_1 = $-\overset{\overset{H}{|}}{C}-CH_3$ (OH); R_2 = H

(IV) R_1 = $-\overset{\overset{OAc}{|}}{C}-CH_3$ (H); R_2 = H

(V) R_1 = $-\overset{\overset{OH}{|}}{C}-CH_3$ (H); R_2 = H

(VI) R_1+R_2 = O

(VII) R_1 = OAc; R_2 = H

(VIII) R_1 = OH; R_2 = H

(IX) R_1 = $-\overset{\overset{O}{\|}}{C}-CH_2OAc$; R_2 = H

(X) R_1 = $-\overset{\overset{O}{\|}}{C}-CH_3$; R_2 = OH

(XI) R_1 = OH; R_2 = CH_3

(XII) R_1 = OH; R_2 = CH_2-CH_3

(XIII) R_1 = OH; R_2 = $CH=CH_2$

(XIV) R_1 = OH; R_2 = $C\equiv CH$

(XV) R_1+R_2 = $CH-CH_2-O-CH_3$

(XVI) R_1 = OH; R_2 = CH_2-COOH

(XVII) R_1 = OH; R_2 = CH_2-CH_2OH

(XVIII) R_1 = OH; R_2 = CH_2-CH_2OAc

Results obtained by clinical experimentation with 3β-methoxy-Δ^5-steroids encouraged us to believe that "blocking" the Δ^5-steroid with a methyl ether at C_3 might, in some cases, largely alter the pharmacodynamic properties of the

[5] Personal communication from Dr. W. K. Ishmael.

[6] We have prepared approximately 175 g. of 17β-hydroxy-5-androsten-3β-yl methyl ether and 600 g. of dehydroisoandrosterone methyl ether for clinical experimentation in rheumatoid arthritis.

compound. We have, therefore, prepared a series of 3β-methoxy-Δ⁵-steroids, starting with steroidal intermediates readily obtainable by us. Thus we have prepared the 3-methyl ethers of 21-acetoxypregnenolone, 17α-hydroxypregnenolone, 17α-methylandrostenediol, 17α-ethylandrostenediol, 17α-vinylandrostenediol, 17α-ethynylandrostenediol, androstenediol-17α-acetic acid, and 17-isopregnene-3,17,21-triol. Most of these C_3-"blocked" steroids were prepared with the thought that one of them might be found to suppress some facet of pituitary action without in itself possessing any hormonal property.[7] For this purpose we have also prepared the two previously known compounds, Δ¹⁶-pregnenolone methyl ether and 16,17-oxidopregnenolone methyl ether (5).

The preparation of the 3-methyl ether of 17α-vinylandrostenediol (XIII) constitutes a special case, inasmuch as there is formed in substantial quantity a by-product which is believed to be 3β,21-dimethoxy-5,17-pregnadiene (XV). Evidently, with 17α-vinylandrostenediol, esterification and subsequent exchange or rearrangement take place at both positions 3 and 17. The rearrangement at

TABLE I

COMPARISON OF OPTICAL ROTATIONS OF STEROIDS

Δ⁵-STEROID	SOLVENT	3β-OH	3β-O-CH_3
Cholesterol	Chloroform	−40° (8)	−39° (2)
5-Pregnen-3β-ol-20-one	Chloroform	+25° (8)	+18° (1)
5-Androsten-3β-ol-17-one	Chloroform	+2° (8)	0° (4)
5-Androsten-3β,17β-diol	Ethanol	−49° (9)	−51°*
17α-Methyl-5-androsten-3β,17β-diol	Chloroform	−85° (8)	−96°*
17α-Ethyl-5-androsten-3β,17β-diol	Ethanol	−68° (10)	−67°*
17α-Vinyl-5-androsten-3β,17β-diol	Ethanol	−64° (10)	−54°*
17α-Ethynyl-5-androsten-3β,17β-diol	Chloroform	−119° (11)	−122°*

* See Experimental, this publication.

C_{17} is believed to be of the allylic type, in agreement with previous rearrangements that have been shown to occur with 17β-hydroxy-17α-vinyl steroids (6, 7). It is interesting to note that the final, rearranged compound apparently bears a methoxyl group at C_{21} instead of an hydroxyl or tosyloxy group.

