Anal. Calcd. for $C_{10}H_{20}O_6$: OMe, 52.5. Found: OMe, 52.4.

When 0.1 g. of the crystalline compound was treated with 1.1 moles of aniline in the usual manner the aniline derivative of 2,3,4,6-tetra-O-methyl-D-glucose was obtained. It crystallized from ether solution and melted at 135°[15] alone or admixed with an authentic specimen.

(15) J. C. Irvine and Agnes M. Moodie, *J. Chem. Soc.*, **93**, 95 (1908).

TORONTO 5, CANADA

[CONTRIBUTION FROM THE COLLIP MEDICAL RESEARCH LABORATORY AND FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WESTERN ONTARIO, LONDON, CANADA]

Steroids and Related Products. I. The Synthesis of 17α-Methyldesoxycorticosterone

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A new hormone analog, 17α-methyldesoxycorticosterone, has been synthetized from desoxycorticosterone. In the course of this investigation it has been shown that the alkali-sensitive α,β-unsaturated 3-ketone, present in many natural steroid hormones, can be protected easily against strong alkaline treatment by the formation of the corresponding enol ethyl ether. 17α-Methyldesoxycorticosterone acetate was found to possess adrenal cortical activity.

Considering that 17α-methyltestosterone[3] is a highly potent, orally active androgen[4] and that 17α-methylprogesterone[5a,b,c] possesses two to three times the progestational activity of the natural corpus luteum hormone, progesterone,[5b,c,6] it seemed of interest to prepare the corresponding 17 homologs of the adrenal cortical hormones and to investigate their biological properties. The interest in such experiments seemed the greater because the important adrenal cortical hormones, cortisone (Kendall's compound E), dihydrocortisone (Kendall's compound F) and 17α-hydroxydesoxycorticosterone (Reichstein's compound S), also have a substituent in the 17α-position in the form of a hydroxyl group.

It was reported in 1950[5b] and again more recently[5c] that parts of such syntheses had been undertaken in the desoxycorticosterone series. The synthesis of 17α-methyldesoxycorticosterone has now been accomplished by different methods by Heusser and co-workers at the Swiss Federal Institute of Technology in Zurich in collaboration with one of us (C.R.E.) and by our laboratory in parallel experiments. It was agreed with the Swiss group to publish the results obtained in Zurich in the *Helvetica Chimica Acta* and to report the findings of our laboratory in THIS JOURNAL.

Whereas in the earlier attempts[5,7] Δ⁵-3,β-hydroxysteroids were used as starting materials, the experiments of this series proceeded from 3α-hydroxysteroids with saturated nuclei belonging to the normal (bile acid) series, or from Δ⁴-3-ketosteroids, today easily obtainable from the 3-keto derivatives of such compounds[8] or by Oppenauer oxidation of Δ⁵-3-hydroxysteroids.[9] Desoxycorticosterone (I) was converted in good yield, according to Reichstein's method,[10] to a mixture of 21-tosyloxyprogesterone (IIa)[10,11] and 21-chloroprogesterone (IIb) in which the latter predominated considerably. We found that when the mixture was not eluted quickly from the chromatographic column (aluminum oxide) no tosylate could be isolated. The chloroketone IIb underwent a rearrangement of the Aston–Greenburg type[12] when treated with potassium methylate in methanol, according to the experimental conditions described by Plattner and co-workers,[13] and gave in 95% yield a mixture of the two epimeric methyl Δ⁴-3-keto-17-methyletienates VI and VII. It was not necessary to employ chloroprogesterone of very high purity to obtain high yields. When a crude mixture of chloroprogesterone and tosyloxyprogesterone containing approximately 60% of chloroprogesterone (in this mixture the ratio of tosyloxyprogesterone was deliberately made greater than in the original reaction product obtained from desoxycorticosterone) was subjected to an identical treatment, the same mixture of VI and VII was isolated from the neutral fraction of the reaction product in approximately 53% yield; the relatively important acid fraction, not obtained when chloroprogesterone alone had been employed, gave upon methylation with diazomethane the same mixture of esters, bringing the total yield of these two esters to approximately 88%. The fact that the ester representing approximately 63% of the mixture was eluted with greater ease from the chromatogram and possessed a higher specific rotation than its

(1) Holder of a Medical Fellowship of the Canadian Life Insurance Officers Association.

(2) This paper is abbreviated from part of the doctoral thesis of G. Just to be presented to the Faculty of Graduate Studies of the University of Western Ontario.

(3) L. Ruzicka, M. W. Goldberg and H. R. Rosenberg, *Helv. Chim. Acta*, **18**, 1487 (1935).

(4) K. Miescher and E. Tschopp, *Schweiz. Med. Wochenschrift*, **68**, 1258 (1938).

(5) (a) Pl. A. Plattner, H. Heusser and P. Th. Herzig, *Helv. Chim. Acta*, **32**, 270 (1949); (b) H. Heusser, Ch. R. Engel, P. Th. Herzig and Pl. A. Plattner, *ibid.*, **33**, 2229 (1950); (c) Hs. H. Günthard, E. Beriger, Ch. R. Engel and H. Heusser, *ibid.*, **35**, 2437 (1952).

(6) See also A. Wettstein and F. Benz, *Ann. Rev. Biochem.*, **18**, 355 (1949).

(7) *Cf.* a forthcoming publication in the "Helvetica Chimica Acta."

(8) *Cf.*, for example, V. R. Mattox and E. C. Kendall, THIS JOURNAL, **70**, 882 (1948); **72**, 2290 (1950); *J. Biol. Chem.*, **188**, 287 (1951); W. F. McGuckin and E. C. Kendall, THIS JOURNAL, **74**, 5811 (1952); B. A. Koechlin, T. H. Kritchevsky and T. F. Gallagher, *J. Biol. Chem.*, **184**, 393 (1950).

