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Sterols. XXII. The Pregnandiols and Pregnanolones

BY RUSSELL E. MARKER, OLIVER KAMM, EUGENE L. WITTLE, THOMAS S. OAKWOOD, ELMER J. LAWSON AND JOSEPH F. LAUCIUS

From human pregnancy urine pregnandiol,[1,2] *allo*-pregnandiol,[3] *epi*-pregnanol-3-one-20,[4] and *epi-allo*-pregnanol-3-one-20[5] have been isolated. Because of the high androgenic activity of the latter, and in order to facilitate the identification of other compounds found in human pregnancy urine, the preparation of the isomeric pregnandiols and pregnanolones has been undertaken. The eight isomeric pregnandiols which are considered in this paper differ in regard to configuration about the asymmetric centers C_3, C_5 and C_{20}, while the eight isomeric pregnanolones differ in regard to the position (3 or 20) of the carbonyl group and in regard to the asymmetric centers C_5, and either C_3 or C_{20}. Isomerism about C_{17}, which has been considered by Butenandt and co-workers,[6] will be discussed only incidentally here.

Since neither of the pregnandiols isolated from human pregnancy urine gives a precipitate with an alcoholic solution of digitonin, the 3-OH is considered to have the *epi* or (α) configuration in both compounds. The two diols differ in isomerism about C_5, pregnandiol being related to coprostane and *allo*-pregnandiol being related to cholestane. While isomerism at C_{20} is possible, natural pregnandiol and *allo*-pregnandiol appear to be homogeneous, since repeated crystallization does not alter the properties of either compound. The catalytic hydrogenation in neutral solution of pregnandione, *allo*-pregnandione, *epi*-pregnanol-3-one-20, or *epi-allo*-pregnanol-3-one-20 gives in every case a product different from pregnandiol or *allo*-pregnandiol found in urine. These facts show that catalytic hydrogenation of a carbonyl group at C_{20} leads to the formation of a hydroxyl group different in configuration from that found in the pregnandiol and *allo*-pregnandiol of human pregnancy urine. We propose to distinguish these isomeric hydroxyl groups at C_{20} by the prefixes (α) for the configuration of both OH groups found in natural pregnandiol and *allo*-pregnandiol, and (β) for their epimers. This corresponds to the designation of the *epi* or (α)[7] hydroxyl group at C_3. Thus pregnandiol will be referred to in this paper as pregnandiol-3(α), 20(α).

The exclusive formation of (β) isomers on reduction in neutral solution of a carbonyl group at C_{20} in the case of both pregnandione and *allo*-pregnandione is in marked contrast to the course of reduction of a carbonyl group at C_3 on these compounds. The reduction in neutral solution of a carbonyl group at C_3 gives, in the case of the pregnane series, a 3-OH with the (α) configuration, while in the case of the *allo*-pregnane series, a 3-OH with the (β) configuration is obtained. If the reductions are carried out in acid solution, the epimeric configurations are obtained.

The partial saponification of pregnandiol-3(α), 20(α) diacetate[8] or of *allo*-pregnandiol-3(β),20-(β) diacetate[9] preferentially removes the acetate group at C_3 in each case. This preferential hydrolysis of an acetate group at C_3 has now been found to occur in all the cases attempted; so one may conclude that an acetate group in either the 3(α) or 3(β) positions in either the pregnane or *allo*-pregnane series is more reactive than an acetate group in either the 20(α) or 20(β) position. The markedly diminished reactivity of an acetate group at C_{20} is in contrast to the intermediate reactivity of an acetate group at C_{17}, for Ruzicka and Goldberg[10] showed that while the partial saponification of androstandiol-3(β), 17 diacetate gives chiefly the 17-monoacetate, partial saponification of the epimeric androstandiol-3(α), 17-diacetate gives chiefly the 3-monoacetate.

When the pregnandiols are refluxed with sodium and xylene, according to the method of Windaus for the epimerization of cholestanols,[11] epi-

(1) Marrian, *Biochem. J.*, **23**, 1090 (1929).

