Pregnane-3α,20β,21-triol-11-one 3,21-Diacetate 20-Tosylate (XVIII).—A cold solution of 6.25 g. of pregnane-3α,20β,21-triol-11-one 3,21-diacetate in 30 cc. of pyridine was treated with 6.0 g. of recrystallized tosyl chloride, After three days at 0° the solution was diluted with water, extracted with benzene, the benzene layer washed with dilute hydrochloric acid, dilute carbonate and with water. then concentrated to dryness *in vacuo*. Crystallization of the residue from ether gave 7.4 g. of the diacetate tosylate, m. p. 175–176°.

Anal. Calcd. for $C_{32}H_{44}O_8S$: C, 65.28; H, 7.53. Found: C, 65.18; H, 7.56.

Pregnane-3α,21-diol-11,20-dione 3-Acetate 21-Formate (XXI).—A portion (500 mg.) of 21-diazopregnane-3α-ol-11,20-dione acetate (dec. 117–124°; prepared according to the method of Lardon and Reichstein, ref. 15) was added to 3.5 cc. of 90% formic acid. After three minutes the crystals had dissolved with evolution of nitrogen. The solution was warmed gently on the steam-bath for a few seconds, until a pink color began to replace the pale yellow cast. The solution was then diluted with water, extracted with ether, the ethereal layer washed with alkali and with water and concentrated to dryness. Crystallization from a small volume of ether gave dense prisms of the formate, m. p. 153° after recrystallization from alcohol and from ether. The mother liquor was chromatographed, giving in all 430 mg. of acetate formate.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 69.02; H, 8.03.

Pregnane-3α,21-diol-11,20-dione 3-Acetate (XXXII).—A solution of 170 mg. of the acetate formate, m. p. 153°, in 5 cc. of methanol was treated with a solution of 200 mg. of potassium bicarbonate in 2.0 cc. of water. The mixture was stirred for ten minutes, acidified with a few drops of acetic acid, concentrated to a small volume *in vacuo* and extracted with ether. Evaporation of the washed ethereal solution, followed by crystallization of the residue from a small volume of ether gave 129 mg. of pregnane-3α,21-diol-11,20-dione 3-acetate, m. p. 137–138°.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.73; H, 8.79. Found: C, 70.69; H, 8.75.

Pregnane-3α,20β,21-triol-11-one (VI) 3-Acetate from Pregnane-3α,21-diol-11,20-dione 2-Acetate (XXXII).—The catalytic reduction of 2.48 g. of pregnane-3α,21-diol-11,20-dione 3-acetate, m. p. 137–138°, in 100 cc. of glacial acetic acid, using 1.0 g. of platinum oxide under 45 lb. of pressure was completed in an hour. The filtered solution was concentrated to dryness *in vacuo*, the residue dissolved in ether, washed with alkali and water and concentrated to dryness. Crystallization from a small volume of cold absolute ether gave 2.1 g. of fluffy solvated crystals, m. p. 120–126°. Recrystallization from ethyl acetate–petroleum ether gave a sample of m. p. 100–106° (bubbling). Saponification gave pregnane-3α,20β,21-triol-11-one, m. p. and mixed m. p. 235–236°. For analysis a sample was dried in a weighing pig at 130°.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.55; H, 9.10. Weight loss: 2.18%.

Acknowledgments.—The author wishes to express his indebtedness to Dr. Karl Folkers for his active association with this work, to Dr. Everett S. Wallis of Princeton University for valuable suggestions, and to Miss Jean E. Andrews for assistance. The author is indebted to Mr. R. N. Boos and his associates for microanalyses.

Summary

The preparation and correlation of derivatives of pregnane-3α,20α and β-diol-11-one and the corresponding 3-ketones have been described. Similar correlations in the pregnane-3α,20α and β-21-triol-11-one series have been made.

RAHWAY, N. J. RECEIVED OCTOBER 20, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Stereoisomeric Substituted 11-Keto-20-hydroxypregnanes. II

BY L. H. SARETT

In Part I of this series[1] the preparation of various derivatives of the stereoisomeric 11-keto-20-hydroxypregnanes and 11-keto-20,21-dihydroxypregnanes was described. Part II deals with the two remaining classes of 11-keto-20-hydroxypregnanes.

Class C. 11-Keto-17(α),20-dihydroxypregnanes[2]

A useful starting material for the preparation of compounds of this class is pregnane-3α,17α-diol-11,20-dione[3] (I). Since the assignment of the α-configuration to the C-17 hydroxyl was, however, based on indirect evidence, it was felt that more conclusive stereochemical proof was desirable before proceeding to an investigation of the reduction products of this compound. To this end a device employed by von Euw and Reichstein[4] for converting substance P to substance L was used. Pregnane-3α,17α,21-triol-11,20-dione 3,21-diacetate,[2] which has been linked[5] sterically with the naturally occurring Δ^4-pregnene-17α,21-diol-3,11,-20-trione (Kendall's compound E), was treated with methylmagnesium iodide, giving 20-methylpregnane-3α,17α,20 (α and β), 21-tetrol-11-one. When periodic acid cleavage of this mixture then yielded I, the α-configuration of the 17-hydroxyl in the latter compound was established.

