was refluxed vigorously under argon for 20 hours. The catalyst was removed with suction and washed with hot chloroform. The very dark filtrate was concentrated, chromatographed on alumina and the strongly fluorescent zone (ultraviolet light) eluted with chloroform. Concentrating with addition of ethanol gave 169 mg. (17%) of yellow prisms, m.p. 269–270°. Vacuum sublimation, followed by repeated chromatography and two recrystallizations from chloroform ethanol provided tiny faintly yellowish needles, m.p. 271–272°.

Anal. Calcd. for $C_{23}H_{30}O_8$: C, 65.09; H, 4.75; OCH_3, 29.25. Found: C, 64.85; H, 4.86; OCH_3, 29.46.

Attempts to prepare this compound by dehydrogenation with lead tetraacetate[11,19] were unsuccessful. Only a trace of material with blue fluorescence, indicative of a naphthalene derivative, was formed.

Acknowledgments.—The authors wish to thank Mrs. Iris J. Siewers of the National Heart Institute for the infrared spectra and Dr. W. C. Alford and his co-workers for the microanalyses.

(19) H. Erdtman, *Ann.*, **513**, 229 (1934); R. D. Haworth and G. Sheldrick, *J. Chem. Soc.*, 636 (1935); R. D. Haworth and D. Woodcock, *ibid.*, 809 (1938).

BETHESDA, MARYLAND

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

"Enamine" Derivatives of Steroidal Carbonyl Compounds. III. The Synthesis of C_{11}-Oxygenated Testosterones

BY M. E. HERR AND F. W. HEYL

RECEIVED JULY 17, 1953

Selective aspects of the reaction of polycarbonyl steroids with secondary amines have been investigated further. 11α- and 11β-hydroxytestosterone have been prepared from 11α-hydroxy-4-androstene-3,17-dione and adrenosterone, respectively, by the formation of the C_3-enamine, reduction of the free carbonyl groups with lithium aluminum hydride and subsequent hydrolysis to regenerate the 3-keto-Δ^4-system. 11β-Hydroxytestosterone thus prepared was readily acylated at the C_{17}-hydroxyl position and the resulting 11β-hydroxy-17-ester upon oxidation yielded the 11-keto-17-ester which was saponified to 11-ketotestosterone. Under certain conditions adrenosterone gave a $C_{3,17}$-bispyrrolidyl enamine which upon reduction and subsequent hydrolysis yielded 11β-hydroxyandrostene-3,17-dione.

In view of the critical importance of C_{11}-oxygen, either as a β-hydroxyl or ketone, for some of the principal adrenal cortical hormone properties it was of interest to investigate the biological properties of C_{11}-oxygenated compounds in the androstane series.

The preparation of C_{11}-oxygenated testosterone derivatives and similar compounds here reported is based on securing as starting material, 11α-hydroxy-4-androstene-3,17-dione (I), by the microbiological oxygenation of 4-androstene-3,17-dione.[1]

The reaction of 3-ketobisnor-4-cholenaldehyde with secondary amines to selectively form C_{22}-enamines and of C_3-carbonyl steroids to form enamines at carbon atom 3 have previously been described.[2] This reaction has been found to be especially useful in the present work as a blocking agent for the C_3-carbonyl group, while conducting a metal hydride reduction elsewhere in the molecule. Thus when 11α-hydroxy-4-androstene-3,17-dione (I) was allowed to react with pyrrolidine, 3-(N-pyrrolidyl)-3,5-androstadien-11α-ol-17-one (II) was readily formed. The C_{17}-carbonyl group of this compound was reduced with lithium aluminum hydride and subsequent hydrolysis of the reduced enamine gave 11α-hydroxytestosterone (IV) which had previously been prepared by the microbiological oxygenation of testosterone[1]; the synthetic compound was identical with the one produced microbiologically.