(2) Butenandt, *Ber.*, **63**, 659 (1930); Butenandt, Hildebrandt and Brucher, *ibid.*, **64**, 2529 (1931).

(3) Hartmann and Locher, *Helv. Chim. Acta*, **18**, 160 (1935).

(4) Marker and Kamm, THIS JOURNAL, **59**, 1373 (1937).

(5) Marker, Kamm and McGrew, *ibid.*, **59**, 616 (1937).

(6) Butenandt and Mamoli, *Ber.*, **68**, 1854 (1935); Butenandt and Fleischer, *ibid.*, **70**, 96 (1937).

(7) This manner of designating epimers has been suggested by Fieser, "Chemistry of Natural Products Related to Phenanthrene," 2d. ed., Reinhold Publishing Corp., New York, N. Y., pp. 389 ff.

(8) Butenandt and Schmidt, *Ber.*, **67**, 1893 (1934).

(9) Marker, Kamm, Jones and Oakwood, THIS JOURNAL, **59**, 614 (1937).

(10) Ruzicka and Goldberg, *Helv. Chim. Acta*, **19**, 99 (1936).

(11) Windaus, *Ber.*, **49**, 1724 (1916).

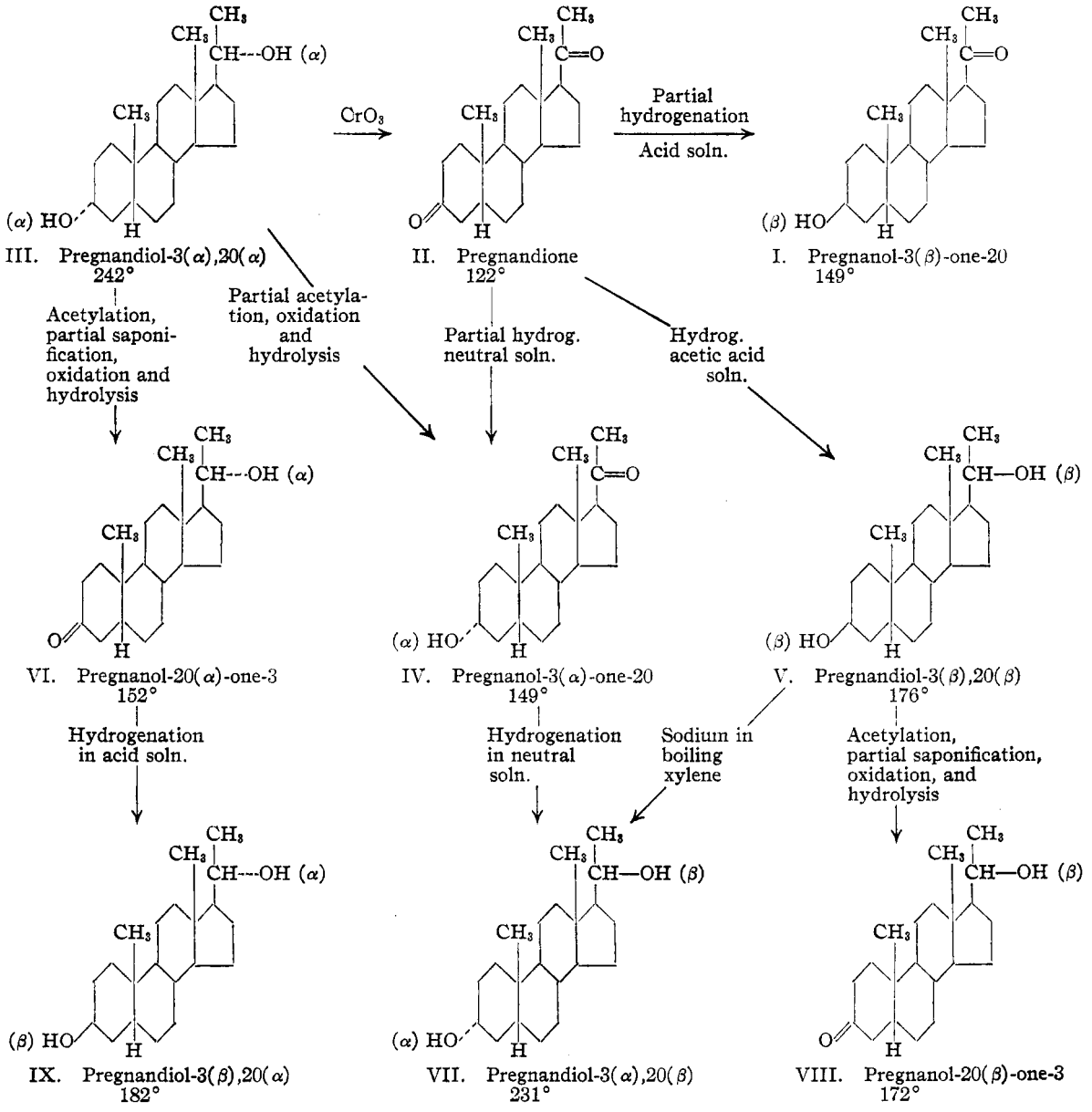

Fig. 1.—Pregnandiols and pregnanolones.

merization occurs chiefly about C_3, so that the principal product is the epimer in which the C_3 hydroxyl group and C_5 hydrogen atom have a *trans* configuration. No appreciable inversion of the hydroxyl group at C_{20} was observed regardless of the initial configuration of the pregnandiol about that center. Had any inversion occurred at C_{20}, an inversion would also be expected to occur at C_{17}, for Hückel and Naab[12] have shown that the epimerization of sodium alcoholates proceeds through the formation of an intermediate sodium enolate.

(12) Hückel and Naab, *Ber.*, **65**, 2137 (1932).

The greater reactivity of the 3-OH as compared with the 20-OH group in the pregnandiols is also shown by the fact that both pregnandiol-3(α), 20(α)[14] and *allo*-pregnandiol-3(α),20(α)[15] may be partially acetylated to give 3-monoacetates. That the difference in reactivities is due to the relatively exposed nature of the 3-position is suggested by the fact that dehydrocholic acid,[13] pregnandione,[14] and *allo*-pregnandione, may be partially hydrogenated to give products in which the 3-carbonyl group has been preferentially reduced.

(13) Kawai, *Z. physiol. Chem.*, **214**, 71 (1933).
(14) Marker, Kamm and Wittle, THIS JOURNAL, **59**, 1841 (1937).
(15) Marker, Kamm and Jones, *ibid.*, **59**, 1595 (1937.)