The senior author has been often asked why he chose the 3β-methoxy-Δ⁵-steroid as a "blocked" steroid for animal and clinical experimentation. The Δ⁵-steroid can now be easily and economically obtained as a starting material, and it is in general more soluble than the saturated analog. A methyl group was chosen as a substitution for the hydroxyl hydrogen at C_3 under the assumption that such a substitution would effect the least change in pattern specificity of the molecule. In this connection it is of interest to note that the optical rotation of a 3β-methoxy-Δ⁵-steroid is but little if any changed from that of the parent 3β-hydroxy-Δ⁵-steroid. In Table I we have listed a comparison of optical rota-

[7] The animal experimentation concerning the suppression of pituitary action with this series of steroids is being done by Professor Allan J. Stanley of the University of Oklahoma School of Medicine.

tions of a few steroids in these two series in which the rotation was determined in the same solvent. Furthermore, the fabrication of the 3β-alkoxy-Δ^5-steroid by the method of Stoll (2) is very simple, short, and economical; the yields are gratifying.

EXPERIMENTAL[8]

Pregnenolone methyl ether (I). This compound was prepared by the usual procedure (1), except that 1.0 ml. of concentrated sulfuric acid was added to each 2500 ml. of exchange solvent. In a large number of preparations (over 25) the average yield was 77% (m.p. 120–123.5°) (highest yield, 89%).

20α-Acetoxy-5-pregnen-3β-yl methyl ether (II). To a solution of 4.15 g. of pregnenolone methyl ether (I) in 415 ml. of absolute ethanol heated to reflux 20.8 g. of sodium in small pieces was rapidly added. After the reaction had ended, the solution was distributed between large volumes of ethyl ether and water, the separated ethereal layer being washed several times with water. Evaporation of the ether gave a semicrystalline residue which was thoroughly dried and acetylated in the usual fashion with acetic anhydride and pyridine. The steroid acetate was crystallized twice from methanol to give 0.99 g. of material melting at 135–139°. Of this product, 155 mg. was recrystallized from 10 ml. of methanol in the ice box to give 100 mg. of leaves melting at 135–135.5° (II); this melting point could not be improved by subsequent recrystallization.

Anal. Calc'd for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23.
Found: C, 77.03, 76.91; H, 10.33, 10.28.

20α-Hydroxy-5-pregnen-3β-yl methyl ether (III). Compound II (0.55 g., m.p. 134–135°) was refluxed in a solution of 88 ml. of 95% ethanol plus 22 ml. of 10% sodium hydroxide for 1 hour, after which 55 ml. of water was added and the solution was distilled to turbidity. The yield of pregnenediol methyl ether melting at 129–130° was 0.49 g. Several recrystallizations from 80% methanol served only to sharpen the melting point to 129.5–130° (leaves) (III); $[\alpha]_D^{25}$ −52° (*c*, 1.37 in 95% ethanol).

Anal. Calc'd for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91.
Found: C, 79.47, 79.53; H, 10.89, 10.92.

Transformation of 20α-acetoxy-5-pregnen-3β-yl methyl ether (II) *to 5-pregnen-3β, 20α-diol diacetate.* Compound II (374 mg., m.p. 134–135°), was covered with 20 ml. of acetic anhydride containing 200 mg. of *p*-toluenesulfonic acid monohydrate (Eastman #984) and the mixture was heated on the steam-bath for 30 minutes with frequent swirlings (14). The reaction mixture was cooled at once and decomposed with 100 ml. of ice-water. After a day in the ice box, the diacetate was filtered and recrystallized twice from aqueous methanol to give 266 mg. melting at 139–140°. Two more recrystallizations from 80% methanol gave 199 mg. of leaves melting sharply at 142–142.5°.

Anal. Calc'd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52.
Found: C, 74.69, 74.71; H, 9.56, 9.50.

Wieland and Miescher (12) give 142–143° as the melting point of 5-pregnen-3β,20α-diol diacetate. Hirschmann (13) lists 145–147° as its melting point.

20β-Acetoxy-5-pregnen-3β-yl methyl ether (IV). To 3.30 g. of pregnenolone methyl ether (I) dissolved in 100 ml. of methanol was added 1.2 g. of solid sodium borohydride, and the reaction mixture was stirred mechanically for 1 hour at room temperature. Then 18 ml. of acetone was stirred in, and after 30 minutes stirring, 100 ml. of water was gradually added. The crystallized steroid was allowed to remain over-night in the ice box, and then filtered and washed copiously with water.