Adrenosterone (V), readily prepared by the chromic acid oxidation of 11α-hydroxy-4-androstene-3,17-dione, reacted with pyrrolidine to form the $C_{3,17}$-bispyrrolidyl enamine (VI) or the C_3-mono enamine (IX) depending upon the conditions employed. A large excess of pyrrolidine and a more concentrated reaction mixture resulted in reaction at both the C_3- and C_{17}-carbonyl groups, whereas when approximately one molecular equivalent of the secondary amine was employed the reaction was selective at the C_3-ketone. In either instance it was found expedient to catalyze the reaction by the addition of a small amount of *p*-toluenesulfonic acid.

This reactivity of the C_{17}-carbonyl group with pyrrolidine was in striking contrast to the unreactivity of the C_{17}-ketone of 4-androstene-3,17-dione, which formed only the C_3-pyrrolidyl compound under similar conditions.[2] It is apparent that the C_{11}-ketone group has influenced the reactivity of the C_{17}-carbonyl group.

Lithium aluminum hydride reduction of the $C_{3,17}$-di-(N-pyrrolidyl)-11-one (VI) and subsequent hydrolysis led to the formation of 11β-hydroxy-4-androstene-3,17-dione (VIII).[3] Aside from being different from the 11α-hydroxy isomer I[1] this compound was further characterized by the preparation of a disemicarbazone and by chromic acid oxidation to adrenosterone (V).

When the C_3-(N-pyrrolidyl)-11,17-dione (IX) was reduced with lithium aluminum hydride followed by hydrolysis, 11β-hydroxytestosterone (XI) was readily obtained.

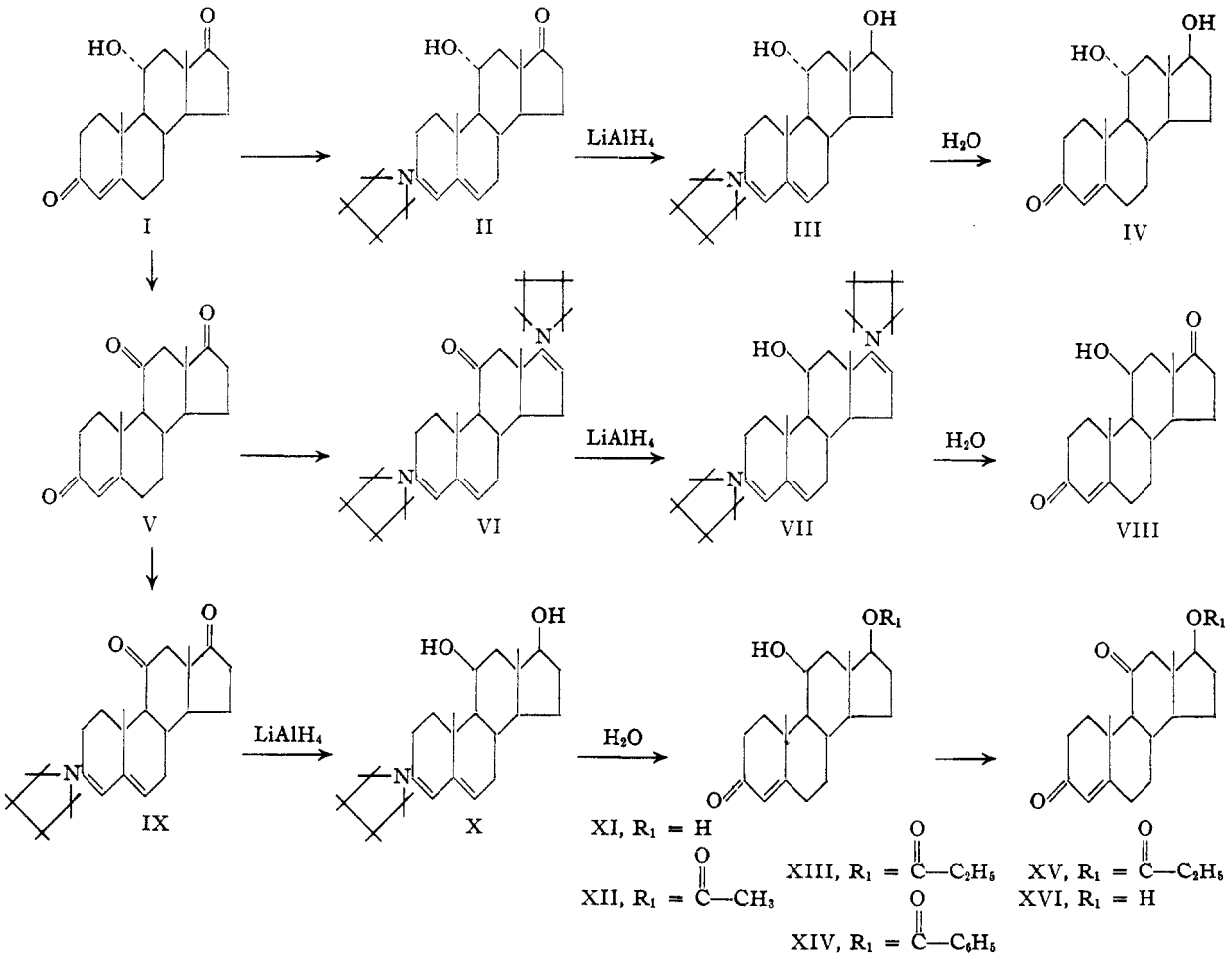
The 11β-hydroxyl group was unreactive to acylating agents[4] under the conditions used and the 17-acetate XII, 17-propionate XIII and 17-benzoate XIV of 11β-hydroxytestosterone were obtained in good yield from the selective acylation of the C_{17}-

