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Stereoisomeric Substituted 11-Keto-20-hydroxypregnanes. I

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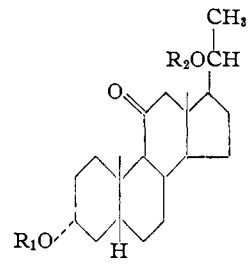
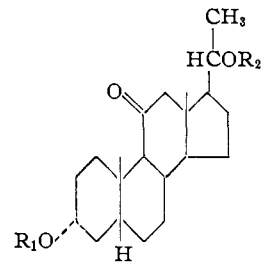
In the course of synthetic studies in this Laboratory in the field of the adrenal steroids[1,2,3,4] a group of substituted 11-keto-20-hydroxypregnanes has been prepared. Some of the reactions which afford members of this group—reduction of a 20-ketopregnane, hydroxylation of a Δ^{17}- or Δ^{20}-pregnene—give both epimers in different but characteristic ratios. In order to illumine regularities peculiar to these reactions, as well as to make a needed nomenclatural integration, we have undertaken the stereochemical correlation of some of these compounds. The results of such an investigation are readily treated in four divisions: first, the correlation of the 11-ketopregnanes bearing the 20-hydroxy (Class A) and the 20,21-dihydroxy (Class B) side chains together with their derivatives which differ only in the substituent at C-3; second, the correlation of 11-ketopregnanes having 17,20-dihydroxy (Class C) and 17,-20,21-trihydroxy (Class D) side chains with their respective derivatives; third, the correlation *inter ipsos* of the four classes; fourth, the linking of this group of compounds with Reichstein's Substances J and O, the adrenal steroids which form the standard of references adopted by Reichstein and co-workers,[5,6,7] for 20-hydroxypregnanes. The present publication is concerned with the first of these divisions. For convenience in reference the results described in the succeeding divisions of this study will be used as the basis for assigning configurational indices to C-20 substituents. The assignment of these indices has been made in such a way as to indicate a very probable configurational correspondence with substances J and O at the C-20 position.

Class A. Simple 11-Keto-20-hydroxypregnanes

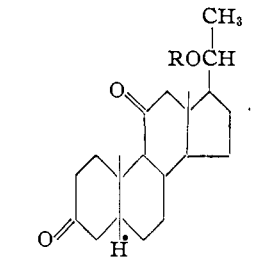
The catalytic reduction of pregnane-3α-ol-11,20-dione acetate to pregnane-3α,20β-diol-11-one 3-acetate (I) and the corresponding 3α,20α-diol (isolated as the diacetate IX)[8] has been described.[3] The corresponding 3-keto derivatives have now been prepared. In the 20β-series this was accomplished by benzoylating I, partially saponifying the acetate benzoate (II), oxidizing the hydroxy benzoate (III) to the ketobenzoate (IV) and finally hydrolyzing to the ol-dione (V). In the 20α-series the 20-monoacetate (X) was obtained by partial saponification[9] of the diacetate (IX). Oxidation then yielded pregnane-20α-ol-3,11-dione acetate (XI).



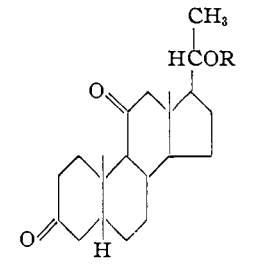
I R_1 = Ac, R_2 = H
II R_1 = Ac, R_2 = COC_6H_5
III R_1 = H, R_2 = COC_6H_5



VIII R_1 = H, R_2 = H
IX R_1 = Ac, R_2 = Ac
X R_1 = H, R_2 = Ac



IV R = COC_6H_5
V R = H
VI R = Ac
VII R = $SO_2C_6H_4CH_3$-*p*



XI R = Ac
XII R = H

An additional source of pregnane-3α,20α-diol-11-one (VIII) was the alcoholic fraction obtained by diazotization of 20-aminopregnane-3α-ol-11-one 3-acetate.[1] After chromatographic separation of the pregnen-3α-ol-11-one acetate isomers, which constituted the chief product of the reaction, the crude alcoholic fraction was saponified and the diolone was readily purified by crystallization. In one experiment the 3α,20β-diolone could also be isolated.[10]