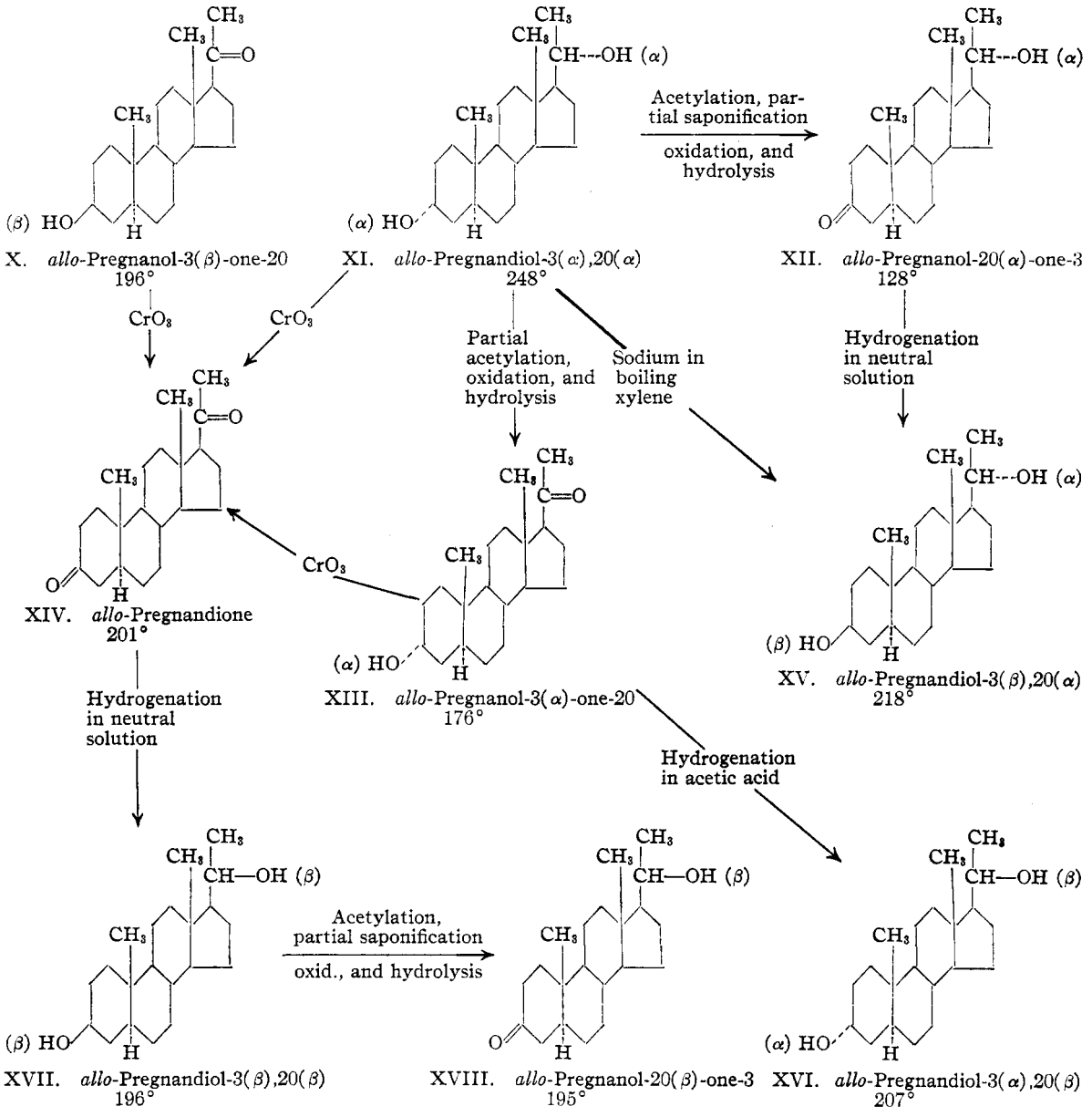

Fig. 2.—*allo*-Pregnandiols and *allo*-pregnanolones.

Pregnanol-3(α)-one-20 (IV) has been isolated from human pregnancy urine[4] and prepared by the partial catalytic hydrogenation of pregnandione in neutral solution,[14] and by the oxidation and subsequent hydrolysis of the 3-acetate of pregnandiol-3(α)-20(α).[14] Pregnanol-3(β)-one-20 (I) has been prepared by the partial catalytic hydrogenation of pregnandione in acid solution.[14]

Pregnanol-20(α)-one-3 (VI) has been prepared[8] by partial saponification of the diacetate of pregnandiol-3(α),20(α) to give the 20-monoacetate, which after oxidation and hydrolysis yields (VI). Pregnanol-20(β)-one-3 (VIII) has now been prepared from the diacetate of pregnandiol-3(β), 20(β) by partial saponification to the 20-monoacetate, and oxidation and hydrolysis of the latter.

allo-Pregnanol-3(α)-one-20 (XIII) has been isolated from human pregnancy urine.[5] It has been synthesized by the degradation and hydrolysis of 3-chloro-*allo*-cholanic acid.[16] The partial acetylation of *allo*-pregnandiol to the 3-monoacetate, followed by oxidation and hydrolysis also yields (XIII).[15] *allo*-Pregnanol-3(β)-one-20 (X)

(16) Marker, Kamm, Jones, Wittle, Oakwood and Crooks, *ibid.*, **59**, 768 (1937).

has been isolated from hog ovary extracts by Butenandt[17] and Allen.[18] It has been prepared from 3-hydroxybisnor-*allo*-cholanic acid by Butenandt and Mamoli,[19] and by Fernholtz.[20]

allo-Pregnanol-20(α)-one-3 (XII) has now been prepared by partially saponifying the diacetate of *allo*-pregnandiol-3(α),20(α) to give the 20-monoacetate. The latter, upon oxidation and hydrolysis, yields (XII). *allo*-Pregnanol-20(β)-one-3 (XVIII) has been prepared from *allo*-pregnandiol-3(β),20(β)[9] by partial saponification to the monoacetate, the latter being oxidized and hydrolyzed to yield (XVIII).