(1) S. H. Eppstein, P. D. Meister, H. Marian Leigh, D. H. Peterson, H. C. Murray, L. M. Reineke and A. Weintraub, Abst. A.C.S., 123rd Meeting, Los Angeles, Calif., 1953; U. S. Patent 2,602,769.

(2) M. E. Herr and F. W. Heyl, THIS JOURNAL, **74**, 3627 (1952); **75**, 1918 (1953).

(3) T. Reichstein, *Helv. Chim. Acta*, **20**, 978 (1937), has obtained this compound from the periodic acid oxidation of 3-keto-4-pregnene-11β,17α,20β,21-tetraol and from the lead tetraacetate oxidation of 17-hydroxycorticosterone.

(4) L. F. and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Edition, Reinhold Publishing Corp., New York, N. Y., 1949, p. 408.



hydroxyl group. Chromic acid oxidation of the 11-hydroxyl group of these esters led to the formation of the 11-ketotestosterone esters as exemplified by the oxidation of 11β-hydroxytestosterone 17-propionate (XIII) to 11-ketotestosterone propionate (XV). Hydrolysis of this later compound gave 11-ketotestosterone (XVI).[5] Infrared spectra showed absorption at 1704 cm.$^{-1}$ characteristic of the C_{11}-carbonyl group and at 3555, 3382, 3317 cm.$^{-1}$ for the hydroxyl group.

As in the previous publication on this subject[2] the structures of the pyrrolidyl enamines prepared from 3-keto-Δ^4-steroids are tentatively represented as $\Delta^{3,5}$-dienes rather than the alternatively possible $\Delta^{2,4}$-structures.[6]

Experimental[7]

3-(N-Pyrrolidyl)-3,5-androstadien-11α-ol-17-one (II).—A solution of 1.21 g. (0.004 mole) of 11α-hydroxy-4-androstene-3,17-dione (I),[1] 25 ml. of benzene and 1.34 ml. of pyrrolidine was refluxed vigorously with stirring for 3$^2/_3$ hours; the water of reaction was removed by use of a Bidwell-Sterling moisture trap placed between the reaction flask and the condenser. The solution was evaporated to dryness under reduced pressure, using precautions to preclude moisture, and the residue dissolved in 10 ml. of ether. The product separated almost immediately and after cooling was recovered by filtration. The product was recrystallized from ether in fine yellow needles, yield 0.81 g., m.p. 161–166° dec., $[\alpha]^{23}D$ −165° (pyridine), λ_{max}^{ether} 282 mμ (log E 4.39).