The catalytic reduction of pregnane-3α,17α-diol-11,20-dione 3-acetate (II) gave both of the epimeric triolones. By benzoylation of the reduction mixture 15% of a highly crystalline 3-acetate 20-benzoate (XII) could be isolated. Upon saponification it yielded the 3α,17α,20α-triolone (VIII) which was identical with that previously obtained[6]

(1) Sarett, THIS JOURNAL, **71**, 1165 (1949).

(2) The formulation of the C-17 hydroxyl group as alpha in the natural series of 17-hydroxypregnanes follows the evidence presented by von Euw and Reichstein (*Helv. Chim. Acta*, **30**, 205 (1947)).

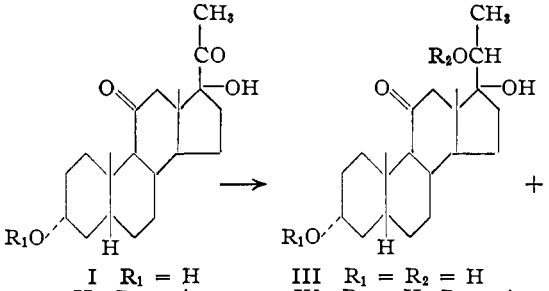
(3) Sarett, THIS JOURNAL, **70**, 1454 (1948).

(4) von Euw and Reichstein, *Helv. Chim. Acta*, **24**, 418 (1941).

(5) A communication describing these results is soon to be published.

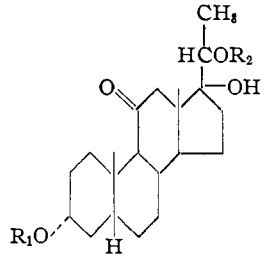
(6) Sarett, THIS JOURNAL, **70**, 1690 (1948).

by hydroxylation of a Δ^{17}-pregnen-3α-ol-11-one. The major product of the reduction was best separated by conversion of the reduction mixture to the diacetates. Repeated crystallization then yielded pregnane-3α,17α,20β-triol-11-one 3,20-diacetate[7] (V). By saponification the new 3α,-17α,20β-triolone (III) was obtained.

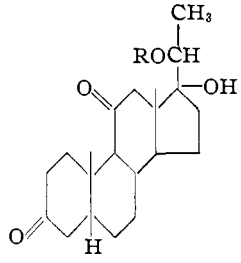


I R_1 = H
II R_1 = Ac

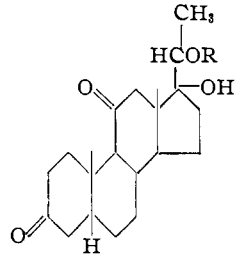
III R_1 = R_2 = H
IV R_1 = H; R_2 = Ac
V R_1 = R_2 = Ac



VIII R_1 = R_2 = H
IX R_1 = R_2 = Ac
X R_1 = H, R_2 = Ac
XI R_1 = Ac, R_2 = H
XII R_1 = Ac, R_2 = C_6H_5CO
XIII R_1 = Ac, R_2 = $SO_2C_6H_4CH_3$



VI R = H
VII R = Ac



XIV R = H
XV R = Ac

In order to prepare the 3-keto derivatives corresponding to the triolones III and VIII, the respective 20-monoacetates were required. In the 20β-series the 20-monoacetate (IV) was readily obtained by partial saponification of the diacetate. Oxidation and hydrolysis then yielded pregnane-17α,20β-diol-3,11-dione (VI). This compound was identical with a pregnane-17,20-diol-3,11-dione previously described in the literature.[8] Pregnane-17α,20α-diol-3,11-dione (XIV) was derived from the free triolone VIII by partial acetylation. Surprisingly enough, the product which was isolated by chromatography was the 20-monoacetate (X), although doubtless the anticipated 3-monoacetate was also formed. Conversion of X to pregnane-17α,20α-diol-3,11-dione (XIV) was then carried out as before.

A second method for obtaining derivatives of 11-keto-17,20-dihydroxypregnanes was the hydroxylation of Δ^{17}-11-ketopregnenes. Insofar as the simple preparation of one or both of the dihydroxypregnanes (III and VIII) was concerned, hydroxylation of one of the mixtures of Δ^{17}- and Δ^{20}-pregnenes formed by various reactions was quite satisfactory. It rapidly became apparent, however, that the nature of the products depended so markedly on the nature of the starting mixture that the simple interpretation of the latter as composed of one of the two possible geometrically isomeric Δ^{17}-pregnenes together with the Δ^{20}-pregnene was dubious. Hence a closer examination of the components of these mixtures was undertaken.

The preparation and hydroxylation of a pure Δ^{17}-pregnene-3α-ol-11-one (XVI) which melted at 192°[7] have been described.[7] When a crystalline product from the mother liquors of this compound was treated with osmium tetroxide, hydrolyzed and the product acetylated, it was not, however, the 3α,17α,20α-triol diacetate (IX) which was isolated but the epimeric 3α,17α,20β-triol diacetate (IV). Only two explanations for these results seemed possible: Either the presence of impurities altered the stereochemical course of the reaction in some unknown way or else a second component reacted with the osmium tetroxide to form IV. In order to test the first possibility, the hydroxylation of mixtures of the pure Δ^{17}-pregnene with coprostanone and also with benzoyl peroxide was carried out. The addition of these substances neither altered the nature of the product (VIII) nor diminished the yield. Hence the second and likelier possibility was explored.