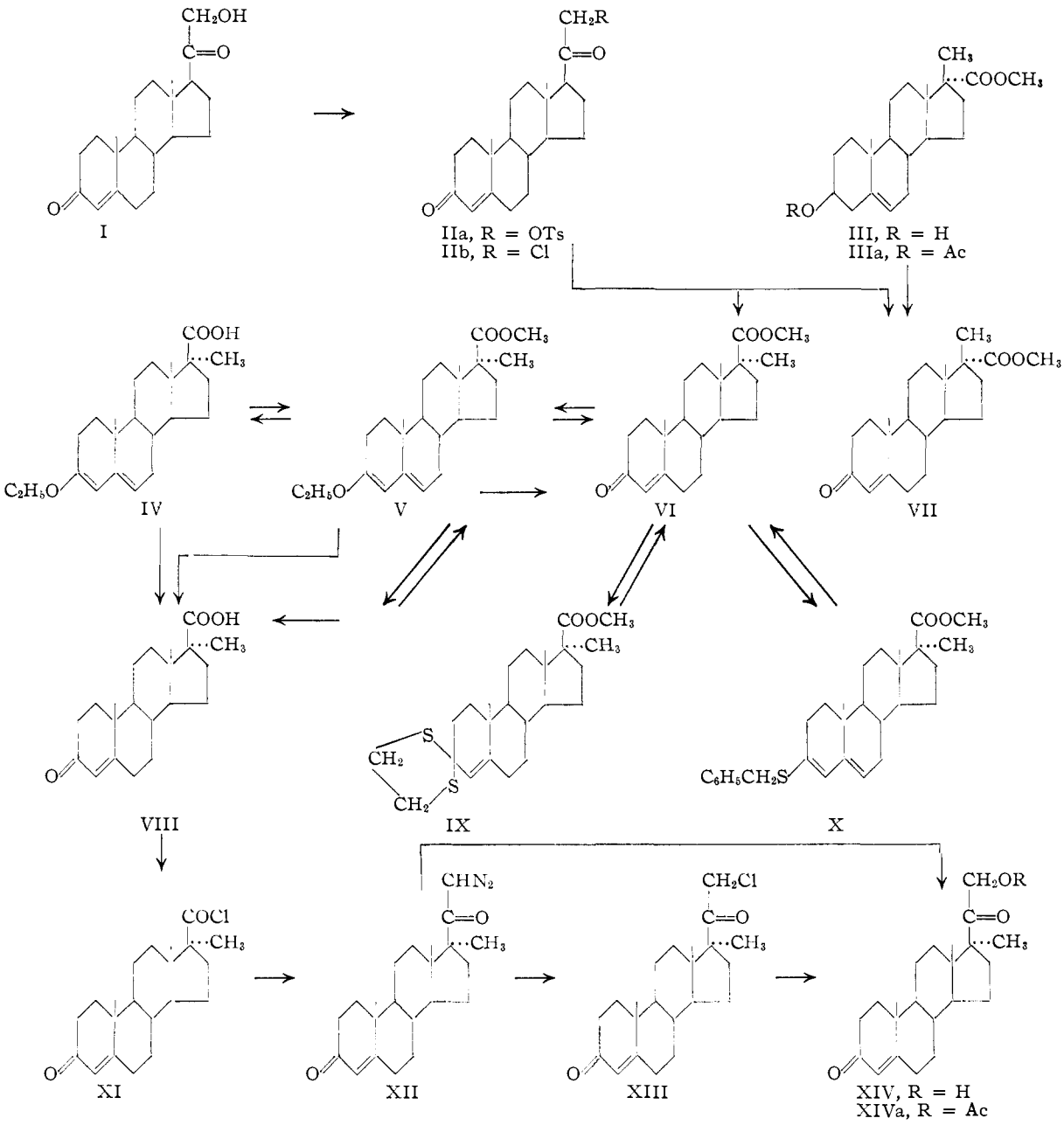
(9) R. V. Oppenauer, *Rec. trav. chim.*, **56**, 137 (1937).

(10) T. Reichstein and H. G. Fuchs, *Helv. Chim. Acta*, **23**, 684 (1940).

(11) T. Reichstein and W. Schindler, *ibid.*, **23**, 669 (1940).

(12) J. G. Aston and R. B. Greenburg, THIS JOURNAL, **62**, 2590 (1940); see also Al. Faworsky, *J. prakt. Chem.*, [2] **88**, 658 (1913).

(13) Pl. A. Plattner, H. Heusser and S. F. Boyce, *Helv. Chim. Acta*, **31**, 603 (1948).



isomer was suggestive that its carbomethoxy grouping had the "natural" β-configuration, the tertiary methyl group the α-configuration (compare VI)[14]; the constitution and configuration of the two esters could furthermore be proven by direct comparison of the more dextrorotatory ester VI with a sample prepared by a different route[5c] and of the more levorotatory ester VII with a product obtained by Oppenauer oxidation of methyl Δ^5-3β-hydroxy-17β-methyl-17-isoetienate (III).[15]

As the side-chains of the natural progestational and adrenal hormones occupy the 17β-position and as only 17α-methylprogesterone and not its 17-isomer show high progestational activity,[14] attention was first given to the synthesis of 17α-methyldesoxycorticosterone.