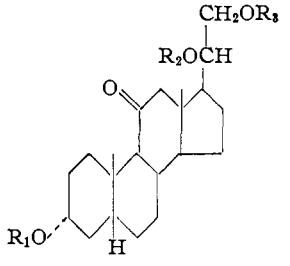
Class B. 11-Keto-20,21-dihydroxypregnanes

The mixture of pregnen-3α-ol-11-one acetate isomers mentioned above has been utilized to prepare pregnane-20β,21-diol-3,11-dione (XXI) and pregnane-20α,21-diol-3,11-dione (XXVIII).[2] If, instead of conversion to the 3-keto derivative, the pregnene mixture was hydroxylated directly, a mixture of three triolones was obtained. These

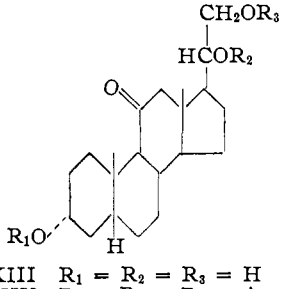
(1) Sarett, *J. Biol. Chem.*, **162**, 601 (1946).
(2) Sarett, THIS JOURNAL, **68**, 2478 (1946).
(3) Sarett, *ibid.*, **70**, 1690 (1948).
(4) Sarett, *ibid.*, **70**, 1454 (1948).
(5) Prins and Reichstein, *Helv. Chim. Acta*, **23**, 1490 (1940).
(6) von Euw and Reichstein, *ibid.*, **24**, 401 (1941).
(7) Salamon and Reichstein, *ibid.*, **30**, 1616 (1947).
(8) In the cited publication the former compound was named without a configurational index for the 20-hydroxy group; the latter compound was called pregnane-3α,20(epi)-diol-11-one. In writing the projection formulas in the present group of papers, a suggestion by Fieser and Fieser, *Experientia*, **4**, 285 (1948), has been followed. According to this suggestion the respective 20β- or 20α-substituent is written on the left or the right of the C-20 carbon atom.
(9) *Cf.* Butenandt and Schmidt, *Ber.*, **67**, 1893 (1934).
(10) Hückel (*Ann.*, **533**, 1 (1938)) has demonstrated that the diazotization of optically active secondary amines with additional centers of asymmetry in the molecule may or may not proceed with retention of configuration.

consisted of the two pregnane-3α,20,21-triol-11-one epimers (XIII and XXIII) corresponding to the dioldiones XXI and XXV, and also a 3α,17α,-20β-triolone.[11] Separation of XIII and XXIII was effected by chromatography of the 3-acetate acetonides (XIV and XXV). By the usual procedures, XIV and XXV could be converted to the partially acetylated triols, such as the 3-monoacetates (XVI and XXVI) and the 3,21-diacetates (XVII and XXVII).

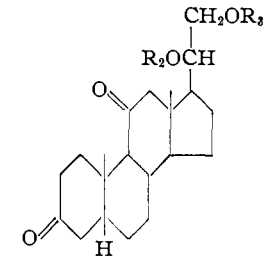
In order to correlate the pair of triolones with the dioldiones one of the former was converted[12] to its acetonide. Oxidation of the latter with N-bromacetamide in dry pyridine–*t*-butanol[13] afforded a nearly quantitative yield of the dioldione acetonide (XX). Hydrolysis and acetylation then yielded the previously described pregnane-20β,21-diol-3,11-dione diacetate (XXII). That the triolone isomeric with XIII must have the structure pregnane - 3α,20α,21 - triol - 11 - one (XXIII) was shown by oxidation to 3α-hydroxy-11-ketoetiocholanic acid. The 3,21-diacetate (XXVII) in the 20α-series, which was required for certain rotation data, was prepared through the intermediate acetonide (XXV) and monoacetate (XXVI).