Pregnandiol-3(α),20(α) (III) has been isolated from human pregnancy urine,[1,2] but has not yet been prepared synthetically. It is found to be unaffected by sodium in boiling xylene. Pregnandiol-3(α),20(β) (VII) has been prepared by the catalytic reduction of pregnanol-3(α)-one-20 in alcohol or acetic acid solution.[4] It is the chief product of the epimerization of pregnandiol-3(β),20(β) by the action of sodium and boiling xylene. This reaction, incidentally, constitutes confirmatory evidence for the structure of pregnanol-3(α)-one-20 isolated from pregnancy urine. Pregnandiol-3(β),20(α) (IX) has now been prepared by the catalytic reduction of pregnanol-20(α)-one-3 (VI) in acetic acid solution containing hydrobromic acid. Pregnandiol-3(β),20(β) (V) has been prepared by the catalytic hydrogenation of pregnandione.[15]

allo-Pregnandiol-3(α),20(α) (XI) has been isolated from human pregnancy urine,[3] but has not yet been prepared synthetically. Sodium in boiling xylene epimerizes it to give chiefly *allo*-pregnandiol-3(β),20(α) (XV). The latter has also been prepared now by the reduction of *allo*-pregnanol-20(α)-one-3 (XII) in acetic acid solution, the isomers being separated by the use of digitonin. *allo*-Pregnandiol-3(α),20(β) (XVI) has been prepared by the catalytic hydrogenation of *allo*-pregnanol-3(α)-one-20.[5] *allo*-Pregnandiol-3(β),20(β) (XVII) has been prepared[9] by the catalytic reduction of *allo*-pregnandione in acetic acid solution.

Experimental

***allo*-Pregnanol-20(α)-one-3.**—To a solution of 10 g. of *allo*-pregnandiol diacetate-(α,α) in 3100 cc. of methyl alcohol at 20° was added a solution of 1.13 g. of potassium hydroxide in 190 cc. of methyl alcohol and 15 cc. of water. The solution was shaken vigorously and allowed to stand at 20° for forty-eight hours and then at 30° for twelve hours. It was made neutral to litmus with dilute sulfuric acid and concentrated to 200 cc. on the steam-bath. The hydrolyzed product was precipitated by adding slowly two liters of water. The suspension was filtered with suction, washed with water and dried. This crude product was oxidized by dissolving it in 250 cc. of acetic acid, cooling to 20°, and adding a solution of 1.5 g. of chromic oxide in 50 cc. of 90% acetic acid. The solution was kept at 20° for eighteen hours, diluted with 2 liters of water, and the product extracted with 750 cc. of ether. The ethereal solution was washed with dilute sodium carbonate, then with water, and evaporated to dryness. To isolate the ketones, the product so obtained was treated with Girard's reagent as follows: the residue was dissolved in 100 cc. of absolute ethyl alcohol and heated to reflux on the steam-bath; Girard's reagent (10 g.) was added and the solution was refluxed for fifteen minutes, poured into 200 cc. of water, and the non-ketonic material removed by extracting the aqueous solution with ether. The aqueous solution was acidified with 50 cc. of concentrated hydrochloric acid and heated thirty minutes on the steam-bath. The solution was cooled and the precipitated ketones were extracted with ether. The ether solution was washed with water and evaporated to dryness. The combined product from five such runs was further purified by dissolving it in 300 cc. of ethyl alcohol and refluxing this solution with 15 g. of potassium hydroxide. The solution was poured into one liter of water and the product was extracted with 500 cc. of ether. The ether solution, after washing with water, was evaporated to dryness. Benzene (50 cc.) was added to the residue and then the mixture distilled to remove traces of water. Dry pyridine (30 cc.) and 20 g. of succinic anhydride were added and the mixture was heated on the steam-bath for one hour. This solution was poured into 500 cc. of water and 500 cc. of ether was added. The pyridine was removed by shaking with dilute hydrochloric acid. The ether layer was separated, washed with water and then extracted twice with 100 cc. of saturated sodium carbonate solution. The alkaline solution was acidified with hydrochloric acid and then extracted with ether. The ether was evaporated and the residue was hydrolyzed with potassium hydroxide solution. The solution was extracted with ether, and the product was crystallized from dilute acetone, methyl alcohol and ethyl alcohol, m. p. 128°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 79.7; H, 10.9.