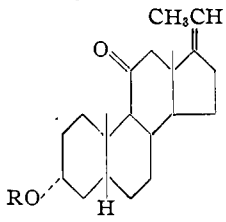
If a second component gave rise to the 3α,17α,-20β-triolone, it could only be the geometrically isomeric Δ^{17}-pregnene-3α-ol-11-one (XVIa), which upon attack of the osmium tetroxide at the rear of the 17,20 linkage would give a 17α,20β-glycol osmate ester. Attempts to isolate this hypothetical geometrical isomer by chromatography and fractional crystallization of the detosylated mother liquor unfortunately were unsuccessful. The higher melting fractions eventually gave pure XVI, while the lower melting fractions remained mixtures with inconstant properties.

The mixture of pregnenes prepared by diazotization of 20-aminopregnane-3α-ol-11-one 3-acetate was then examined. Since only one 3α,17,20-triolone was obtained by hydroxylation of this mixture and it was the 17α,20β-isomer (see Part I), it seemed possible that the sought for Δ^{17}-geometrical isomer might be present. Accordingly, the pregnene mixture was submitted to extensive recrystallization. A compound which melted at 154° was isolated in small amount but it appeared

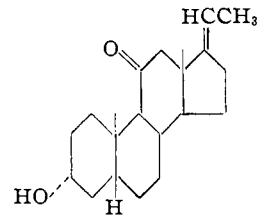
(7) Evidence for the assignment of configuration to the C-20 hydroxyl group is presented in Part III of this series.

(8) Sarett, THIS JOURNAL, **68**, 2478 (1946).

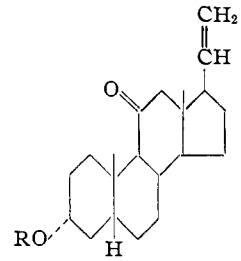
to be identical[9] with Δ^{20}-pregnene-3α-ol-11-one (see diagram).



XVI R = H
XVII R = Ac



XVIa



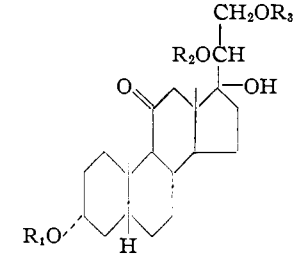
XVIII R = H
XIX R = Ac

When Δ^{17}-21-bromopregnene-3α-ol-11-one acetate[10] was reduced with zinc and acetic acid and the product saponified, a compound which gave pregnane-3α,20(α and β),21-triol-11-one upon hydroxylation was isolated. Evidently the bromide was reduced as a resonating ion, giving a mixture of isomeric pregnenes of which only the least soluble—the Δ^{20}—was separated. The dehydration of pregnane-3α,17β-diol-11-one acetate with phosphorus oxychloride also gave a mixture of crystalline unsaturates, from which no pure compound was obtained. However, in spite of the failure to obtain a pure sample of the geometrical isomer of Δ^{17}-pregnene-3α-ol-11-one, the evidence described appears strongly to indicate its existence in those mixtures which yielded the triolone III on hydroxylation.

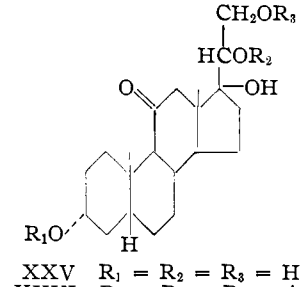
An interesting and perhaps generally useful procedure for the hydrolysis of osmate esters under milder conditions than previously suggested[11] was uncovered in our work on the 17,20-glycols. Since even the relatively gentle conditions described by Criegee and co-workers[11] lead to partial hydrolysis of acetate groups in the molecule, the restoration of such an acetate group must ordinarily be accomplished by preferential esterification. This must be the approach, for example, in the preparation of the 3-monoacetate of a 3,-17,20-triol, in which the protection of the glycol group by an acetonide bridge is not possible. It was found, however, that if the aqueous sodium sulfite solution was added at room temperature to the solution of osmate ester in alcohol containing about 20% of ether, hydrolysis of the osmate linkages occurred far more rapidly than hydrolysis of the acetate group. By this method Δ^{17}-pregnene-3α-ol-11 one acetate gave 80% of pregnene-3α,17α,20α-triol-11-one 3-acetate (XI). The difference is probably to be ascribed to the physical state of the sodium sulfite, which in the presence of ether separates as a gummy, moderately soluble layer instead of the ordinary nearly insoluble crystals.