Anal. Calcd. for $C_{23}H_{33}NO_2$: C, 77.69; H, 9.36; N, 3.94. Found: C, 77.68; H, 9.15; N, 4.00.

Reduction of II and Hydrolysis to 11α-Hydroxytestosterone (IV).—A benzene solution of 3.02 g. of 11α-hydroxy-4-androstene-3,17-dione and 1.65 ml. of pyrrolidine was allowed to react as described above except that 15 mg. of *p*-toluenesulfonic acid was added to the mixture. This shortened the reaction time to one hour. The benzene solution was cooled to room temperature and added with stirring during five minutes to a mixture of 3 g. of lithium aluminum hydride in 400 ml. of ether. The mixture was heated at reflux for five minutes and the heating source replaced by an ice-bath. The metal complex was decomposed by the cautious addition of 10 ml. of water. The mixture was concentrated *in vacuo* almost to dryness and the residue heated at reflux for four hours with a buffered solution of 4 g. of sodium acetate, 10 ml. of water, 4 ml. of glacial acetic acid and 50 ml. of methanol. After concentrating *in vacuo* the residue was treated with 100 ml. of dilute hydrochloric acid and the product extracted with methylene chloride. The solution was washed with dilute sodium carbonate, water and dried over sodium sulfate. Upon evaporation of the solvent the residue was recrystallized directly from ethyl acetate in prisms, m.p. 180–181°. There was no melting point depression upon admixture with 11α-hydroxytestosterone obtained from the bioconversion of testoster-

(5) The partial synthesis of 11-ketotestosterone by two independent routes has recently been described by H. L. Herzog, M. A. Jevnik, P. L. Perlman, A. Nobile, and E. B. Hershberg, THIS JOURNAL, **75**, 266 (1953). NOTE ADDED IN PROOF: Recently two other papers have appeared describing the preparations of C_{11}-oxygenated compounds in the androstane series by independent routes: O. Mancera, G. Rosenkranz and F. Sondheimer, *J. Chem. Soc.*, 2189 (1953); S. Bernstein, R. H. Lenhard and J. H. Williams, *J. Org. Chem.*, **18**, 1166 (1953).

(6) Personal communications from Dr. J. L. Johnson, of our Physics Department, reveals that there may actually be justification for the $\Delta^{2,4}$-structure. His observation is based on salt formation of enamines in conjunction with ultraviolet absorption studies and will be published at a later date.

(7) Melting points are as read on a Fisher–Johns block which checked the melting points of standard compounds within ±1° over a range from 70 to 237°.

one[1] and the infrared absorption curves were identical, $[\alpha]^{24}D$ +92° ($CHCl_3$).

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.97; H, 9.27. Found: C, 74.96; H, 9.15.

Adrenosterone (V) from 11α-Hydroxy-4-androstene-3,17-dione (I).—The microbiological fermentation of 4-androstene-3,17-dione offered a convenient starting point for preparing adrenosterone in quantity. The fermentation of 60 g. of dione when worked up by the method described[1] gave, upon extraction with methylene chloride, a crude residue weighing 89.0 g. This residue after extracting with hot water, was triturated with 300 ml. of ether containing 15 ml. of acetone and allowed to stand in the refrigerator. The insoluble crystalline residue, after filtration, was washed with ether and dried when it weighed 31.95 g. (m.p. 200–207°).