The product, after having been fully dried in the warm box, was acetylated with acetic anhydride in pyridine in the usual fashion. A recrystallization of the acetate from 90 ml. of

[8] All melting points, unless otherwise given, are uncorrected. Microanalyses and optical rotations are by Dr. E. W. D. Huffman, Denver.

methanol (ice box) gave 2.43 g. of material melting at 115–118°. A further recrystallization from 50 ml. of methanol gave 2.01 g. melting at 119.5–121.5°. Subsequent recrystallization from methanol served to narrow the melting point of the fine needles to 121–121.5° (IV). Further recrystallization did not improve this product.

Anal. Calc'd for $C_{24}H_{38}O_3$: C, 76.96; H, 10.23.

Found: C, 76.79, 76.86; H, 10.24, 10.21.

20β-Hydroxy-5-pregnen-3β-yl methyl ether (V). Compound IV, saponified by refluxing for 2 hours in 0.5 *N* aqueous alcoholic sodium hydroxide, gave a nearly quantitative yield of 20β-hydroxy-5-pregnen-3β-yl methyl ether melting at 152.5–154.5°. Subsequent recrystallizations from 80% methanol and from 95% ethanol served only to sharpen the melting point of the long silky needles to 152–153°; $[\alpha]_D^{25} - 71°$ (*c*, 1.52 in 95% ethanol) (V).

Anal. Calc'd for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91.

Found: C, 79.35, 79.44; H, 10.95, 10.97.

Reacetylation of this material with acetic anhydride in pyridine gave the 20-acetate, melting, as before, at 121–121.5° upon repeated crystallization.

Transformation of 20β-acetoxy-5-pregnen-3β-yl methyl ether (IV) *to 5-pregnen-3β,20β-diol diacetate.* Product IV (98 mg., m.p. 121–121.5°) was swirled on the steam-bath with 5.4 ml. of acetic anhydride and 54 mg. of *p*-toluenesulfonic acid monohydrate for 30 minutes in the usual fashion (14). Two recrystallizations from aqueous methanol gave 83 mg. of needles melting at 126.5–127°. Another recrystallization from 80% methanol gave 61 mg. of long flat needles melting at 127.5–128°.

Anal. Calc'd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.52.

Found: C, 74.76, 74.63; H, 9.57, 9.50.

Wieland and Miescher (12) give for 5-pregnen-3β,20β-diol diacetate the melting point of 125–126°. Hirschmann (13) reports a melting point of 130–131°.

Dehydroisoandrosterone methyl ether (VI). This compound was prepared in large quantity by the same procedure as that used for preparing pregnenolone methyl ether, except that no sulfuric acid was added to the exchange solvent. The average yield of methyl ether of suitable purity for clinical investigation (m.p. 139.5–140°) was 83%, based upon dehydroisoandrosterone acetate as a starting material (highest yield, 92%).

Butenandt and Grosse (4), who first prepared this steroid, list the melting point of very pure dehydroisoandrosterone methyl ether as 140–142°.

17β-Acetoxy-5-androsten-3β-yl methyl ether (VII). Dehydroisoandrosterone methyl ether (VI) (21.08 g.) (yield from a batch of 25.0 g. of dehydroisoandrosterone acetate) was stirred mechanically at 20° in 350 ml. of methanol. A solution of 4.1 g. of sodium borohydride in 170 ml. methanol was added, and stirring was continued for 40 minutes. The sides of the flask were then rinsed down with 20 ml. of methanol, followed by an additional 15 minutes' stirring. The excess reducing agent was then destroyed by stirring in 75 ml. of acetone, and the solution then was alkalinized by stirring in 14.5 g. of NaOH in 400 ml. of 50% methanol. Finally 2275 ml. of water was added, and the reduced steroid was allowed to crystallize overnight at room temperature. It was filtered, washed copiously with water, dried thoroughly, and acetylated in 100 ml. of dry pyridine using 100 ml. of acetic anhydride by permitting the solution to stand a day at room temperature. The acetylation mixture was decomposed with much ice-water, and the steroid recrystallized from absolute methanol. The yield was 21.85 g. melting at 154–155° (VII). The melting point of the long colorless rods was not improved upon repeated crystallization.

Anal. Calc'd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89.

Found: C, 76.21, 76.30; H, 9.88, 9.93.

17β-Hydroxy-5-androsten-3β-yl methyl ether (VIII). Compound VII (20 g.) was saponified by refluxing for one hour in a solution of 200 ml. of 2 *N* sodium hydroxide in 800 ml. of methanol. Then 300 ml. of water was added and the alkaline solution was distilled until incipient crystallization began in the hot solution. The saponified steroid was allowed to crystallize overnight in the ice box. Material melting at 141–141.5° was obtained in an average yield of 70% based upon dehydroisoandrosterone acetate as original starting material (highest

yield, 81%). Repeated recrystallization from 80% methanol furnished the compound in long white needles melting at 142.5–143° (VIII) and with $[\alpha]_D^{25}$ −51° (*c*, 1.47 in 95% ethanol).