Class D. 11-Keto-17α,20,21-trihydroxypregnanes

An important source of members of this class is the Δ^{17}-21-hydroxypregnenes. These have been prepared by the classical allylic rearrangement method[12] and also by the 20-tosylate–collidine reaction.[6] Since the problem of geometrical isomerism arose in connection with the preparation of 17,20-dihydroxypregnanes from Δ^{17}-pregnenes, evidence for this type of isomerism in the 21-hydroxy-Δ^{17}-pregnene series was sought. However, it was found that by either method of preparation only one Δ^{17}-pregnene-3α,21-diol-11-one[8] was obtained. Hydroxylation of this compound yielded pregnane-3α,17α,20β,21-tetrol-11-one (**XX**), which could be linked sterically with the previously described pregnane-17α,20β,21-triol-3,11-dione[13] by oxidation of the acetonide (**XXIII**). The 3,21-diacetate (**XXI**) was prepared by reduction of pregnane-3α,17α,21-triol-11,20-dione 3,21-diacetate. Acetylation of the mother



XX $R_1 = R_2 = R_3 = H$
XXI $R_1 = R_3 = Ac$, $R_2 = H$
XXII $R_1 = R_2 = R_3 = Ac$
XXIII $R_1 = H$, $R_2R_3 = >C(CH_3)_2$
XXIV $R_1 = Ac$, $R_2R_3 = >C(CH_3)_2$



XXV $R_1 = R_2 = R_3 = H$
XXVI $R_1 = R_2 = R_3 = Ac$

(9) The two samples agreed in all properties except the melting points of the acetates. Very likely neither sample was entirely free from isomorphous pregnene-3α-ol-11-one isomers.

(10) Sarett, *J. Biol. Chem.*, **162**, 601 (1946).

(11) See, for example, Criegee, Marchand and Wannowius, *Ann.*, **550**, 99 (1942); Prins and Reichstein, *Helv. Chim. Acta*, **25**, 300 (1942); Criegee, *Ann.*, **522**, 75 (1936).

(12) Ruzicka and Müller, *Helv. Chim. Acta*, **23**, 416 (1939).

(13) This compound was named according to the earlier system of nomenclature pregnane-17β,20β,21-triol-3,11-dione.

liquors of XXI, followed by chromatographic separation permitted the isolation of 10% of the epimer (XXVI), pregnane-3α,17α,20α,21-tetrol-11-one triacetate.

Experimental[14]

Pregnane-3α,17α-diol-11,20-dione (I) from Pregnane-3α,17α,21-triol-11,20-dione Diacetate.—A solution of 511 mg. of pregnane-3α,17α,21-triol-11,20-dione 3,21-diacetate, m. p. 233–236°, in 40 cc. of warm anhydrous benzene was treated with 20 cc. of an ethereal solution of methylmagnesium iodide prepared from 5 g. of methyl iodide and 0.75 g. of magnesium. The suspension was permitted to stand at room temperature for two days, then poured into 0.1 *N* hydrochloric acid, the benzene layer washed and concentrated to dryness. The residue deposited 160 mg. of poorly formed crystals from a small volume of acetone, which after recrystallization gave 44 mg., m. p. 215–237°. This partially purified product, 20-methylpregnane-3α,17α,20,21-tetrol-11-one, was then dissolved in 3 cc. of methanol, and treated with 1.5 cc. of 0.200 *N* periodic acid. The solution was then concentrated *in vacuo* to half-volume, left at room temperature for three hours, then concentrated to *ca.* 1.5 cc. *in vacuo*. Recrystallization of the precipitate from dilute methanol and from ether gave pregnane-3α,17α,diol-11,20-dione, m. p. 205–207°. A mixed m. p. with an authentic sample, m. p. 206–208°, showed no depression.

Pregnane-3α,17α,20α-triol-11-one 3-Acetate 20-Benzoate (XII).—A solution of 250 mg. of pregnane-3α,17α-diol-11,20-dione 3-acetate (II) in 25 cc. of acetic acid was shaken under hydrogen with 300 mg. of platinum oxide until 1.0 mole of hydrogen was consumed. After the usual working up, the residue was dissolved in 2.0 cc. of pyridine and treated with 0.4 cc. of benzoyl chloride. The mixture was left at room temperature overnight, diluted with water, extracted with ether, the ethereal layer washed with dilute hydrochloric acid, dilute carbonate solution and with water. Concentration to dryness gave 350 mg. of residue which deposited 48 mg. of crystals from a small volume of methanol. Recrystallization from chloroform–alcohol and chloroform–ether gave the 3α,17α,20α-triolone acetate benzoate, m. p. 264–265°.

Anal. Calcd. for $C_{30}H_{40}O_6$: C, 72.55; H, 8.11. Found: C, 72.88; H, 7.84.

Saponification of a sample of the acetate benzoate gave pregnane-3α,17α,20α-11-one; m. p. 211–212°, $[\alpha]^{25}D$ +23°. A mixed m. p. with an authentic sample gave no depression. It was found that an unsolvated, well-crystallized form could be obtained by crystallization from anhydrous acetone.

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.95; H, 9.79. Found: C, 71.97; H, 9.81.

Pregnane-3α,17α,20β-triol-11-one 3,20-Diacetate (V) from Pregnane-3α,17α-diol-11,20-dione (I).—The crude product from the catalytic reduction of 420 mg. of pregnane-3α,17α-diol-11,20-dione was acetylated in the usual manner. After several recrystallizations of the product from dilute acetone, 320 mg. of pregnane-3α,17α,20β-triol-11-one 3,20-diacetate was obtained, m. p. and mixed m. p. 249–250°. Chromatography of the mother liquors gave lower melting mixtures from which no pure 3α,17α,20α-triolone diacetate could be isolated.