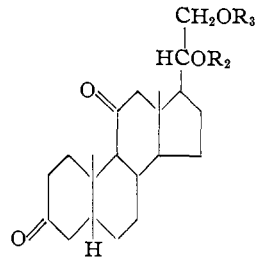
XIII $R_1 = R_2 = R_3 = H$
XIV $R_1 = Ac$, $R_2R_3 = >C(CH_3)_2$
XV $R_1 = R_2 = R_3 = Ac$
XVI $R_1 = Ac$, $R_2 = R_3 = H$
XVII $R_1 = R_3 = Ac$, $R_2 = H$
XVIII $R_1 = R_3 = Ac$, $R_2 = SO_2C_6H_4CH_3$-*p*
XIX $R_1 = R_2 = Ac$, $R_3 = SO_2C_6H_4CH_3$-*p*



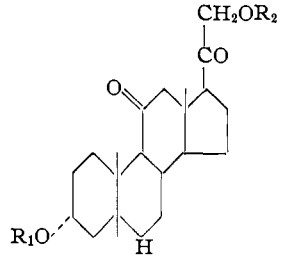
XXIII $R_1 = R_2 = R_3 = H$
XXIV $R_1 = R_2 = R_3 = Ac$
XXV $R_1 = Ac$, $R_2R_3 = >C(CH_3)_2$
XXVI $R_1 = Ac$, $R_2 = R_3 = H$
XXVII $R_1 = R_3 = Ac$, $R_2 = H$



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



XXVIII $R_2 = R_3 = H$
XXIX $R_2 = R_3$ Ac



XXX $R_1 = R_2 = Ac$
XXXI $R_1 = Ac$, $R_2 = OCH$
XXXII $R_1 = Ac$, $R_2 = H$

The preparation of 11-keto-20,21-dihydroxypregnanes by catalytic reduction of the ketol or ketol acetate gave results similar to those found on reduction of the simple 11,20-diketone. One isomer was the major product and it also belonged to the 20β-series.[14] Reduction of pregnane-3α,21-diol-11,20-dione diacetate (XXX) yielded pregnane - 3α,20β,21 - triol - 11 - one 3,21 - diacetate (XVII), acetylation of which gave the triacetate (XV).

A second and more convenient method of preparing pregnane-3α,20β,21-triol-11-one 3-acetate (XVI) employed as starting material 21-diazopregnane-3α-ol-11,20-dione acetate.[15] This was treated with 90% formic acid, giving the acetate formate (XXXI), which hydrolyzed very rapidly in aqueous methanolic potassium bicarbonate to pregnane - 3α,21 - diol - 11,20 - dione 3 - acetate (XXXII). Catalytic reduction then gave XVI. The partial tosylation of this compound gave an amorphous 21-monotosylate which could be acetylated to give the crystalline diacetate tosylate (XVIII).

Experimental[16]

Pregnane-3α,20β-diol-11-one 3-Acetate 20-Benzoate (II).—A solution of 1.85 g. of pregnane-3α,20β-diol-11-one 3-acetate (I), m.p. 205–206°, in 10 cc. of pyridine was treated with 2.0 cc. of benzoyl chloride and warmed at

(11) The structure of this compound is discussed in Part II.

(12) A slight modification of the method of Fischer and Taube (*Ber.*, **60**, 485 (1927)), using a 5% solution of zinc chloride in acetone, has been found to give excellent results with steroid glycols including the 17,20,21-triols.

(13) Reich and Reichstein (*Helv. Chim. Acta*, **26**, 562 (1943)) have shown that N-bromacetamide in aqueous acetone solution smoothly oxidizes secondary alcohols to ketones. These conditions are unsuitable, however, for molecules containing acid-sensitive functional groups.

(14) This relationship is discussed in Part III.

(15) The preparation of the 3β-acetoxy isomer of this compound from the corresponding etio acid has been described by Lardon and Reichstein (*Helv. Chim. Acta*, **26**, 747 (1943)).

(16) Melting points were taken on the Kofler micro hot stage and thus represent corrected values. Rotations were taken in acetone, c = 1.0, except where otherwise indicated.

50° for five minutes. The product after recrystallization from alcohol melted at 188–189°; yield, 1.90 g.

Anal. Calcd. for $C_{30}H_{40}O_5$: C, 74.97; H, 8.39. Found: C, 75.25; H, 8.60.

Pregnane-3α,20β-diol-11-one 20-Benzoate (III).—A solution of 2.05 g. of acetate benzoate (II) in 10 cc. of benzene was treated at 25° with 10 cc. of 1.1 *N* methanolic potassium hydroxide. After eight minutes the solution was neutralized with acetic acid and the benzene removed *in vacuo*, giving the crystalline hydroxybenzoate (III). After recrystallization from dilute alcohol and acetone, it melted at 236–237°; yield, 1.58 g.