This crude 11α-hydroxy-4-androstene-3,17-dione (I) was oxidized as follows: Twelve grams of the crude was dissolved in 500 ml. of glacial acetic acid and treated at room temperature with a solution of 6.0 g. of chromic anhydride in 12 ml. of water and 375 ml. of acetic acid. After 4.5 hours the excess oxidizing agent was reduced with methanol, and the solution was concentrated *in vacuo*. After trituration of residue with water the insoluble product was obtained by filtration, washed with water and dried, yield 7.66 g., m.p. 208–214°. This material was dissolved in 125 ml. of benzene and chromatographed over 50 g. of activated alumina. Benzene and benzene + 10% acetone eluted the adrenosterone yield 6.55 g., m.p. 220–223°. A sample recrystallized from methylene chloride–Skellysolve B mixture melted at 223–225°. This material, by infrared spectra comparison, mixed melting point, and analysis was identical with the natural product.

3,17-Di-(N-pyrrolidyl)-3,5,16-androstatrien-11-one (VI).—A mixture of 1.5 g. (0.005 mole) of adrenosterone, 20 ml. of benzene, 1.67 ml. of pyrrolidine and 10 mg. of *p*-toluenesulfonic acid monohydrate was heated at reflux while stirring, using a graduated water trap to collect the water of reaction. After 3.5 hours two mole equivalents of water had collected; 10 ml. of Skellysolve C was added and the mixture concentrated to remove 20 ml. of solvent. The remaining solution was diluted with 10 ml. of Skellysolve C and cooled. The yellow crystalline precipitate was recovered and washed with a little Skellysolve C and dried, yield 1.76 g. (87%), m.p. 182–190° dec., $[\alpha]^{24}D$ −26° (dioxane).

Anal. Calcd. for $C_{27}H_{38}N_2O$: N, 6.89. Found: N, 7.08.

Reduction of VI to 3,17-Di-(N-pyrrolidyl)-3,5,16-androstatrien-11β-ol (VII) and Hydrolysis to 11β-Hydroxy-4-androstene-3,17-dione (VIII).—Three grams of adrenosterone (0.01 mole) was converted to the dipyrrolidyl enamine (VII) as described above. The reaction mixture was concentrated to dryness under reduced pressure using precaution to preclude moisture. The yield of crystalline yellow solid was 4.09 g. (theory for the di-enamine, 4.07 g.). This material was dissolved in 100 ml. of anhydrous tetrahydrofuran and added during five minutes, with stirring, to a mixture of 2.0 g. of lithium aluminum hydride in 350 ml. of anhydrous ether. The mixture was brought to reflux and after five minutes the heating mantle was replaced by an ice-bath and the metal complex decomposed by the cautious addition of 10 ml. of water. To this mixture was added a solution of 16 g. of sodium acetate in 20 ml. of water, 10 ml. of glacial acetic acid and 200 ml. of methanol. About 350 ml. of solvent consisting mostly of ether was distilled from the mixture and the remainder heated at reflux for three hours. It was then concentrated under reduced pressure and the residue, diluted with 2 *N* hydrochloric acid was extracted separately with ether and methylene chloride. These extracts were washed with dilute sodium carbonate solution, water and then combined and dried over sodium sulfate. Upon evaporation of the solvent there was obtained 2.22 g. (78%) of crystalline product, m.p. 187–190°. Direct recrystallization did not remove traces of impurities so the product was dissolved in 80 ml. of benzene and passed over 55 g. of activated alumina followed by elution with 50 ml. of benzene, 500 ml. of 10% acetone–benzene, 500 ml. of 20% acetone–benzene, 500 ml. of 50% acetone–benzene. The 10% acetone–benzene and 20% acetone–benzene elutions contained the product, 1.45 g. of needles, m.p. 196–198°. Recrystallization from chloroform–Skellysolve C mixture gave 1.35 g. of long, silk needles, m.p. 200°. Infrared absorption showed the presence of the C_{17}-carbonyl group, λ_{max}^{alc} 242 mμ (log *E* 4.19), $[\alpha]^{23}D$ +220° ($CHCl_3$).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 74.97; H, 8.92.

Treatment of this compound with an excess of methanolic semicarbazide acetate gave a disemicarbazone, m.p., decomposes above 300°.