Pregnane-3α,17α,20β-triol-11-one (III).—Saponification of pregnane-3α,17α,20β-triol-11-one 3,20-diacetate, m. p. 249–250°, afforded the free triolone, m. p. 220° after recrystallization from dilute methanol or acetone–ether. A double melting point of 179°, 220° was occasionally observed; $[\alpha]^{25}D$ +38°.

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.95; H, 9.79. Found: C, 72.04; H, 9.76.

Pregnane-3α,17α,20β-triol-11-one 20-Acetate (IV).—To a warm mixture of 10.0 cc. of benzene and 1.0 cc. of methanol was added 565 mg. of pregnane-3α,17α,20β-triol-11-one 3,20-diacetate. The solution was quickly cooled to 25° and treated with 10 cc. of a solution of 1.1*N* methanolic potassium hydroxide. After two and one-half minutes, the potassium hydroxide was neutralized with acetic acid, the solvents removed *in vacuo*, and the residue extracted with chloroform. The washed chloroform extract was concentrated to dryness, the partially crystalline residue dissolved in benzene and chromatographed over 15 g. of acid-washed alumina. After elution of diacetate (ether) 235 mg. of crude 20-monoacetate was eluted with chloroform. Recrystallization from ethyl acetate and dilute methanol gave 180 mg. of the 3α,17α,20β-triolone 20-acetate; m. p. 231–234°, $[\alpha]^{25}D$ + 55°.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.34; H, 9.44.

Pregnane-17α,20β-diol-3,11-dione 20-Acetate (VII) from Pregnane-3α,17α,20β-triol-11-one 20-Acetate (IV).—A solution of 17 mg. of the 3α,17α,20β-triolone 20-acetate, m. p. 231–234°, in 1.0 cc. of 90% acetic acid was treated at 15° with 0.30 cc. of 90% acetic acid containing 15 mg. of chromic acid. The solution was allowed to warm to 25° and, after forty-five minutes, water was added to induce crystallization of the product. Recrystallization from methanol gave pregnane-17α,20β-diol-3,11-dione 20-acetate, m. p. 222–224°. Admixture with an authentic specimen, m. p. 222.0–224.5°, showed no depression.[15]

Pregnane-3α,17α,20α-triol-11-one 20-Acetate (X).—To 0.60 cc. of pyridine containing 91 mg. of acetic anhydride was added 248 mg. of pregnane-3α,17α,20α-triol-11-one, m. p. 211–212°. After standing at room temperature overnight, the solution was concentrated to dryness *in vacuo*, the residue dissolved in benzene and chromatographed. The fractions eluted with chloroform gave 164 mg. of crystalline 3α,17α,20α-triolone 20-acetate; m. p. 212°, $[\alpha]^{25}D$ +2°.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.65; H, 9.40.

Pregnane-17α,20α-diol-3,11-dione 20-Acetate (XV).—A solution of 131 mg. of pregnane-3α,17α,20α-triol-11-one 20-acetate (X) was oxidized with chromic acid in the usual manner. Dilution of the oxidation mixture with water and addition of sufficient solid potassium carbonate to neutralize most of the acetic acid gave a crystalline precipitate, which after recrystallization from dilute methanol and ether afforded 90 mg. of pure 17α,20α-diol-dione 20-acetate; m. p. 182–183°, $[\alpha]^{25}D$ + 12°.

Anal. Calcd. for $C_{23}H_{34}O_5$: C, 70.73; H, 8.79. Found: C, 70.77; H, 8.53.

Pregnane-17α,20α-diol-3,11-dione (XIV).—A solution of 90 mg. of pregnane-17α,20α-diol-3,11-dione 20-acetate, m. p. 182–183°, in a mixture of 3.0 cc. of methanol and 1.0 cc. of 1 *N* aqueous potassium hydroxide was refluxed for three minutes. The methanol was then removed *in vacuo*, the aqueous suspension acidified with a few drops of acetic acid and extracted with chloroform. The washed chloroform solution was concentrated to dryness *in vacuo*, the residue crystallized from ether and again from acetone–ether; m. p. 190–191°, $[\alpha]^{25}D$ +32.5°.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.39; H, 9.25. Found: C, 72.55; H, 9.31.

Pregnane-3α,17α,20β-triol-11-one Diacetate (IV) from Crude Δ[17]-Pregnene-3α-ol-11-one.—The mother liquors obtained from the methanol recrystallizations of Δ[17]-pregnene-3α-ol-11-one (prepared by treatment of the 3α,20β-diolone acetate tosylate with collidine, followed by saponification of the product) were concentrated to a small volume, diluted with a small volume of water, and left at 0°. A fluffy crystalline precipitate formed, m. p. 130–160°. Since fractional recrystallization of this mixture led only to the isolation of small amounts of the high

(14) Melting points were taken on the Kofler micro hot stage; rotations unless otherwise indicated were taken in acetone, c = 1.0.