In order to elaborate the ketol side-chain by the diazoketone synthesis originated by Reichstein,[16] the methyl ester VI had to be saponified to the free acid. It has been shown[5a,b,13,14,17] that 17-methylated etioesters of the type of VI and VII can be hydrolyzed only by vigorous methods; the presence of the α,β-unsaturated keto grouping forbade strong alkaline treatment without suitable protection in position 3. In the course of this investigation formation of an enol ether proved to be the method of choice for the protection of this grouping against

(14) Compare H. Heusser, Ch. R. Engel and Pl. A. Plattner, *Helv. Chim. Acta*, **33**, 2237 (1950).

(15) We wish to thank Dr. H. Heusser for kindly providing us with a sample of VI prepared by the route described in the paper indicated under footnote 5c, and with the acetate IIIa of the ester III

(16) (a) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **20**, 1164 (1937); (b) see also T. Reichstein and E. von Euw, *ibid.*, **23**, 136 (1940).

(17) R. E. Marker and R. B. Wagner, THIS JOURNAL, **64**, 216 (1942)

strong alkaline treatment. Previously, Schwenk and co-workers[18a] had been able to hydrolyze the ester grouping of testosterone-3-enol-ethyl-ether-17-propionate in alkaline medium without removing the ethoxyl group; similarly, Serini and Köster[18b] protected the Δ^4-3-ketone against the reducing action of sodium and propyl alcohol by formation of an enol ether; Meystre and Miescher[18c] extended this method to the protection of this grouping against the attack of lithium aluminum hydride.[19] The enol ether V was prepared in 90% yield by reaction of the Δ^4-3-ketoester VI with triethyl orthoformate in ethanol–dioxane solution[20] and was easily reconverted to the keto ester VI by mild acid hydrolysis; upon heating at 170° for 50 hours in 7% methanolic potassium hydroxide solution and subsequent acidification of the reaction product it gave Δ^4-3-keto-17α-methyletienic acid (VIII) in 80–90% yield. The structure of this compound was ascertained by its reconversion to the methyl ester VI by treatment with diazomethane and by direct comparison with a sample obtained by a different route.[5c] When compound V was submitted to the same alkaline treatment, the reaction mixture not acidified but diluted with much water and extracted with ether, a crystalline, highly hygroscopic substance melting between 209 and 211° could be isolated in 8% yield. To this product the structure of $\Delta^{3,5}$-3-ethoxy-17α-methyletiadienic acid (IV) was assigned, as it afforded after mild acid hydrolysis the keto acid VIII and after treatment with diazomethane the enol ether V. (The main part of the enol ether acid IV remained, of course, as sodium salt, in the alkaline solution, acidification of which gave immediately the free keto acid, VIII.)

The keto ester VI reacted also with ethane-1,2-dithiol in the presence of anhydrous zinc chloride and sodium sulfate to give an excellent yield of the corresponding thioketal IX,[21] but this compound could not be hydrolyzed to the free keto ester VI in yields exceeding 15%, even under vigorous conditions, and was therefore considered unsuitable for the protection of the α,β-unsaturated 3-ketone. The hydrolysis in position 3 of the benzyl thioether X resulted in a somewhat better yield, but its preparation from VI by reaction with benzyl mercaptan in the presence of zinc chloride and sodium sulfate[22] was not very satisfactory. A direct acid hydrolysis of VI to VIII was attempted but is of no particular interest, the highest yields obtained with hydrochloric acid in dioxane amounting only to 5%.

The unsaturated keto acid VIII was converted by treatment of its sodium salt with oxalyl chloride according to Wilds[23] to its chloride XI which reacted with an excess of diazomethane at low temperature[24] to give the diazoketone XII. In previous experiments[25] 17-methyl-diazoketones of type XII would not react with acetic acid to the corresponding ketol acetates (type XIVa), or with sulfuric acid to the free ketols (type XIV), contrary to the findings in the homologous desoxycorticosterone series void of the 17-methyl group.[16b] It has now been possible to convert the diazoketone XII to the ketol XIV by addition of a suspension of the crude diazoketone XII in dioxane to a mixture of one part 2 *N* aqueous sulfuric acid solution and one part dioxane, at room temperature, and subsequent warming of the mixture to 80°, the whole experiment being carried out in a nitrogen atmosphere. Heating over 80° had to be avoided. The crude reaction product was acetylated in the usual way with acetic anhydride in pyridine and yielded after chromatography 17α-methyldesoxycorticosterone acetate (XIVa), 21-chloro-17α-methylprogesterone (XIII),[5a] Δ^4-3-keto-17α-methyletienic acid (VIII) and small amounts of the methyl ester VI of this acid; the over-all yields of the ketol acetate XIVa and the chloroketone XIII from acid VIII, considering the recovery of parts of this acid, were 14.4 and 6.8%, respectively. Earlier, Plattner, Heusser and Herzig[5a] reported the relative inertness of 17-methylated haloketones of type XIII compared to the corresponding compounds possessing no alkyl substituent in position 17. Neither hydrolysis to the free ketol of type XIV nor replacement of the 21-halogen atom by an acetoxy grouping, using potassium, lead or silver acetate in acetic acid and in the presence of acetic anhydride, under various conditions, could be carried out successfully.[5a,26] Replacement of the chlorine atom of 21-chloro-17α-methylprogesterone (XIII) by an acetoxy grouping was achieved by the use of a modification of a method introduced in the carbohydrate series by Hardegger and co-workers[27]; the chloroketone XIII was treated with silver acetate, in the presence of acetic anhydride in boiling pyridine, giving the ketol acetate XIVa in 40–45% yield.[28] The total yield of the transformation of acid VIII to the ketol acetate XIVa amounted to 17.4%. XIVa was hydrolyzed by letting it stand for four days, under nitrogen and at room temperature, with sodium bicarbonate in methanol–water. The free alcohol, 17α-methyldesoxycorticosterone (XIV), could be reconverted to the acetate XIVa by treatment with acetic anhydride in pyridine. The acetate gave no depression of melting point upon admixture with a sample obtained by a different

(18) (a) E. Schwenk, G. Fleischer and B. Whitman, THIS JOURNAL, **60**, 1702 (1938); (b) A. Serini and H. Köster, *Ber.*, **71**, 1766 (1938); (c) Ch. Meystre and K. Miescher, *Helv. Chim. Acta*, **32**, 1758 (1949).