Anal. Calcd. for $C_{21}H_{32}N_6O_3$: N, 20.18. Found: N, 20.31.

Chromic acid oxidation of 100 mg. of this compound (VIII) in acetic acid at room temperature gave 72 mg. of adrenosterone, m.p. 219–221°, identical with the natural product.

3-(N-Pyrrolidyl)-3,5-androstadiene-11,17-dione (IX).—Six grams of adrenosterone, 90 ml. of benzene, 1.84 ml. of pyrrolidine and 20 mg. of *p*-toluenesulfonic acid was stirred and heated at brisk reflux for 2 hours. The apparatus was so arranged that the vapor condensate returned to the reaction flask through a layer of calcium carbide which served to remove the water of reaction. This arrangement also served to return any pyrrolidine which azeotroped with the benzene vapors. The mixture was cooled to room temperature and divided into two equal aliquots. One part was concentrated *in vacuo* on a hot water-bath and the dark yellow residue was recrystallized from ether; yield 3.22 g. (88%), melting point gradually decomposed above 180°, λ_{max}^{ether} 282 mμ (log *E* 4.37), $[\alpha]^{24}D$ −46° (pyridine).

Anal. Calcd. for $C_{23}H_{31}NO_2$: C, 78.14; H, 8.84; N, 3.96. Found: C, 78.24; H, 8.72; N, 4.09.

Reduction of IX to 3-(N-Pyrrolidyl)-3,5-androstadiene-11β-17β-diol (X) and Hydrolysis to 11β-Hydroxytestosterone (XI).—The remaining benzene aliquot from the above experiment was diluted with an equal volume of anhydrous ether and added during five minutes, with stirring, to a mixture of 1.1 g. of lithium aluminum hydride in 175 ml. of anhydrous ether. The mixture was heated at reflux for five minutes and cooled to room temperature. While stirring 10 ml. of ethyl acetate was added cautiously followed by 15 ml. of water. The mixture was concentrated *in vacuo* and the residue heated at reflux with a mixture of 4 g. of sodium acetate, 10 ml. of water, 4 ml. glacial acetic acid and 50 ml. of methanol for 4 hours. The hydrolyzed mixture was concentrated *in vacuo* and the residue treated with 150 ml. of 2 *N* HCl breaking up the lumps in the process. The insoluble material was recovered by filtration, washed well with water, and dried *in vacuo* at 100°; yield 2.20 g. (73% from adrenosterone), m.p. 233–235°. For analysis a sample was recrystallized from benzene to constant melting point, 241°, λ_{max}^{alc} 242 mμ (log *E* 4.19), $[\alpha]^{24}D$ +159° ($CHCl_3$).

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.97; H, 9.27. Found: C, 74.77; H, 9.17.

11β-Hydroxytestosterone-17-acetate (XII).—A mixture of 0.30 g. of 11β-hydroxytestosterone in 2 ml. of dry and freshly distilled pyridine was treated with 1.5 ml. of acetic anhydride and allowed to stand at 25° for 18 hours. The mixture was poured into 40 ml. of ice and water and stirred for 2 hours. The white solid product was recovered, washed with water and dried. This material (0.30 g.) was recrystallized from ether–hexane mixture to constant melting point, 150°, yield 0.23 g. $[\alpha]^{22}D$ +125° ($CHCl_3$).

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 73.20; H, 9.18.

11β-Hydroxytestosterone-17-propionate (XIII).—This ester was prepared as described above using propionic anhydride. The yield of crude ester, m.p. 148–152°, was 92%. Recrystallized from ether–hexane mixture the pure compound melted at 157–158°, yield 81%, $[\alpha]^{22}D$ +122° ($CHCl_3$).

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.29; H, 8.95. Found: C, 73.25; H, 9.05.