(15) These values are characteristic of freshly prepared samples of this compound. Long heating *in vacuo* raises the m. p. as much as 7°.

melting Δ^{17}-pregnene-3α-ol-11-one, together with various fractions of inconstant properties, and chromatography likewise gave no appreciable separation, a portion of the crystalline mixture was hydroxylated with osmium tetroxide in the usual manner, and the product acetylated. After chromatography about 25% of the 3α,17α,20β-triolone diacetate, m. p. and mixed m. p. 249–250°, was obtained.

Reaction of Pure Δ^{17}-Pregnene-3α-ol-11-one with Osmium Tetroxide in the Presence of:

A. Benzoyl Peroxide.—A solution of 100 mg. of Δ^{17}-pregnene-3α-ol-11-one, m. p. 192°, in 20 cc. of absolute ether containing 25 mg. of benzoyl peroxide was treated with 100 mg. of osmium tetroxide followed by 0.05 cc. of pyridine. The precipitated osmate ester was filtered, hydrolyzed and the triol acetylated as usual. Pregnane-3α,17α,20α-triol-11-one diacetate, m. p. 228–229°, was obtained in 80% yield.

B. Acetone.—Repetition of the reaction, substituting 45 mg. of acetone for the benzoyl peroxide led to the same results.

C. Coprostanone.—Substitution of 125 mg. of coprostanone for the benzoyl peroxide gave the same results.

Δ^{20}-Pregnene-3α-ol-11-one (XVIII) from 20-Amino-pregnane-3α-ol-11-one 3-Acetate.—One gram of the chromatographically purified mixture of pregnene-3α-ol-11-one acetate isomers obtained by diazotization of the 20-amine was saponified by refluxing for fifteen minutes with 20 cc. of 1 *N* methanolic potassium hydroxide. Dilution and cooling of the solution gave 380 mg. of an almost gelatinous crystal mass, m. p. 136–140°. Repeated recrystallization from dilute methanol and ether–petroleum ether raised the melting point to 153–154°; $[\alpha]^{25}D$ +37°. It did not depress the m. p. of Δ^{20}-pregnene-3α-ol-11-one (see below). Acetylation gave an acetate, m. p. 115–116°.

The addition of water to the mother liquors of the original saponification product caused the slow deposition of 400 mg. of crystals of the same appearance as the pregnene-3α-ol-11-one of m. p. 153°. They melted, however, at 97–99° and, after four recrystallizations, more or less constantly at 116–117°; there was not enough of this material for an analysis of the hydroxylation products.

Δ^{20}-Pregnene-3α-ol-11-one (XVIII) from Δ^{17}-21-Bromopregnene-3α-ol-11-one Acetate.—To a solution of 1.35 g. of Δ^{17}-21-bromopregnene-3α-ol-11-one acetate in 10 cc. of acetic acid was added 2.0 g. of zinc dust portionwise, with warming on the steam-bath. After fifteen minutes, the solution was cooled, diluted with water, extracted with ether, the ether layer washed with aqueous carbonate and concentrated to dryness. The residue was refluxed with 1.0 *N* methanolic potassium hydroxide for ten minutes, water added, the methanol removed *in vacuo* and the precipitated product extracted with ether. The residue from the concentration of the ethereal solution weighed 935 mg. and was purified chromatographically, giving 550 mg. of Δ^{20}-pregnene-3α-ol-11-one; m. p. 153–154°; $[\alpha]^{25}D$ + 38.5°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.68; H, 10.12. Found: C, 79.46; H, 10.26.

Acetylation of a sample of this alcohol gave an acetate, m. p. 106°. A mixed m. p. with the Δ^{20} acetate of m. p. 116° was 109–111°. Refluxing a sample of the alcohol with collidine–collidinium tosylate did not appreciably alter its properties.

Treatment of the Δ^{20}-pregnenolone, m. p. 153–154°, with osmium tetroxide and acetylation of the hydrolysis product in the usual manner gave a mixture of prismatic crystals and clusters of needles, resembling the usual mixture of pregnane-3α,20(α and β), 21-triol-11-one triacetate. Recrystallization from methanol gave the pure 3α,20α,21-triolone triacetate, m. p. and mixed m. p. 147.5–148.5°. Several crystallizations of the mother liquors from ether yielded the 3α,20β,21-triolone triacetate, m. p. and mixed m. p. 157–159°.

Pregnane-3α,17β-diol-11-one 3-Acetate.—A solution of 899 mg. of Δ^{20}-pregnene-3α,17β-diol-11-one in 50 cc. of alcohol was shaken under hydrogen with 200 mg. of platinum oxide until absorption of hydrogen ceased. The solution was then filtered, concentrated to a small volume and precipitated as the crystalline hydrate, m. p. 123°; 175–177°, by addition of water. Recrystallization from wet ether did not change the properties. The acetate was prepared by permitting 815 mg. of the diol to stand at room temperature overnight in 2.0 cc. of pyridine and 2.0 cc. of acetic anhydride. It melted at 208–209°; $[\alpha]^{25}D$ + 60°.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.58; H, 9.70.