It gave a semicarbazone melting with decomposition at 245°.

Anal. Calcd. for $C_{22}H_{37}N_3O_2$: C, 70.3; H, 9.9. Found: C, 69.6; H, 10.1.

***allo*-Pregnanol-20(α)-one-3 Acetate.**—A solution of 100 mg. of *allo*-pregnanol-20(α)-one-3 in 10 cc. of acetic anhydride was refluxed for thirty minutes. The solvent was evaporated *in vacuo* and the residue was crystallized from dilute ethyl alcohol, m. p. 117°. It crystallized in small needles.

(17) Butenandt and Westphal, *Ber.*, **69**, 443 (1936), and earlier papers.

(18) Allen and Goetsch, *J. Biol. Chem.*, **116**, 653 (1936), and earlier papers.

(19) Butenandt and Mamoli, *Ber.*, **67**, 1893 (1934).

(20) Fernholtz, *Z. physiol. Chem.*, **230**, 185 (1934).

Anal. Calcd. for $C_{28}H_{36}O_3$: C, 76.8; H, 10.1. Found: C, 77.0; H, 10.2.

3(β),20(α)-*allo*-Pregnandiol.—A mixture of 1.0 g. of *allo*-pregnanol-20(α)-one-3 and 0.5 g. of platinum oxide in 150 cc. of acetic acid was shaken for one hour at 30° with hydrogen at 3 atmospheres pressure. The solution was then filtered to remove the catalyst and the filtrate was diluted with 500 cc. of water and extracted with ether. The ether solution was washed with water and dilute sodium carbonate and then evaporated to dryness. The carbinol mixture so obtained was dissolved in 50 cc. of alcohol and poured into a solution of 300 cc. of ethyl alcohol containing 4 g. of digitonin. After twelve hours the precipitated digitonide was filtered and dried. This was then heated on the steam-bath for fifteen minutes with 10 cc. of dry pyridine and the resulting solution then poured into 250 cc. of ether. After standing for thirty minutes, the solution was filtered and the filtrate poured into 500 cc. of dilute hydrochloric acid. The ethereal layer was separated, washed with water, and evaporated to dryness. The residue was crystallized from dilute ethyl alcohol to give 0.3 g. of product melting at 218°. It crystallized in small plates.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 79.2; H, 11.5.

Diacetate of 3(β),20(α)-*allo*-Pregnandiol.—A solution of 100 mg. of 3(β),20(α)-*allo*-pregnandiol dissolved in 10 cc. of acetic anhydride was refluxed for thirty minutes. The solvent was evaporated to dryness *in vacuo* and the residue was crystallized from dilute acetone giving large angular plates melting at 168°.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.4; H, 10.0. Found: C, 74.5; H, 10.1.