Anal. Calcd. for $C_{28}H_{38}O_4$: C, 76.67; H, 8.74. Found: C, 76.95; H, 8.45.

Pregnane-20β-ol-3,11-dione Benzoate (IV).—A solution of 1.55 g. of hydroxybenzoate (III) in 25 cc. of 90% acetic acid was treated at 15° with the solution of 0.80 g. of chromic acid in 16 cc. of 90% acetic acid. After one hour the solution was diluted with water, extracted with benzene, the latter washed with aqueous carbonate and concentrated to dryness *in vacuo*. The keto benzoate after crystallization from ether and from methanol melted at 161–162°; yield, 1.10 g.

Anal. Calcd. for $C_{28}H_{36}O_4$: C, 77.03; H, 8.31. Found: C, 77.00; H, 8.24.

Pregnane-20β-ol-3,11-dione (V).—A solution of 1.0 g. of the keto benzoate in 15 cc. of 0.7 *N* methanolic potassium hydroxide was refluxed for forty-five minutes with gradual addition of water. The methanol was then removed *in vacuo*, the aqueous suspension extracted with chloroform, the latter washed with water and concentrated to dryness *in vacuo*. Crystallization from acetone gave 700 mg. of the ol-dione; m. p. 200°, $[\alpha]^{25}D$ + 52.5°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.85; H, 9.70. Found: C, 75.99; H, 9.40.

Pregnane-20β-ol-3,11-dione Acetate (VI).—A sample (22 mg.) of the ol-dione was warmed on the steam-bath for a few minutes with pyridine–acetic anhydride. Addition of water and recrystallization from a small volume of methanol gave the acetate; m. p. 201–203°, $[\alpha]^{25}D$ + 75.5°.

Pregnane-20β-ol-3,11-dione Tosylate (VII).—A solution of 498 mg. of 20β-ol-dione in 2.1 cc. of pyridine was treated at 0° with 600 mg. of freshly recrystallized tosyl chloride. After three hours the solution was warmed to room temperature and permitted to stand overnight. After the addition of water, the tosylate was extracted with ether, washed with dilute hydrochloric acid, dilute potassium carbonate and water. Concentration of the ethereal solution and several recrystallizations of the residue from alcohol and ethyl acetate–petroleum ether gave crystals, m. p. 153°; yield, 500 mg.

Anal. Calcd. for $C_{28}H_{38}O_5S$: C, 69.11; H, 7.87. Found: C, 68.89; H, 8.10.

The tosylate reacted with refluxing collidine to give a crystalline mixture, m. p. 158–162°, the analysis of which corresponded roughly to a formula of $C_{21}H_{30}O_3$.

Pregnane-3α,20α-diol-11-one 20-Acetate (X).—To a solution of 230 mg. of pregnane-3α,20α-diol-11-one diacetate (IX), m. p. 235–236°, in 5 cc. of benzene was added 5 cc. of 1.1 *N* methanolic potassium hydroxide at 25°. After two and one-half minutes, the solution was acidified with acetic acid, concentrated to dryness *in vacuo* and extracted with benzene. The washed benzene solution was concentrated to a small volume and percolated through a column of alumina. Elution with petroleum ether–benzene mixtures removed diacetate and with ether–chloroform the 20-monoacetate (X). The latter weighed 80 mg. after recrystallization from dilute methanol and ether; m. p. 184–185°; $[\alpha]^{25}D$ + 50°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.36; H, 9.65. Found: C, 73.47; H, 9.48.

Pregnane-20α-ol-3,11-dione Acetate (XI).—Oxidation of 53 mg. of the 20α-monoacetate with chromic acid in the usual manner gave 51 mg. of crude crystals which were purified first by the use of Girard reagent T and then by chromatography. Twenty-four milligrams of the pure 20α-ol-dione acetate was obtained; m. p. 135°, $[\alpha]^{25}D$ + 54°. A mixture with pregnane-3α-ol-11,20-dione acetate (m. p. 136°) melted at 110–120°.