Dehydration of Pregnane-3α,17β-diol-11-one 3-Acetate.—A solution of 800 mg. of pregnane-3α,17β-diol 3-acetate in 4 cc. of pyridine was treated with 0.5 cc. of phosphorus oxychloride and the solution left overnight. Dilution with water, followed by extraction with petroleum ether and concentration of the washed solution gave 680 mg. of a mobile colorless oil which would not crystallize from a small volume of cold methanol, even upon seeding with any of the low melting isomorphous mixtures of pregnene-3α-ol-11-one acetate isomers. Saponification of the unsaturated acetate and dilution of the cold methanolic solution gave a flocculent mass which melted at *ca.* 130°. Recrystallizations from dilute methanol gave similar mixtures, m. p. 125–128°.

Pregnane-3α,17α,20α-triol-11-one 3-Acetate (XI).—To a solution of 900 mg. of Δ^{17}-pregnene-3α-ol-11-one acetate, m. p. 122–123°, in 10 cc. of absolute ether was added 800 mg. of osmium tetroxide and 0.4 cc. of pyridine. After five minutes the precipitated osmate ester was redissolved by addition of 45 cc. of alcohol and 5 cc. of benzene. To this solution was added 2.0 g. of sodium sulfite dissolved in 30 cc. of water, and the reddish mixture was shaken for ten minutes at room temperature. The upper layer, which was then nearly colorless, was decanted, the semi-solid lower layer washed with 70% alcohol, the combined alcoholic extracts acidified with a few drops of acetic acid and concentrated to a small volume *in vacuo*. The crystalline precipitate (920 mg.) was filtered, washed with water, and recrystallized from dilute alcohol and acetone–petroleum ether, giving 750 mg. of the 3α,17α,20α-triolone 3-acetate; m. p. 220–223°, $[\alpha]^{25}D$ + 43°.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.22; H, 9.23.

Upon acetylation a sample gave pregnane-3α,17α,20α-triol-11-one 3,20-diacetate, m. p. and mixed m. p. 228–229°.

Pregnane-3α,17α,20α-triol-11-one 3-Acetate 20-Tosylate (XIII).—A solution of 456 mg. of pregnane-3α,17α,20α-triol-11-one 3-acetate, m. p. 220–223°, in 1.0 cc. of pyridine was treated with 450 mg. of tosyl chloride and left at 0° overnight. After dilution with water, extraction with benzene, washing with dilute hydrochloric acid, dilute sodium carbonate and with water and concentration to dryness *in vacuo*, the tosylate was obtained as prisms from ether; yield, 489 mg. The compound melted with decomposition at temperatures ranging from 145–146° to 158–159°, depending on the rate of heating.

Anal. Calcd. for $C_{30}H_{42}O_7S$: C, 65.92; H, 7.73. Found: C, 66.08; H, 7.51.

Δ^{17}-Pregnene-3α,21-diol-11-one from Pregnane-3α,-20β,21-triol 3,21-Diacetate 20-Tosylate.—A solution of 9.0 g. of pregnane-3α,20β,21-triol-11-one 3,21-diacetate 20-tosylate in 50 cc. of collidine (purified through the hydrobromide), was refluxed for twenty-five minutes. The cooled solution was diluted with ether, cooled with ice and washed with sufficient dilute hydrochloric acid to remove the collidine. The ethereal solution was then washed with dilute sodium carbonate and with water and concentrated to dryness. The residue was dissolved in 50 cc. of benzene–petroleum ether and put on a column of 130 g. of alumina. Elution with 500 cc. of ether gave 6.4 g. of colorless oil, which was saponified by heating with 1 *N* methanolic potassium hydroxide. Dilution of the cooled solution with water gave crystals which after recrystallization from dilute alcohol and acetone–ether yielded 2.6 g. of impure Δ^{17}-pregnene-3α,21-diol-11-one.

This was purified through the diacetate, m. p. and mixed m. p. 112–113°. Saponification afforded the diol, m. p. and mixed m. p. 200–201°. Further crystallization of the mother liquors led only to isolation of an additional amount of the same diol.

Pregnane-3α,17α,20β,21-tetrol-11-one 20,21-Acetonide (XXIII).—A sample (422 mg.) of Δ^{17}-pregnene-3α,21-diol-11-one diacetate, m. p. 113°, in absolute ether was treated with osmium tetroxide and pyridine, then hydrolyzed with hot aqueous alcoholic sodium sulfite in the usual manner. The filtered and concentrated aqueous suspension was extracted thrice with 50 cc. of chloroform and the chloroform solution concentrated to dryness. The residue (271 mg.) was crystallized from acetone and from alcohol. The crude tetrol melted at 245–255° and was purified through the acetonide; 196 mg. of crude tetrol was dissolved in 10 cc. of a 5% solution of zinc chloride in acetone. After standing at room temperature overnight, the solution was treated with aqueous sodium carbonate, the acetone layer decanted, concentrated to a small volume *in vacuo*, extracted with ether and the product crystallized from ether, giving 170 mg. of the acetonide, m. p. 187°.

Anal. Calcd. for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 70.82; H, 9.56.