Acetate of Pregnanol-20(α)-one-3.—The following procedure is a modification of that used by Butenandt and Schmidt.[8] To a solution of 10 g. of the diacetate of pregnandiol-(α,α), m. p. 178°, in 3100 cc. of methyl alcohol at 20° was added a solution of 1.13 g. of potassium hydroxide in 190 cc. of methyl alcohol. The solution was allowed to stand at 20° for forty-eight hours and then carefully neutralized with sulfuric acid. The methyl alcohol was distilled off, the residue was dissolved in 250 cc. of acetic acid at 20° and a solution of 1.5 g. of chromic oxide in 50 cc. of 90% acetic acid was added. After standing eighteen hours the solution was diluted with water and the precipitated product was filtered. The precipitate was dissolved in 100 cc. of alcohol and heated for fifteen minutes with 6 g. of Girard's reagent. The solution was poured into water and extracted with ether. The aqueous layer was acidified with hydrochloric acid and heated to 80° for fifteen minutes. The solution was extracted with ether, and the ether was evaporated. The solid remaining was crystallized from alcohol, m. p. 144.5°.

Pregnandiol-3(β),20(α) Monoacetate.—A solution of 2.0 g. of the acetate of pregnanol-20(α)-one-3 in 100 cc. of acetic acid containing 1 cc. of hydrobromic acid was added to a suspension of 1.0 g. of previously reduced platinum oxide in acetic acid. The mixture was shaken for eighty minutes with hydrogen at 45 pounds (3 atm.) pressure. The catalyst was filtered and the acetic acid was evaporated to 25 cc. Water was added and the product was extracted with water. The ether was evaporated and the residue was dissolved in 50 cc. of alcohol. This solution was added to a hot solution of 8 g. of digitonin in 400 cc. of alcohol. After standing overnight, the insoluble digitonide was filtered and washed with alcohol. The digitonide was heated with pyridine on a steam-bath for fifteen minutes. The solution was poured into 800 cc. of ether and filtered. The ethereal filtrate was washed with dilute hydrochloric acid and then the ether was evaporated. The residue was crystallized from alcohol, m. p. 147.5°.

Anal. Calcd. for $C_{23}H_{38}O_3$: C, 76.2; H, 10.6. Found: C, 76.1; H, 10.7.

Diacetate of Pregnandiol-3(β),20(α).—A solution of 115 mg. of pregnandiol-3(β),20(α) monoacetate in 3 cc. of acetic anhydride was refluxed for one hour. The product was crystallized from alcohol, m. p. 141°.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.2; H, 10.0. Found: C, 74.8; H, 10.2.

Pregnandiol-3(β),20(α).—To a solution of 240 mg. of pregnandiol-3(β),20(α) monoacetate dissolved in 50 cc. of alcohol was added 0.5 g. of sodium hydroxide in 2 cc. of water. The solution was heated for one hour, neutralized with hydrochloric acid and the product precipitated by the addition of water. It was filtered and crystallized from alcohol, m. p. 182°.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.7; H, 11.3. Found: C, 78.9; H, 11.5.

Pregnanol-20(β)-one-3.—To a solution of 5 g. of the diacetate of pregnandiol-3(β),20(β) in 2 liters of methyl alcohol was added 0.8 mole of potassium hydroxide. The solution was kept at 20° for forty hours. The hydroxyketone was prepared and purified by means of Girard's reagent and the succinic ester as described for *allo*-pregnanol-20(α)-one-3. It was crystallized from dilute methyl alcohol, m. p. 172°.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 79.5; H, 11.1.

It gave a semicarbazone melting with decomposition at 245°.

Anal. Calcd. for $C_{22}H_{37}N_3O_2$: C, 70.3; H, 9.9. Found: C, 70.0; H, 10.1.

Action of Sodium and Xylene on allo-Pregnandiol-3(α),20(α).—A mixture of 2.0 g. of *allo*-pregnandiol-3(α),20(α), 3.0 g. of sodium, and 150 cc. of dry xylene was refluxed for nine hours. The sodium was destroyed with alcohol, and the alkali neutralized by adding 10 cc. of concentrated hydrochloric acid in 45 cc. of water. The mixture was poured into about 500 cc. of water, and the emulsion filtered to remove suspended solid material. This filtrate was extracted with ether, and the filtered solid was added to this extract. After evaporating off the solvents the residue was dissolved in 100 cc. of alcohol and poured into a solution of 8.0 g. of digitonin in 500 cc. of alcohol. After standing for fourteen hours, the digitonide was filtered and washed well with alcohol. The dried digitonide weighed 7.5 g., corresponding to 1.55 g. of pregnandiol-3(β),20(α). The digitonide was warmed for fifteen minutes with 75 cc. of dry pyridine, and the resulting solution poured into 500 cc. of ether. The precipitated digitonin was filtered, and washed with ether. The