(19) After completion of this work A. Sandoval, L. Miramontes, G. Rosenkranz, C. Djerassi and F. Sondheimer reported in a preliminary communication [THIS JOURNAL, **75**, 4117 (1953)] the protection of the α,β-unsaturated 3-ketone by the formation of an ethyl enol ether during ethinylation with potassium in *t*-amyl alcohol.

(20) Compare P. L. Julian, E. W. Meyer, W. J. Karpel and W. Cole, *ibid.*, **73**, 1982 (1951).

(21) Compare R. Antonucci, S. Bernstein, R. Littell, K. J. Sax and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952). See also H. Hauptmann, THIS JOURNAL, **69**, 562 (1947).

(22) Compare C. Rosenkranz, S. Kaufmann and J. Romo, *ibid.*, **71**, 3689 (1949).

(23) (a) A. L. Wilds, U. S. Patent 2,538,611; (b) A. L. Wilds and C. H. Shunk, THIS JOURNAL, **70**, 2427 (1948); (c) see also R. Adams and L. H. Ulich, *ibid.*, **42**, 599 (1920).

(24) Compare F. Arndt, B. Eistert and W. Partale, *Ber.*, **60**, 1364 (1927); F. Arndt and J. Amende, *ibid.*, **61**, 1122 (1928); F. Arndt, B. Eistert and J. Amende, *ibid.*, **61**, 1949 (1928).

(25) Unpublished results from H. Heusser, Ch. R. Engel and E. Beriger, Swiss Federal Institute of Technology, Zurich.

(26) Unpublished experiments by H. Heusser, P. Th. Herzig and Ch. R. Engel, Swiss Federal Institute of Technology, Zurich.

(27) E. Hardegger, R. M. Montavon and O. Jucker, *Helv. Chim. Acta*, **31**, 1863, 2247 (1948).

(28) A more detailed discussion of this method and a new improved modification will be reported in the "Helv. Chim. Acta."

route in the Zurich laboratory.[7] It showed in the ultraviolet a maximum of absorption at 240 mμ(log ε 4.26); its structure was furthermore confirmed by its infrared absorption spectrum for which we are indebted to Dr. T. F. Gallagher and Miss F. Herling of the Sloan-Kettering Institute for Cancer Research, New York.

Preliminary biological investigations of 17α-methyldesoxycorticosterone acetate indicate that this compound shows activity in life maintenance of adrenalectomized rats. The detailed physiological results will be reported elsewhere.

Acknowledgments.—We wish to express warm thanks to Dr. H. Heusser from the Swiss Federal Institute of Technology for his very kind coöperation and for his agreement to the arrangements by which this paper was published. We are very greatful to the Ciba Company Limited in Basle for supplying us with desoxycorticosterone as starting material. To Dr. T. F. Gallagher and Miss F. Herling of the Sloan-Kettering Institute for Cancer Research, New York, N.Y., and to Dr. R. N. Jones of the National Research Council, Ottawa, we extend our sincere thanks for the infrared spectral analyses. We are deeply indebted to Dean J. B. Collip whose continued interest and generosity have made this work possible. Sincere thanks are due to Professor J. A. Gunton who kindly made laboratories and facilities of his department available for this investigation. One of us (G. J.) wishes to acknowledge the receipt of a summer studentship from the Department of Medical Research.

Experimental[29,30]

21-Tosyloxyprogesterone (IIa) and 21-Chloroprogesterone (IIb) from Desoxycorticosterone (I). (a).—Following exactly Reichstein's procedure,[10] 1.115 g. of desoxycorticosterone (I), m.p. 134–135°, was treated with *p*-toluenesulfonyl chloride. The resulting amorphous product (2.203 g.) was rapidly chromatographed on 33 g. of aluminum oxide.[31] Petroleum ether–benzene (1:1 and 1:4) eluted 487 mg. (42.6%) of a crystalline material, m.p. 194–201°, which showed a positive halogen test. The product crystallized from acetone–hexane in fine colorless needles. A sample was recrystallized four times for analysis, m.p. 201–201.5°, $[\alpha]^{24}D$ 193.8° (*c* 0.915 in $CHCl_3$), λ_{max}^{EtOH} 240 mμ (log ε 4.14).

Anal. Calcd. for $C_{21}H_{29}O_2Cl$: C, 72.29; H, 8.38; Cl, 10.16. Found: C, 72.56, 72.38; H, 8.29, 8.43; Cl, 10.12, 10.16.

The benzene and benzene–ether (4:1) fractions of the above-mentioned chromatogram eluted 406 mg. of crystals melting between 164–168.5° (35.7% based on IIb), consisting of a mixture of IIa and IIb. The benzene–ether (1:1) elutions yielded 176 mg. (11.8%) of an oil which upon trituration with ether and hexane crystallized in fine needles decomposing at 133–135°. The Lassaigne test for sulfur was positive. Recrystallization from a mixture of acetone–ether–hexane raised the decomposition point to 153.5–154°. Further recrystallization did not change the decomposition point. Upon admixture of IIb, the decomposition point was depressed by 3°; $[\alpha]^{24}D$ 130° (*c* 0.776 in $CHCl_3$).