Pregnane-20α-ol-3,11-dione (XII).—The acetate (23 mg.) was saponified by warming on the steam-bath with dilute methanolic potassium hydroxide (0.5 *N*) for ten minutes. Recrystallization of the product gave 12.5 mg. of the 20α-ol-dione; m. p. 190–192°, $[\alpha]^{25}D$ +69.5° (*c* = 0.5). A mixed m. p. with pregnane-20β-ol-3,11-dione showed a depression of 20°.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.85; H, 9.70. Found: C, 76.13; H, 9.52.

Pregnane-3α,20α-diol-11-one Diacetate (IX) from 20-Aminopregnane-3α-ol-11-one 3-Acetate.—A portion (7.0 g.) of 20-aminopregnane-3α-ol-11-one acetate was heated with sodium nitrite and pyridine hydrochloride in aqueous pyridine as previously described.[1] Chromatography of the product gave 3.7 g. of unsaturated compounds, eluted with 8:2 petroleum ether–ether and 2.2 g. of material eluted with ether. Several crystallizations of the latter from ether and dilute acetone gave 200 mg. of pregnane-3α,20β-diol-11-one 3-acetate, m. p. 201–204°. A mixed m. p. with an authentic sample (m. p. 204–205°) was 202–204°. The mother liquors of the 3α,20β-diol monoacetate (2.0 g.) were acetylated and the product recrystallized from acetic acid, giving 600 mg. of pregnane-3α,20α-diol-11-one diacetate (IX), m. p. and mixed m. p. 234–235°. Saponification gave the 3α,20α-diol, m. p. and mixed m. p. 219°, $[\alpha]^{25}D$ + 61° (alc.). A number of repetitions of this experiment, using 2.0 equivalents of mineral acid in place of the pyridine hydrochloride yielded only the 3α,-20α-diol monoacetate in the ether eluates (isolated as the diacetate from acetylation).

Pregnane-3α,20β,21-triol-11-one 3-Acetate 20,21-Acetonide (XIV) and Pregnane-3α,20α,21-triol-11-one Acetate 20,21-Acetonide (XXV).—The chromatographically purified mixture of pregnene-3α-ol-11-one acetates from the diazotization of 3.0 g. of 20-aminopregnane-3α-ol-11-one 3-acetate amounted to 1.8 g. This material was treated with osmium tetroxide, the osmate esters hydrolyzed with hot aqueous alcoholic sodium sulfite and the product extracted in the usual manner (*e. g.*, ref. 2). The residual crude triols were dissolved in 45 cc. of acetone containing 2.3 g. of anhydrous zinc chloride and the solution permitted to stand overnight. A solution of 3.5 g. of potassium carbonate in 10 cc. of water was added, the mixture was shaken for a few minutes and the supernatant layer decanted. The residue was extracted again with acetone, the extracts combined and concentrated to a small volume after the addition of 5 cc. of a 10% solution of potassium carbonate. The oily precipitate was then extracted with ether, washed with water and concentrated to dryness. The residue (2.0 g.) was heated on the steam-bath with a mixture of 2.0 cc. of pyridine and 1.0 cc. of acetic anhydride for ten minutes, the solvents then removed *in vacuo*, the residue dissolved in 8:2 petroleum ether–benzene and chromatographed over 60 g. of (alkaline) alumina. The fractions eluted with 4:6 petroleum ether–benzene were combined and gave, after several recrystallizations from methanol, 400 mg. of pregnane-3α,20β-21-triol-11-one 3-acetate 20,21-acetonide (XIV); m. p. 137–139°, $[\alpha]^{25}D$ + 63.5°.

Anal. Calcd. for $C_{25}H_{40}O_5$: C, 72.20; H, 9.32. Found: C, 72.43; H, 9.38.

Subsequent elution with benzene and recrystallization of the combined eluates gave an equal amount of pregnane-3α,20α,21-triol-11-one 3-acetate 20,21-acetonide (XXV); m. p. 160–162°, $[\alpha]^{25}D$ + 68°.

Anal. Calcd. for $C_{26}H_{40}O_5$: C, 72.20; H, 9.32. Found: C, 72.46, 72.34; H, 9.23, 9.30.

Further elution with ether–benzene mixtures gave pregnane-3α,17α,20β-triol-11-one 3,20-diacetate, m. p. 249–250°, $[\alpha]^{25}D$ + 78.5°.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.10; H, 8.82. Found: C, 69.06; H, 8.60.