Anal. Calc'd for $C_{20}H_{32}O_2$: C, 78.89; H, 10.59.

Found: C, 78.81, 78.95; H, 10.49, 10.57.

Transformation of 17β-acetoxy-5-androsten-3β-yl methyl ether (VII) *to 5-androsten-3β,17β-diol diacetate.* The 3-methoxy group of compound VII was replaced by a 3-acetate in the usual fashion (228 mg. of steroid VII, 13.3 ml. of acetic anhydride, 133 mg. of *p*-toluenesulfonic acid monohydrate). The first crop of crystals (191 mg.) melted at 152.5–154°. The material was recrystallized from methanol until the melting point was no longer improved; yield 52 mg. of large leaves melting at 157.5–158°. A mixture melting point using authentic 5-androsten-3β,17β-diol diacetate showed no depression.

21-Acetoxypregnenolone methyl ether (IX). 21-Acetoxypregnenolone (Schering, 20.00 g.) was dissolved in 160 ml. of dry pyridine, and the solution was cooled to 0° using an ice-salt bath. Then 40 g. of *p*-toluenesulfonyl chloride was added and the stoppered mixture was swirled at 0° until the tosyl chloride had completely dissolved. The reaction was allowed to continue for 24 hours, the ice-bath being permitted spontaneously to come to room temperature. The reaction mixture was decomposed by mixing in 400 ml. of ice-water, and the tosylate was allowed to collect overnight in the ice chest. After filtration and copious water washing, the tosylate was dried thoroughly *in vacuo* over sulfuric acid and potassium hydroxide.

The exchange reaction was carried out by refluxing in 2000 ml. of absolute methanol for 2 hours (moisture protection), and then the solvent was concentrated to 400 ml. by distillation. After the concentrated methanolic solution had been cooled to room temperature, 3600 ml. of ice-water was rapidly mixed in. After a day in the ice box the steroid ether was filtered, and the product was dried *in vacuo* as before. The dried product was again dissolved in 400 ml. of methanol and precipitated with 3600 ml. of ice-water plus 500 ml. of saturated aqueous sodium chloride. The recovered product, after having been vacuum-dried, was reacetylated with acetic anhydride (200 ml.) and pyridine (200 ml.) in the usual fashion, and the reacetylated product crystallized from 400 ml. of methanol. The yield was 16.64 g. (80%), melting at 146–148°. Recrystallizations from ethanol served to narrow the melting point of the diamond-shaped blocks to 146.5–147°; $[\alpha]_D^{25}$ +38° (*c*, 0.98 in dioxane) (IX).

Anal. Calc'd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34.

Found: C, 74.04, 74.15; H, 9.33, 9.36.

17α-Hydroxy-20-keto-5-pregnen-3β-yl methyl ether (X). This compound was prepared by the careful tosylation and exchange of 17α-hydroxypregnenolone (Glidden). The product once crystallized from aqueous methanol melted at 172–175.5° (84%). Repeated crystallization from ethyl acetate-heptane gave fine needles melting at 174.5–176.5° (X). The compound was dried to constant weight *in vacuo* at 100° over phosphorus pentoxide before analysis.

Anal. Calc'd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89.

Found: C, 76.32, 76.34; H, 10.00, 9.94.

17α-Methyl-17β-hydroxy-5-androsten-3β-yl methyl ether (XI). To a Grignard solution prepared from 3.4 g. of activated magnesium turnings, 20 g. of methyl iodide, and 100 ml. of absolute ethyl ether, there was added a solution of 5.00 g. of dehydroisoandrosterone methyl ether (VI) in 300 ml. of dry ether, and the resulting mixture was refluxed gently for 7 hours. The reaction mixture was treated with ice and dilute hydrochloric acid and partitioned between ethyl ether and ice-water. The separated ethereal phase was washed with 0.1 *molar* sodium thiosulfate and then washed several times with water. Evaporation of the ethereal solution yielded a crystalline residue which was recrystallized twice from Skellysolve B (5°) and once from methyl ethyl ketone-heptane (5°) to give 2.59 g. (49%) of crystals melting at 167–169°. A further recrystallization from methyl ethyl ketone-heptane gave 2.29 g. of flat needles melting at 166.5–168.5° (XI). This melting point could not be improved by subsequent recrystallization. The optical rotation was $[\alpha]_D^{25}$ −96° (*c*, 1.05 in chloroform).