Anal. Calcd. for $C_{28}H_{36}O_5S$: C, 69.39; H, 7.49; S, 6.62. Found: C, 69.37; H, 7.46; S, 6.52.

(b).—Treatment of 1.65 g. of desoxycorticosterone (I) as under (a) gave 2.93 g. of an amorphous product which was chromatographed in the usual manner on 85 g. of aluminum oxide (total time of elution 10 hours). Petroleum ether–benzene (1:1 and 1:4) and benzene eluted 1.135 g. of chloroketone IIb, m.p. 184–204° (65% yield). The benzene–ether (4:1 and 1:1) elutions afforded 222 mg. of a product melting between 150 and 173°, from which no pure product could be obtained either by repeated chromatography or by fractional crystallizations.

When 17.772 g. of desoxycorticosterone (I) were treated in an analogous way (total time of elution from the aluminum oxide column 12 hours), 9.615 g. of chloroketone IIb was obtained, as well as 4.192 g. of a product melting between 130 and 154°, from which no pure substance could be isolated.

Methyl Δ⁴-3-Keto-17α-methyletienate (VI) and Methyl Δ⁴-3-Keto-17β-methyl-17-isoetienate (VII). (a) **From 21-Chloroprogesterone (IIb).**—To a solution of 2.1 g. of potassium in 220 cc. of absolute methanol was added portionwise 9.615 g. of chloroprogesterone (IIb), m.p. 179–191°. The reaction mixture was refluxed for 2 hours with exclusion of moisture, then, after cooling, poured into water and extracted with ether. The ethereal solution was washed until neutral, dried and the solvent removed. The resulting oil (9.687 g.) was chromatographed on 250 g. of aluminum oxide. The petroleum ether–benzene (4:1,1:1) fractions yielded after recrystallization from acetone–hexane 2.945 g. of coarse cubes, m.p. 170–171°. Repeated recrystallization raised the m.p. to 173–173.5°. The mixed melting point with a sample of methyl ester VI prepared by a different route[5c,15] was not depressed: $[\alpha]^{23}D$ 100.7° (*c* 1.078 in $CHCl_3$), λ_{max}^{EtOH} 241 mμ (log ε 4.16).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.62; H, 9.62.

The benzene and benzene–ether elutions afforded after crystallization from acetone–hexane 578 mg. of fine needles, m.p. 152–153°. Repeated recrystallization raised the m.p. to 155.5–156°, $[\alpha]^{22}D$ 74.8° (*c* 1.018 in $CHCl_3$), λ_{max}^{EtOH} 241 mμ (log ε 4.21).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.60; H, 9.36. Found: C, 76.67; H, 9.25.

Repeated chromatography of the petroleum ether–benzene (1:1, 1:4) fractions, consisting of a mixture of the two stereoisomers, and of the mother liquors of the esters VI and VII (5.022 g.) raised the yield of the ester VI to 5.53 g. (58.5%) and of the ester VII to 2.37 g. (25%).

After the above described extraction of the neutral fraction of the reaction mixture, the alkaline aqueous solution was acidified and extracted with chloroform. The organic solution was washed with water, dried and the solvent removed. Only minute amounts of amorphous material were obtained.

(b) **From a Mixture of 21-Tosyloxyprogesterone (IIa) and 21-Chloroprogesterone (IIb).**—A mixture (634 mg.) of the tosylate IIa and the chloroketone IIb, containing approximately 40% IIa and 60% IIb, was treated and worked up as under (a). Chromatography of the neutral fraction (560 mg.) afforded 166 mg. of the methyl ester VI, 16 mg. of the methyl ester VII and 112 mg. of a mixture of VI and VII. The amorphous acid fraction was dissolved in a mixture of absolute methanol and absolute ether, methylated with diazomethane and worked up in the usual way. Chromatography of the resulting oil (474 mg.) yielded 125 mg. of the ester VI, 50 mg. of the ester VII and 28 mg. of a mixture of the isomers. The mixtures of the isomeric esters from the neutral and the methylated acid fractions were combined and rechromatographed. The total yield of the ester VI was 321 mg. (57.6%), of the methyl ester VII 98 mg. (17.6%); 74 mg. (13.3%) of remaining mixture was not further purified.

Methyl Δ⁴-3-Keto-17β-methyl-17-isoetienate (VII) from Methyl Δ⁵-3β-Acetoxy-17β-methyl-17-isoetienate (IIIa).—Methyl Δ⁵-3β-hydroxy-17β-methyl-17-isoetienate (III)[14,15] was obtained by refluxing 908 mg. of the acetate IIIa for 1 hour in 90 cc. of a 5% methanolic potassium hydroxide solution. The reaction mixture was worked up in the usual

(29) The microanalyses were carried out by Mr. J. F. Alicino, Metuchen, N. J., to whom we wish to express our sincere appreciation.

(30) All melting points were taken in evacuated capillaries and the temperatures corrected.