Pregnane-3α,20β,21-triol-11-one 3-Acetate (XVI).—A solution of 200 mg. of pregnane-3α,20β,21-triol-11-one 3-acetate 20,21-acetonide, m. p. 136–138°, in 2.0 cc. of acetic acid was diluted with 2.0 cc. of water and the mixture heated at 100° for fifteen minutes. Dilution with water, and extraction with ether followed by concentration of the washed ethereal solution to dryness gave 179 mg. of residue, which was crystallized from a small volume of cold ether, giving fluffy crystals of pregnane-3α,20β,21-triol-11-one 3-acetate; m. p. 121–123°, $[\alpha]^{25}D$ + 66°. The rotation was taken on a sample which had been heated briefly *in vacuo* at 130° to remove solvent of crystallization, which clung tenaciously to the crystals.

Pregnane-3α,20α,21-triol-11-one 3-Acetate (XXVI).—This compound was prepared from the corresponding 3-acetate acetonide (XXV) in the same manner. After recrystallization from dilute methanol it melted at 156–158°; $[\alpha]^{25}D$ + 74°.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.24. Found: C, 70.22; H, 9.21.

The two epimeric 3-monoacetates (XXVI and XVI) formed a molecular compound, m. p. 188–193°. A sample of this compound was chromatographed and then melted at about 195–197°.

Pregnane-3α,20β,21-triol-11-one Triacetate (XV).—Acetylation of pregnane-3α,20β,21-triol-11-one 3-acetate, m. p. 121–123°, with pyridine–acetic anhydride in the usual manner gave the triacetate; m. p. 158–159°, $[\alpha]^{25}D$ + 78°.

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 68.11; H, 8.40.

Pregnane-3α,20α,21-triol-11-one Triacetate (XXIV).—Acetylation of the corresponding 3α,20α,21-triolone 3-acetate, m. p. 156–158°, gave the triacetate; m. p. 148°, $[\alpha]^{25}D$ + 49.5°.

Anal. Calcd. for $C_{27}H_{40}O_7$: C, 68.04; H, 8.46. Found: C, 67.96; H, 8.17.

Pregnane-3α,20β,21-triol-11-one (XII).—Saponification of pregnane-3α,20β,21-triol-11-one triacetate, m. p. 158–159°, gave the readily crystalline triol as heavy prisms from dilute alcohol; m. p. 235°, $[\alpha]^{25}D$ + 53° (alc.).

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.95; H, 9.77. Found: C, 72.03; H, 9.51.

Pregnane-3α,20α,21-triol-11-one (XXIII).—Saponification of the 3α,20α,21-triolone triacetate gave the free triolone, m. p. 219–221°, $[\alpha]^{25}D$ + 55°.

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.95; H, 9.77. Found: C, 72.10; H, 9.40.

Pregnane-3α,20α,21-triol-11-one 3,21-Diacetate (XXVII).—A solution of 207 mg. of pregnane-3α,20α,21-triol-11-one 3-acetate, m. p. 156–158°, in 0.58 cc. of pyridine containing 58 mg. (1.2 molecular equivalents) of acetic anhydride was left at room temperature overnight. Removal of the solvents *in vacuo* and chromatography of the residue gave 113 mg. of crude diacetate fractions following the elution of 60 mg. of the triacetate, m. p. 148°. Recrystallization from ether–petroleum ether afforded 90 mg. of the 3,21-diacetate; m. p. 136–137°, $[\alpha]^{25}D$ + 67°.

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.10; H, 8.81. Found: C, 69.32; H, 8.99.

3α-Hydroxy-11-ketoetiocholanic Acid from Pregnane-3α,20α,21-triol-11-one.—To a solution of 30 mg. of pregnane-3α,20α,21-triol-11-one, m. p. 219–221°, in 3 cc. of methanol was added 0.20 cc. of a 0.200 *N* solution of periodic acid. After standing at room temperature for two hours, the solution was diluted with 5 cc. of water, the methanol removed *in vacuo* and the oily aldehyde extracted with ether. The washed ethereal solution was concentrated to dryness, the residue dissolved in 1.5 cc. of acetone and treated with 0.40 cc. of a 5% aqueous solution of potassium permanganate. After ten minutes a few drops of dilute sulfurous acid was added, the acetone removed *in vacuo* and the crystalline precipitate filtered and washed with water. Recrystallization by concentration in a relatively large volume of acetone gave 3α-hydroxy-11-ketoetiocholanic acid, m. p. 282–286°. A mixed m. p. with an authentic sample (m. p. 289–293°) melted at 282–286°.