Anal. Calc'd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76.

Found: C, 79.13, 79.04; H, 10.78, 10.70.

17α-Ethly-17β-hydroxy-5-androsten-3β-yl methyl ether (XII). To a Grignard solution prepared from 1.17 g. of activated magnesium turnings, 5.0 g. of ethyl bromide, and 50 ml. of dry ether, there was added a solution of 5.00 g. of dehydroisoandrosterone methyl ether (VI) in 200 ml. of dry ether. The resulting solution was refluxed 2 hours, decomposed with ice-water plus dilute hydrochloric acid, and then partitioned between ether and water. The well-washed ethereal phase was evaporated to give an oil, which was thoroughly dried *in vacuo* over sulfuric acid and potassium hydroxide. The oil was leached well with Skellysolve B to remove the unreacted 17-ketone and then crystallized from 80% methanol to give 1.33 g. (24%) melting at 179–182° after softening at 177.5°. The product was recrystallized once from ethanol and twice from ethyl acetate-heptane to yield needles which melted at 181.5–182°, after softening at 179°; $[\alpha]_D^{25}$ −67° (*c*, 0.58 in 95% ethanol) (XII).

Anal. Calc'd. for $C_{22}H_{36}O_2$: C, 79.46; H, 10.91.

Found: C, 79.52, 79.61; H, 10.95, 10.83.

17α-Ethynyl-17β-hydroxy-5-androsten-3β-yl methyl ether (XIV). This 3-methyl ether was prepared by the cautious tosylation and exchange of 17α-ethynylandrostenediol (Ciba). It crystallizes directly from the exchange solvent as small leaves decomposing at 237–240° (73%). Of this material, 0.53 g. was recrystallized twice from 95% ethanol to give 0.36 g. of large leaves melting at 241–243.5° dec., $[\alpha]_D^{25}$ −122° (*c*, 0.64 in chloroform) (XIV).

Anal. Calc'd for $C_{22}H_{32}O_2$: C, 80.44; H, 9.82.

Found: C, 80.18, 80.24; H, 9.86, 9.84.

17α-Vinyl-17β-hydroxy-5-androsten-3β-yl methyl ether (XIII). Vinylandrostenediol (Ciba, 1.00 g.) and *p*-toluenesulfonyl chloride (4.0 g.) were covered with 24 ml. of dry pyridine and the mixture was swirled in a cold water-bath until solution of all components had been effected. The reaction mixture was permitted to remain 48 hours at room temperature, after which it was decomposed with ice-water in the usual fashion, and the recovered tosylated product was dried *in vacuo*. The dried product was refluxed for 2 hours in 100 ml. of absolute methanol plus 8 drops of concentrated sulfuric acid (moisture protection), and the solution was distilled to one-half volume. To the cold solution, water (23 ml.) was added gradually to turbidity, and crystallization was allowed to take place at 5°. Yield, 795 mg. of a mixture of materials melting between 108° and 153°. The 795 mg. was recrystallized once from 30 ml. of Skellysolve B in the ice box. The resulting crystals were washed twice with ice cold Skellysolve B, dried in the oven at 90°, and recrystallized from aqueous methanol to yield 243 mg. of needles melting at 166–168° (23%). A recrystallization from ethyl acetate-heptane and a recrystallization from aqueous methanol raised the melting point to 170.5–171.5° (XIII). The tiny flat needles showed $[\alpha]_D^{25}$ −54° (*c*, 0.94 in 95% ethanol).

Anal. Calc'd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37.

Found: C, 79.80, 79.88; H, 10.38, 10.31.

5,17-Pregnadien-3β,21-diol dimethyl ether (?) (XV). The Skellysolve B filtrate and washings from the preparation of 17-vinylandrostenediol methyl ether in the preceding experiment were combined and evaporated to dryness. The resulting nicely crystalline product was recrystallized once from aqueous methanol to give 416 mg. melting at 118.5–120°. After treatment with charcoal and recrystallization from aqueous methanolic acetone the needles weighed 313 mg. and melted at 121.5–122°, after sintering at 119°. This melting point could be raised to 122.5–123.5° (sintering at 120.5°) after repeated crystallization. The long, keen needles (XV) were dried to constant weight *in vacuo* over phosphorus pentoxide at 80° before analysis.