(31) We are indebted to Merck and Co., Montreal, for providing us with activated aluminum oxide for chromatography. This commercial product was neutralized by allowing it to stand with ethyl acetate for 30 hours, filtered, washed with water and methanol and reactivated by heating *in vacuo* for approximately four hours to 210–218°. Its activity, according to the Brockmann scale [*Ber.*, **74**, 73 (1941)], was II–III.

manner and afforded 878 mg. of III, m.p. 173.5–175°. After recrystallization from methanol, the product melted at 175–175.5°.[14]

To a solution of 590 mg. of dried hydroxy ester III in 24 cc. of absolute benzene, 10.5 cc. of absolute toluene and 4.5 cc. of freshly distilled cyclohexanone was added 665 mg. of aluminum *t*-butoxide; the reaction mixture was refluxed gently for 12 hours (bath temperature 125°) and worked up in the usual manner.[9,14] Chromatography of the partly crystalline material on 15 g. of aluminum oxide afforded 407 mg. (70%) of ester VII, m.p. 140–153°. Recrystallization from acetone–hexane raised the m.p. to 155–156°. The mixed melting point with ester VII obtained by rearrangement of IIb was not depressed. A sample was recrystallized three times for analysis; m.p. 155.5–156°, $[\alpha]^{21}D$ 73.4° (*c* 1.295 in $CHCl_3$).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.83; H, 9.19.

Methyl Δ⁴-3-Keto-17α-methyletienate-3-ethylene-thioketal (IX).—At 0° there were added 2 g. of anhydrous sodium sulfate, 1 g. of freshly fused zinc chloride and 0.8 cc. of ethanedithiol to a solution of 900 mg. of methyl ester VI in 10 cc. of absolute benzene.[21] The reaction mixture was allowed to stand at room temperature for three days, then poured into water, extracted with ether–benzene (9:1) and the organic solution washed with aqueous sodium bicarbonate and water. After drying the solvents were removed *in vacuo*. The thioketal crystallized from acetone–methanol in two different forms, one melting at 118.5–119.5° (coarse needles), the other at 154.5–155.5° (fluffy needles). Crystallization afforded 840 mg. of thioketal (76.3%), m.p. 117–119.5°, and a second crop of 142 mg. (12.9%), m.p. 112.5–114°. A sample was recrystallized four times from acetone–methanol for analysis; m.p. 154.5–155.5°, $[\alpha]^{23}D$ 80.3° (*c* 1.117 in $CHCl_3$).

Anal. Calcd. for $C_{24}H_{36}O_2S_2$: C, 68.52; H, 8.63; S, 15.25. Found: C, 68.44; H, 8.39; S, 15.44.

Hydrolysis.—A solution of 56 mg. of thioketal IX in 2 cc. of dioxane was refluxed for 3 hours with 2 cc. of concentrated hydrochloric acid. The reaction mixture was worked up in the usual manner and yielded an amorphous product (60 mg.). Chromatography on 5 g. of aluminum oxide afforded 42 mg. of thioketal IX, m.p. 150–152°, and 7 mg. of methyl ester VI, m.p. 169.5–170°.

3-Benzyl-thioenol Ether of Methyl Δ⁴-3-Keto-17α-methyletienate (X).—At 0° there was added 1 cc. of benzyl mercaptan to a finely powdered mixture of 300 mg. of methyl ester VI, 500 mg. of anhydrous sodium sulfate and 500 mg. of freshly fused zinc chloride. The mixture was allowed to stand at room temperature for 3 days, poured into water and extracted with ether–chloroform. The organic layer was washed with water, dried and the solvents removed *in vacuo*. Crystallization of the resulting oil from acetone afforded 109 mg. (27.8%) of fine needles, m.p. 155.5–156°. The thioenol ether was recrystallized twice from acetone for analysis, m.p. 156°, $[\alpha]^{22}D$ −115° (*c* 1.219 in $CHCl_3$–pyridine), λ_{max}^{EtOH} 269 mμ (log ε 4.06), $\nu_{max}^{CS_2}$ 1728 cm.$^{-1}$ (17-carbomethoxy), $\nu_{max}^{CHCl_3}$ 1596 cm.$^{-1}$[32]

Anal. Calcd. for $C_{29}H_{36}O_2S$: C, 77.29; H, 8.50; S, 7.11. Found: C, 77.67; H, 8.54; S, 6.92.

Hydrolysis.—A solution of 26 mg. of the thioenol ether X, m.p. 154–155°, in 2 cc. of dioxane and 2 cc. of methanol, containing 0.15 cc. of concentrated hydrochloric acid, was refluxed for 1 hour. The reaction mixture was poured into water and the white precipitate filtered off and washed with water. Crystallization of this precipitate from acetone–hexane afforded 13 mg. of coarse cubes, m.p. 172–173°, which showed no depression of melting point upon admixture with authentic ester VI.

Methyl Δ³,⁵-3-Ethoxy-17α-methyletiadienate (V).—Following the procedure described by Julian and co-workers,[20] 2.939 g. of ester VI was converted into its enol ethyl ether. Crystallization of the reaction product from acetone–methanol, in the presence of a few drops of pyridine, afforded 2.66 g. of V (84%), m.p. 132–133.5°. A sample was recrystallized three times for analysis; shiny scales, m.p. 133–133.5°, $[\alpha]^{22}D$ −89.4° (*c* 0.519 in $CHCl_3$–pyridine), λ_{max}^{EtOH} 241 mμ (log ε 4.1).

(32) The infrared analysis was kindly carried out and interpreted by Dr. R. N. Jones, National Research Council, Ottawa.

Anal. Calcd. for $C_{24}H_{36}O_3$: C, 77.37; H, 9.74. Found: C, 77.49; H, 9.76.

The mother liquors from the recrystallizations were acidified with 2 *N* hydrochloric acid to *p*H 1, and after 24 hours worked up in the usual manner. The resulting oil (500 mg.) was chromatographed on 15 g. of aluminum oxide. The petroleum ether–benzene fractions were recrystallized from acetone–hexane and gave 150 mg. of methyl ester VI, m.p. 170.5–171.5° (total yield of enol ether V, considering the recovery of VI, 89.4%).