11β-Hydroxytestosterone-17-benzoate (XIV).—To 0.30 g. of 11β-hydroxytestosterone suspended in 12 ml. of benzene was added 0.33 ml. of freshly distilled dry pyridine, and 0.32 ml. of freshly distilled benzoyl chloride. The mixture was stirred at room temperature for 17 hours during which time the starting material went into solution and the benzoate separated out. The product was obtained by filtration, washed with benzene, ether and dried, yield 0.36 g.,

m.p. 275–277° dec. Recrystallized from ethyl acetate the prisms melted at 286° dec., $[\alpha]^{22}D$ +178° ($CHCl_3$).

Anal. Calcd. for $C_{26}H_{32}O_4$: C, 76.45; H, 7.90. Found: C, 76.40; H, 7.83.

11-Ketotestosterone-propionate (XV).—A solution of 1.48 g. of 11β-hydroxytestosterone 17-propionate in 80 ml. of glacial acetic acid was treated with a solution of 0.74 g. of chromic anhydride in 4 ml. of water and 80 ml. of acetic acid at room temperature for five hours. After destroying excess oxidant with methanol the solution was concentrated *in vacuo*, the residue diluted with water and the product extracted with ether. The ether solution was processed for the neutral fraction which weighed 1.29 g. Recrystallization from a mixture of ether and Skellysolve B gave 1.13 g. (76%), m.p. 139–140°, $[\alpha]^{22}D$ +169° ($CHCl_3$).

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.70; H, 8.44. Found: C, 73.84; H, 8.64.

11-Ketotestosterone (XVI).—A solution of 1.07 g. of 11-ketotestosterone propionate in 50 ml. of 1 *N* methanolic potassium hydroxide containing 3 ml. of water was refluxed for 30 minutes. The solution was poured onto ice and the resulting mixture was slightly acidified with dilute sulfuric acid. The precipitate was recovered by filtration, washed with water and dried. It weighed 0.79 (88%), m.p. 187–188°. When the aqueous filtrate was extracted with methylene chloride an additional yield of 0.09 g. of product, m.p. 182–186° was recovered. Recrystallized from methylene chloride–ether mixture the product still melted at 187–188°, $[\alpha]^{22}D$ +224° ($CHCl_3$).

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.63; H, 8.57.

The infrared spectrum in nujol of this compound showed absorption for the following functional groups: OH, 3555, 3382, 3317 cm.$^{-1}$; 11-ketone, 1704 cm.$^{-1}$, Δ^4-3-ketone, 1664 cm.$^{-1}$, conj. Δ^4-C=C, 1614 cm.$^{-1}$.

Acknowledgment.—The authors are indebted to Drs. D. H. Peterson, H. C. Murray and P. D. Meister for suggestions with regard to obtaining a supply of 11α-hydroxy-4-androstene-3,17-dione. Our thanks are due to Dr. J. L. Johnson, Mr. J. E. Stafford and Mrs. G. S. Fonken for the ultraviolet and infrared analyses, and to Mr. W. A. Struck and his associates for the optical rotations and microanalyses.

KALAMAZOO, MICHIGAN

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. L.[1] The Oxidation of Steroidal Allylic Alcohols with Manganese Dioxide. A Novel Synthesis of Testosterone[2]

BY FRANZ SONDHEIMER, C. AMENDOLLA AND G. ROSENKRANZ

RECEIVED JUNE 25, 1953

The oxidation of a number of steroidal allylic alcohols to the corresponding carbonyl compounds by means of manganese dioxide is described [Δ^4-3β-ol (I) → Δ^4-3-one (II); Δ^5-7α-ol (III) → Δ^5-7-one (IV); $\Delta^{9(11)}$-12ξ-ol (V) → $\Delta^{9(11)}$-12-one (VI) and $\Delta^{17(20)}$-21-ol (VII) → $\Delta^{17(20)}$-21-al (VIII)]. Δ^4-Androstene-3,17-dione (IX) on reduction with lithium aluminum hydride gives a mixture of Δ^4-androstene-3β,17β-diol (Xa) and the 3α,17β-diol (Xb), which on oxidation with manganese dioxide furnishes testosterone (XI)—in 90% over-all yield. Similarly progesterone (XII) is converted to Δ^4-pregnen-20β-ol-3-one (XIVa).