Hydrolysis of a sample of the acetonide with hot aqueous acetic acid gave pure pregnane-3α,17α,20β,21-tetrol-11-one; m. p. 263–264°, $[\alpha]^{25}D$ + 37° (alc.).

Pregnane-17α,20β,21-triol-3,11-dione Diacetate from Pregnane-3α,17α,20β,21-tetrol-11-one Acetonide (XXIII).—A solution of 102 mg. of the 3α,17α,20β,21-tetrolone acetonide, m. p. 187°, in 5 cc. of dry benzene was treated with 3 cc. of anhydrous acetone and 300 mg. of aluminum isopropoxide. The mixture was refluxed overnight, then diluted with ether, washed with dilute hydrochloric acid and water and concentrated to dryness. The residue was heated with 1.0 cc. of 75% acetic acid for fifteen minutes, the solvents removed *in vacuo* and the residue heated with a mixture of acetic anhydride–pyridine for five minutes on the steam-bath. The solvents were again removed *in vacuo* and the residue chromatographed giving 20 mg. of the 17α,20β,21-triol-dione diacetate, m. p. 208–210°. A mixed melting point with an authentic sample (m. p. 209–211°) did not show a depression. A total of 65 mg. of the original tetrolone, in the form of its triacetate, m. p. 200–201°, was also obtained from the chromatogram.

Pregnane-3α,17α,20β,21-tetrol-11-one 3,21-Diacetate (XXI).—A solution of 2.25 g. of pregnane-3α,17α,21-triol-11,20-dione 3,21-diacetate in 75 cc. of acetic acid was shaken with 1.0 g. of platinum oxide under a pressure of 45 lb. of hydrogen until hydrogen uptake nearly ceased (1.0 mole consumed). Filtration of the solution and concentration *in vacuo* to dryness gave a residue which after crystallization from ether and from methanol yielded 1.15 g. of dense prisms. The 3α,17α,20β,21-tetrolone 3,21-diacetate melted at 201–203°; $[\alpha]^{25}D$ + 67°.

Anal. Calcd. for $C_{25}H_{38}O_7$: C, 66.54; H, 8.50. Found: C, 66.64; H, 8.74.

Pregnane-3α,17α,20β,21-tetrol-11-one 3,20,21-Triacetate (XXII).—The acetylation of a sample of the 3α,17α,-20β,21-tetrolone with pyridine–acetic anhydride gave crystals from dilute methanol; m. p. 201°, $[\alpha]^{25}D$ + 103°.

Anal. Calcd. for $C_{27}H_{30}O_8$: C, 65.83; H, 8.18. Found: C, 66.01; H, 7.88.

Pregnane-3α,17α,20α,21-tetrol-11-one 3,20,21-Triacetate (XXVI).—The mother liquors from the crystallization of pregnane-3α,17α,20β,21-tetrol-11-one 3,21-diacetate (see above), amounting to 1.15 g., were chromatographed on 40 g. of alumina. Elution with ether–chloroform mixtures with an increasing proportion of chloroform gave oily fractions which were combined and deposited an additional 300 mg. of the 3α,17α,20β,21-tetrolone diacetate from a small volume of ether. The mother liquors from this crystallization were evaporated to dryness and the residue (416 mg.) acetylated with acetic anhydride–pyridine. Dilution of the reaction mixture with water gave 353 mg. of crude 3α,17α,20α,21-tetrolone triacetate. After six recrystallizations from dilute acetone and from methanol, the pure triacetate was obtained; m. p. 213–214°, $[\alpha]^{25}D$ + 18°.

Anal. Calcd. for $C_{27}H_{40}O_8$: C, 65.83; H, 8.18. Found: C, 65.90; H, 8.19.

Pregnane-3α,17α,20α,21-tetrol-11-one (XXV).—Saponification of 30 mg. of the 3α,17α,20α,21-tetrolone triacetate, m.p. 213–214°, followed by concentration of the solution *in vacuo* and extraction of the aqueous suspension with a large volume of chloroform gave 16 mg. of amorphous residue. Crystallization from a small volume of acetone yielded 14 mg. of the tetrolone; m.p. 208–209°, $[\alpha]^{25}D$ + 44° (alc., $c = 0.5$).

Pregnane-3α,17α,20β,21-tetrol-11-one 3-Acetate 20,21-Acetonide (XXIV).—A portion (700 mg.) of pregnane-3α,17α,20β,21-tetrol-11-one 20,21-acetonide was dissolved in a mixture of 2.0 cc. of pyridine and 1.0 cc. of acetic anhydride and heated on the steam-bath for ten minutes. The solvents were removed *in vacuo* and the residue chromatographed over alkaline alumina. Mixtures of ether–petroleum ether eluted 700 mg. of the crystalline acetate acetonide, which melted after recrystallization from benzene–petroleum ether at 190–191°.

Anal. Calcd. for $C_{26}H_{40}O_6$: C, 69.62; H, 8.98. Found: C, 69.53; H, 8.91.

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Summary

The preparation and properties of a number of pregnane-3α,17α,20(α and β)-triol-11-one derivatives and correlations with the corresponding 3-keto compounds are described. Similar investigations of the 3α,17α,20(α and β), 21-tetrol-11-one series are described.

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