Pregnane-3α,20β,21-triol-11-one 20,21-Acetonide.—A suspension of 7.75 g. of pregnane-3α,20β,21-triol-11-one (XIII), m. p. 235°, in 300 cc. of acetone containing 15 g. of anhydrous zinc chloride was stirred until all of the crystals dissolved. After twenty hours the solution was treated in the usual manner (see above), giving a residue after removal of ether, which crystallized readily from ether–petroleum ether. The yield was 7.0 g. of acetonide, m. p. 138–141°, with 0.80 g. of a second crop melting slightly lower. Recrystallization of a sample from acetone–petroleum ether raised the m. p. to 141–142°.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.51; H, 9.57.

Pregnane-20β,21-diol-3,11-dione Acetonide (XX).—To a solution of 7.0 g. of pregnane-3α,20β,21-triol-11-one acetonide, m. p. 141–142°, in 100 cc. of dry *t*-butyl alcohol was added 5.0 g. of N-bromacetamide (monohydrate) followed by 10 cc. of pyridine. After the bromacetamide had gone into solution, the mixture was permitted to stand at room temperature for eighteen hours, then poured into a separatory funnel containing ether and a solution of 10 g. of sodium sulfite in 60 cc. of water. The mixture was shaken vigorously, the ethereal layer washed with water and concentrated to dryness. Crystallization from dilute alcohol gave 6.2 g. of diol-dione acetonide, which melted at about 163°, partially resolidified and melted again at 171–174°. A sample which was chromatographed and recrystallized from ether–petroleum ether consisted of fine needles, m. p. 168.5–169.0° with transformation into prisms; m. p. 179–180°, $[\alpha]^{25}D$ +55°.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.18; H, 9.34. Found: C, 74.25; H, 9.14.

Pregnane-20β,21-diol-3,11-dione Diacetate (XXII) from Pregnane-20β,21-diol-3,11-dione Acetonide (XX).—A sample of pregnane-20β,21-diol-3,11-dione acetonide, m. p. 169°; 180°, was hydrolyzed with hot dilute acetic acid, the solvents removed *in vacuo* and the residue acetylated in the usual manner. Crystals of pregnane-20β,21-diol-3,11-dione diacetate were obtained, m. p. and mixed m. p. 175°.

Pregnane-3α,20β,21-triol-11-one 3,21-Diacetate (XVII).—Pregnane-3α,21-diol-11,20-dione diacetate (XXX) (13.2 g., containing 10% of ether of crystallization) was dissolved in 30 cc. of acetic acid. The solution was concentrated to two-thirds volume *in vacuo* to remove ether, then diluted with 80 cc. of acetic acid and reduced under a pressure of 45 lb. of hydrogen, using 1.0 g. of platinum oxide as catalyst. After 1.0 mole of hydrogen had been consumed the reduction came nearly to a halt. The solution was filtered, concentrated to dryness *in vacuo* and taken up in ether. The ethereal solution was washed with dilute carbonate solution and with water, and concentrated to dryness. Crystallization of the residue from benzene–petroleum ether gave 8.35 g. of the 3α,20β,-21-triolone diacetate. After recrystallization from dilute methanol it melted at 189–190°; $[\alpha]^{25}D$ + 65° (+68° in alcohol).

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.10; H, 8.81. Found: C, 69.21; H, 8.90.

With acetic anhydride–pyridine the diacetate was converted to the 3α,20β,21-triolone triacetate, m. p. 159°. The mother liquors from the reduction product were acetylated and chromatographed. In addition to some starting material (diketone) and 3α,20β,21-triolone triacetate, about 5% of the 3α,20α,21-triolone triacetate, m. p. and mixed m. p. 148°, was isolated. Fractional crystallization of the two isomeric triacetates was facilitated by the fact that the 20β-triacetate was somewhat less soluble in cold ether than the 20α, while the latter was less soluble in cold methanol.

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%.

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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.

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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).