Hydrolysis.—To a solution of 102 mg. of enol ether V, m.p. 133–133.5°, in 5 cc. of ether and 3 cc. of methanol was added 0.5 cc. of 2% hydrochloric acid. After 24 hours, the reaction mixture was worked up in the usual manner. Crystallization of the resulting product (150 mg.) from acetone–hexane afforded 78 mg. (83.5%) of ester VI, m.p. 169–171°. The m.p. was not depressed upon admixture of authentic material.

Δ⁴-3-Keto-17α-methyletienic Acid (VIII) and Δ³,⁵-3-Ethoxy-17α-methyletiadienic Acid (IV) from Enol Ether V. (a).—In a sealed tube 2.896 g. of enol ether V was heated with 140 cc. of 7% methanolic potassium hydroxide solution for 48 hours at 168–170°. After dilution with much water and extraction of the neutral fraction with ether, the alkaline solution was acidified and, after 1 hour, extracted with chloroform. The chloroform solution was washed with water, dried and the solvent removed; 2.82 g. of crude acid VIII, m.p. 290–296.5°, was obtained. Recrystallization from methanol yielded 1.979 g. (77.2%) of colorless blades, m.p. 304–305°, and 157 mg. (6.1%) of crystals melting between 292 and 299°. A sample was recrystallized four times for analysis, m.p. 304–305°. The mixed melting point with a sample prepared by a different route[5c] was not depressed; $[\alpha]^{22}D$ 85.5° (*c* 0.671 in dioxane).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.75; H, 8.89.

Methyl Ester (VI).—At 0° there was added 8 cc. of a 2% ethereal solution of diazomethane to 139 mg. of acid VIII, m.p. 303–304°, dissolved in 25 cc. of absolute methanol. After 15 hours, the solvents were removed *in vacuo*. Chromatography of the resulting oil (150 mg.) on 6 g. of aluminum oxide and elution with petroleum ether–benzene afforded 100 mg. of ester VI, m.p. 168–170°. It was recrystallized four times for analysis, m.p. 173–173.5°.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.60; H, 9.36. Found: C, 76.52; H, 9.25.

The neutral fraction from the saponification of the enol ether ester V afforded 354 mg. of **Δ³,⁵-3-ethoxy-17α-methyletiadienic acid** (IV), m.p. 209–211°, a highly hygroscopic and unstable substance from which no analysis preparation could be obtained. Its structure was ascertained by its methylation to the enol ether V and its hydrolysis to the free keto acid VIII.

Methylation of IV.—Enol ether acid IV (105 mg.) was dissolved in 15 cc. of absolute ether and one drop of pyridine and methylated in the manner described above. The resulting amorphous product afforded, after crystallization from acetone–methanol in the presence of small amounts of pyridine, 10 mg. of enol ether V, m.p. 133–133.5°, giving no depression of melting point upon admixture of authentic material.

Hydrolysis of IV.—To a solution of 249 mg. of IV in 20 cc. of ether and 20 cc. of methanol was added 1.5 cc. of 2% hydrochloric acid. The reaction mixture was allowed to stand at room temperature for 24 hours and worked up in the usual manner. Crystallization of the resulting amorphous product from methanol yielded 88 mg. of acid VIII, m.p. 302–304°; mixed m.p. with the pure acid was not depressed. From the mother liquors 18 mg. of a less pure product could be obtained.

(b).—Enol ether V (4 g.) was treated with 180 cc. of methanolic potassium hydroxide solution in a sealed tube for 48 hours at 168–170°. The reaction mixture was poured into 1 *N* hydrochloric acid and extracted with chloroform. The organic layer was washed with water, dried and the solvent removed. Crystallization of the crude acid from methanol afforded 2.73 g. acid VIII, m.p. 300–303° (77%). The mother liquors (802 mg.) yielded upon remethylation 300 mg. of the methyl ester VI (total yield of saponification, 85%).

Δ⁴-3-Keto-17α-methyletienic Acid (VIII) by Acid Hydrolysis.—A solution of 404 mg. of ester VI in 12 cc. of dioxane

was refluxed for 5 hours with 10 cc. of concentrated hydrochloric acid. After cooling, the mixture was made alkaline with 1 *N* methanolic potassium hydroxide, diluted with water extracted with ether, and the ethereal solution washed until neutral, dried and the solvent removed. Crystallization of the resulting oil from acetone–hexane afforded 340 mg. of the starting material, m.p. 171–172°. The alkaline layer was acidified, extracted with chloroform and the organic layer washed with water until neutral. After drying and removal of the solvent, 92 mg. of an oil was obtained, from which 8.5 mg. of VIII, m.p. 300–303°, could be isolated by crystallization from methanol. Mixed m.p. with authentic acid VIII gave no depression.