Anal. Calc'd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53.

Found: C, 79.93, 79.90; H, 10.51, 10.60.

3β-Methoxy-17β-hydroxy-5-androsten-17α-acetic acid (XVI). Dehydroisoandrosterone methyl ether (VI), 5.50 g., was dissolved in 150 ml. of dry benzene and the solution was distilled down to a volume of 50 ml. To this solution was added 7.0 g. of activated 20-mesh zinc, followed by the addition of 8.2 ml. of ethyl bromoacetate. The mixture was then refluxed for 4 hours with good moisture protection. Hydrolysis of the zinc complex was accomplished with 200 ml. of 2 *N* hydrochloric acid, and the two layers were added to ethyl

ether and partitioned between ethyl ether and water. The separated organic phase was washed once with dilute hydrochloric acid and several times with water. Evaporation of the organic phase gave a residue which was saponified by 30 minutes' refluxing in 100 ml. of methanol containing 15 ml. of 50% potassium hydroxide. The alkaline solution was partitioned between 0.5 *N* potassium hydroxide and ethyl ether. The separated alkaline phase was acidified and re-extracted with ether, which, after separation, was then washed with water and evaporated.

Recrystallization of the ethereal residue, once from acetone, once from aqueous acetone, and once from acetone-Skellysolve B gave 2.48 g. of an organic acid melting at 187.5–189.5° (XVI). This melting point was not improved by recrystallization from acetone or from methyl ethyl ketone-heptane. From the latter solvent mixture the compound crystallizes as colorless prisms, $[\alpha]_D^{26}$ −77° (*c*, 1.00 in chloroform).

Anal. Calc'd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45.

Found: C, 72.99, 72.89; H, 9.52, 9.48.

17-Iso-17β,21-dihydroxy-5-pregnen-3β-yl methyl ether (XVII). To 1.50 g. of compound XVI in solution in 420 ml. of absolute ether under an atmosphere of nitrogen was added 1.5 g. of solid lithium aluminum hydride. After the vigorous reaction had subsided, the mixture was refluxed for 2 hours. The excess reducing agent was destroyed, first with ethyl acetate, and then with water, after which the reaction mixture was partitioned between ethyl ether and 1 *N* sulfuric acid. The separated ethereal phase was then washed successively with 1 *N* sulfuric acid, with water, with 1 *N* potassium hydroxide, and with water. The residue from evaporation of the ethereal solution was recrystallized from aqueous methanol and from acetone-Skellysolve B to yield large leaves (1.23 g.) melting at 180–182.5°, after softening slightly at 176.5°. Recrystallization, twice from acetone-Skellysolve B, once from aqueous methanol, and once from methyl ethyl ketone-heptane served only to raise the melting point to 181.5–183° (soft. at 178°) (XVII).

Anal. Calc'd for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41.

Found: C, 75.80; H, 10.49.

17-Iso-21-acetoxy-17β-hydroxy-5-pregnen-3β-yl methyl ether (XVIII). Compound XVII (221 mg.) was acetylated in 4 ml. of dry pyridine and 2 ml. of acetic anhydride during 24 hours at room temperature. The recovered 21-acetate, after a recrystallization from acetone-Skellysolve B, melted at 162.5–164° and weighed 223 mg. Recrystallizations from aqueous methanol and from acetone-Skellysolve B raised the melting point to 165.5–166.5° (144 mg.). The fine needles showed $[\alpha]_D^{24}$ −61° (*c*, 0.46 in acetone) (XVIII).

Anal. Calc'd for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81.

Found: C, 73.91; H, 9.82.

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SUMMARY

Methods are given for preparing the 3-methyl ethers of the following steroids: 5-pregnen-3β,20α-diol, 5-pregnen-3β,20β-diol, 5-pregnen-3β,21-diol-20-one (as 21-acetate), 5-pregnen-3β,17α-diol-20-one, 5-androsten-3β,17β-diol, 17α-methyl-5-androsten-3β,17β-diol, 17α-ethyl-5-androsten-3β,17β-diol, 17α-vinyl-5-androsten-3β,17β-diol, 17α-ethynyl-5-androsten-3β,17β-diol, 5-androsten-3β,17β-diol-17α-acetic acid, and 17-iso-5-pregnen-3β,17β,21-triol.

The preparation from vinylandrostenediol of a compound, probably 3β,20-dimethoxy-5,17-pregnadiene, is given. This compound was not further investigated.

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