The use of manganese dioxide for the oxidation of polyene alcohols to the corresponding carbonyl compounds was first described in 1948 by Morton and collaborators,[3] who oxidized vitamin A to vitamin A aldehyde with this reagent. Since that time other polyene alcohols, both primary and secondary, have been oxidized with manganese dioxide,[4] and it has been shown that even simple singly unsaturated alcohols may be oxidized to the corresponding carbonyl compounds with the reagent (allyl alcohol → acrolein, oct-3-yn-2-ol → oct-3-yn-2-one).[5] We have investigated the manganese dioxide oxidation of a number of singly unsaturated allylic alcohols of the steroid series, and have found that oxidation to the corresponding carbonyl compounds may often be brought about smoothly and in satisfactory yield.

The first alcohol to be oxidized was Δ^4-cholesten-3β-ol, containing the Δ^4-3β-ol system I. In this and subsequent oxidations it was found that commercial manganese dioxide gave erratic and unreproducible results, and with some samples no oxidation at all was observed. The dioxide prepared from manganese sulfate and potassium permanganate,[6] however, proved to be quite satisfactory, and this material could be kept for several months in a stoppered bottle without loss of activity.[7] When Δ^4-cholesten-3β-ol was shaken at room temperature with this reagent in any one of a variety of solvents, such as benzene, chloroform, ethylene chloride or acetone, oxidation to Δ^4-cholesten-3-one (type II) proceeded rapidly, and the latter could be isolated in almost quantitative yield. Similarly the mixture of Δ^4-cholesten-3α-ol and -3β-ol (predominantly the latter[8]), obtained by the lithium aluminum hy-

(1) Steroids. XLIX, A. Sandoval, L. Miramontes, G. Rosenkranz, Carl Djerassi and Franz Sondheimer, THIS JOURNAL, **75**, 4117 (1953).

(2) Presented in part at the Los Angeles Meeting of the American Chemical Society, March, 1953. A preliminary announcement of part of this work has been published (F. Sondheimer and G. Rosenkranz, *Experientia*, **9**, 62 (1953)).

(3) S. Ball, T. W. Goodwin and R. A. Morton, *Biochem. J.*, **42**, 516 (1948).

(4) *Cf.* N. L. Wendler, H. L. Slates, N. R. Trenner and M. Tishler, THIS JOURNAL, **73**, 719 (1951); E. A. Braude, *et al.*, *J. Chem. Soc.*, 1755 (1951); 1419, 1430 (1952); B. C. L. Weedon and R. J. Woods, *ibid.*, 2687 (1951); K. R. Farrar, J. C. Hamlet, H. B. Henbest and E. R. H. Jones, *ibid.*, 2657 (1952); R. Ahmad, F. Sondheimer, B. C. L. Weedon and R. J. Woods, *ibid.*, 4089 (1952); R. Ahmad and B. C. L. Weedon, *Chemistry and Industry*, 882 (1952).

(5) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.*, 1094 (1952).

(6) O. Mancera, G. Rosenkranz and F. Sondheimer, *ibid.*, 2189 (1953).

(7) These observations are essentially in agreement with those of Attenburrow, *et al.* (reference 5). We did not, however, treat our dioxide with alkali, although it was later reported by the English workers that they found it essential to do so.

(8) P. A. Plattner, H. Heusser and A. B. Kulkarni, *Helv. Chim. Acta*, **32**, 265 (1949); W. G. Dauben, R. A. Micheli and J. F. Eastham, THIS JOURNAL, **74**, 3852 (1952). Both these groups found that at least 70% of the 3β-isomer was formed in this reduction, despite an earlier report by H. McKennis and G. W. Gaffney (*J. Biol. Chem.*, **175**, 217 (1948)) that the reduction led approximately to equal amounts of the 3β- and the 3α-isomers.