ethereal filtrate and washings were combined and then shaken with 200 cc. of concentrated hydrochloric acid in 500 cc. of water to remove the pyridine, and then the ether was evaporated. The residue was dissolved in alcohol, treated with bone black, and concentrated. The crystals which separated on cooling were filtered and recrystallized to give a product melting at 217°. This gave no depression in melting point when mixed with *allo*-pregnandiol-3(β),20(α) prepared by the reduction of *allo*-pregnanol-20(α)-one-3.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 78.8; H, 11.5.

Action of Sodium and Xylene on Pregnandiol-3(α), 20(α).—A mixture of 2.0 g. of pregnandiol-3(α),20(α), 3.0 g. of sodium and 150 cc. of dry xylene was refluxed for nine hours. The sodium was destroyed with alcohol and the alkali neutralized as described in the previous experiment. The xylene layer was separated while the mixture was still hot, and washed with water. After evaporating off the xylene, the residue was dissolved in alcohol, treated with Norit, and concentrated until crystals separated. The product was recrystallized from alcohol, giving 1.3 g. of pregnandiol-3(α)-20(α), m. p. 238°. The product showed no depression in melting point when mixed with natural pregnandiol-3(α),20(α).

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 78.3; H, 11.3.

Action of Sodium and Xylene on Pregnandiol-3(β), 20(β).—A mixture of 2.0 g. of pregnandiol-3(β),20(β), m. p. 176°, 3.0 g. of sodium, and 150 cc. of dry xylene was refluxed for eight hours. The reaction mixture was treated as described before with alcohol and dilute hydrochloric acid. While the mixture was still hot, the xylene layer was separated, and washed with water. After evaporating the xylene, the residue was dissolved in alcohol, treated with Norit, and the alcoholic solution concentrated. After standing overnight in the refrigerator, the crystals which had separated were filtered. The product was recrystallized to give 0.7 g. of pregnandiol-3(α),20(β), m. p. 231°. The product showed no depression in melting point with pregnandiol-3(α),20(β) obtained by the reduction of *epi*-pregnanolone,[4] but gave a depression to 211° with pregnandiol-3(α),20(α) (m. p. 238°).

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.8; H, 11.3. Found: C, 78.5; H, 11.4.

Diacetate of Pregnandiol-3(α),20(β).—A mixture of 200 mg. of pregnandiol-3(α),20(β) and 5 cc. of acetic anhydride was refluxed for thirty minutes. The acetic anhydride was evaporated and the residue was crystallized three times from dilute alcohol, giving needles, m. p. 110°.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.2; H, 10.0. Found: C, 74.7; H, 10.0.

Summary

In order to distinguish between hydroxypregnane derivatives which are epimeric about C_{20}, it is suggested that the compounds configurationally related to pregnandiol and *allo*-pregnandiol from urine be called the (α)-forms, their epimers being designated by the prefix (β).

Partial saponification of all the pregnandiol diacetates and *allo*-pregnandiol diacetates studied leads to the formation of 20-monoacetates regardless of the configuration about the asymmetric centers C_3, C_5, or C_{20}.

The action of sodium in boiling xylene on a pregnandiol or an *allo*-pregnandiol gives, as the chief product, the epimer in which the 3-OH occupies a position *trans* to the hydrogen atom at C_5. Regardless of its initial configuration, the hydroxyl group at C_{20} remains unaffected.

The series of the eight isomeric pregnandiols and the eight isomeric pregnanolones has been completed by the preparation of pregnandiol-3(β),20(α), *allo*-pregnandiol-3(β),20(α), pregnanol-20(β)-one-3, and *allo*-pregnanol-20(α)-one-3.

STATE COLLEGE, PENNA.
DETROIT, MICHIGAN

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