17α-Methyldesoxycorticosterone Acetate (XIVa) and 21-Chloro-17α-methylprogesterone (XIII) from Δ⁴-3-keto-17α-methyletienic Acid (VIII).—As previously described,[5c] 1.579 g. of acid VIII was transformed to the acid chloride XI, according to Wilds' method.[23] The product obtained was dissolved in 75 cc. of absolute benzene and added with vigorous stirring to 27 cc. of a 4% ethereal diazomethane solution (5.5 mole) cooled to −15°. After 20 hours, the solvents were removed *in vacuo* at 15°. The crude diazoketone XII, suspended in 100 cc. of absolute dioxane and 10 cc. of absolute ethanol, was added slowly, with stirring, to a mixture of 25 cc. of dioxane and 25 cc. of 2 *N* sulfuric acid. The reaction mixture was slowly heated to 80° and kept at that temperature for 15 minutes. The whole operation was carried out in a nitrogen atmosphere. It was found important not to overheat the reaction mixture. After cooling, the mixture was poured into ice-water and extracted with ether. The ethereal solution was washed with iced sodium bicarbonate solution and water and dried. The ether was removed, first at atmospheric pressure, the last 500 cc. *in vacuo* and a slightly yellow oil (2.296 g.) obtained. The product was acetylated and worked up in the usual manner. The resulting oil (1.965 g.) was chromatographed on 60 g. of aluminum oxide. Petroleum ether–benzene (1:4) eluted a mixture of methyl ester VI, chloroketone XIII and acetate XIVa. Benzene and benzene–ether mixtures afforded mainly the acetate XIVa; ethyl acetate–methanol eluted acid VIII. After repeated chromatography and recrystallizations the substances were obtained with the following yields: 2 mg. of ester VI, m.p. 168–169°, not depressed upon admixture of authentic VI; 100 mg. of 21-chloro-17α-methylprogesterone (XIII), m.p. 163–164°; 225 mg. of 17α-methyldesoxycorticosterone acetate (XIVa), m.p. 178°; 240 mg. of Δ⁴-3-keto-17α-methyletienic acid (VIII), m.p. 298–301°, not depressed upon admixture of authentic acid VIII. Taking into account the recovery of acid VIII, the chloroketone XIII was obtained in 6.8% yield, the acetate XIVa in 14.4% yield.

The chloroketone XIII was recrystallized five times from acetone–hexane for analysis; colorless needles, m.p. 165°, $[\alpha]^{23}D$ 106.7° (*c* 0.806 in $CHCl_3$).

Anal. Calcd. for $C_{22}H_{31}O_2Cl$: C, 72.80; H, 8.61; Cl, 9.77. Found: C, 72.96; H, 8.46; Cl, 9.60.

A sample of the acetate XIVa was recrystallized from acetone–hexane for analysis; colorless needles, m.p. 178°, no depression of melting point with a sample obtained by a different route[7]; $[\alpha]^{23}D$ 97.9 (*c* 0.963 in $CHCl_3$), λ_{max}^{EtOH} 240 mμ (log ε 4.26), $\nu_{max}^{CS_2}$ 3030 cm.$^{-1}$ (double bond); 1756 and 1722 cm.$^{-1}$ [21-acetoxy-20-keto-(17-methyl)]; 1676 cm.$^{-1}$ (Δ⁴-3-keto); 1228 cm.$^{-1}$ (21-acetoxy); $\nu_{max}^{CHCl_3}$ 1749 and 1719 cm.$^{-1}$ (21-acetoxy-20-keto); 1666 and 1618 cm.$^{-1}$ (Δ⁴-3-keto). The fingerprint region is different from the one shown by desoxycorticosterone acetate. The lower 20-carbonyl-band, especially in CS_2 solution, shows a small but noticeable shift to lower frequencies, compared with analogous substances devoid of the 17-methyl grouping (compare the article cited in footnote 5c).[33]

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.56; H, 8.60.

17α-Methyldesoxycorticosterone Acetate (XIVa) from 21-Chloro-17α-methylprogesterone (XIII).—To 80 mg. of 21-chloro-17α-methylprogesterone (XIII), m.p. 163–164°, dissolved in 1.1 cc. of acetic anhydride, was added a solution of 225 mg. of silver acetate in 0.8 cc. of hot pyridine. The mixture was heated 100 minutes at 135–140° bath temperature in a nitrogen atmosphere. After cooling and filtration, the reaction mixture was poured into ice-water and allowed to stand for 1 hour. The ether extract of the product was washed with iced dilute hydrochloric acid, cold sodium bicarbonate solution and water, dried and the ether removed first at atmospheric pressure, the last 300 cc. *in vacuo*. The resulting oil (148 mg.) was chromatographed on 5 g. of aluminum oxide. The petroleum ether–benzene mixtures yielded 37 mg. of acetate XIVa, m.p. 157–172° (43.4% yield; by this reaction the total yield of acetate XIVa from acid VIII was raised to 17.4%). The product was recrystallized three times from acetone–hexane for analysis, m.p. 177.5–178°. The melting point was not depressed upon admixture of a sample of acetate XIVa obtained in the previous experiment.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.73; H, 8.70.

17α-Methyldesoxycorticosterone (XIV) from 17α-Methyldesoxycorticosterone Acetate (XIVa).—A solution of 48 mg. of potassium bicarbonate in 0.8 cc. of water was added to 48 mg. of acetate XIVa, dissolved in 5 cc. of methanol. The reaction mixture was kept in a nitrogen atmosphere for four days, then poured into water, extracted with ether and the ethereal solution washed with water and dried. The solvent was removed *in vacuo*. The amorphous residue (34 mg.) crystallized upon trituration with ether–hexane (m.p. 156–165°). The melting point was depressed upon admixture of the acetate XIVa. Two recrystallizations from acetone–hexane afforded colorless prisms, m.p. 171.5–172.5°, $[\alpha]^{23}D$ 95° (*c* 0.546 in $CHCl_3$).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.41; H, 9.25.

Acetylation.—A solution of 26 mg. of 17α-methyldesoxycorticosterone (XIV) in 4 cc. of pyridine was allowed to stand at room temperature with 2 cc. of acetic anhydride for 16 hours. The reaction product was worked up in the usual manner. The resulting amorphous product was chromatographed on 2 g. of aluminum oxide. The crystalline fractions afforded upon recrystallization from acetone–hexane 17α-methyldesoxycorticosterone acetate (XIVa), m.p. 173–175°; mixed m.p. with authentic XIVa was not depressed.

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