[CONTRIBUTION FROM THE CHEMICAL RESEARCH & DEVELOPMENT DIVISION OF THE SCHERING CORPORATION]

11-Oxygenated Steroids. XIV. New Syntheses of Corticosterone[1]

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Two new syntheses of corticosterone are described. (A) Ozonolysis of 3α-hydroxy-21-benzylidenepregnane-11,20-dione (Ia) gave 3,11-diketoetianic acid (III). This was converted to 3-keto-11β-hydroxyetianic acid (VI), and without protection of the 11β-hydroxyl group, the diazo-ketone synthesis was then employed to build up the acetone side chain to give 11β,21-dihydroxypregnane-3,20-dione 21-acetate (IX). (B) Compound IX was also prepared from 3α,21-dihydroxypregnane-11,20-dione using protective ketal formation.

(A) Although it has been stated[2] that "the diazo-ketone synthesis cannot be employed for the synthesis of corticosterone because the 11β-hydroxyl group is eliminated under the conditions required for preparation of the acid chloride and cannot be acylated for protection," Lardon and Reichstein[3] recently have described the preparation of this adrenal hormone *via* the diazo-ketone route in which the sensitive 11β-hydroxyl group was protected as the easily hydrolyzed trifluoroacetate. We wish to report on the synthesis of corticosterone by a similar route, but one in which the 11β-hydroxyl group is not protected.

The starting material in our first synthesis was 3α-hydroxy-21-benzylidenepregnane-11,20-dione (Ia).[4] Ozonolysis of its 3-acetate Ib at −7° with 2 moles of ozone followed by treatment with periodic acid gave the previous workers[4] an 86% yield of 3α-acetoxy-11-ketoetianic acid. In our hands, ozonolysis of Ia at −70° with excess ozone and omitting the periodic acid treatment gave a 71% yield of 3,11-diketoetianic acid (III). Ozonolysis of Ia under these conditions not only oxidized the side-chain to the etio-acid, but also oxidized the 3-hydroxyl group to the ketone. While steroid hydroxyls have been oxidized by ozone before,[5] the omission of a chemical oxidation after ozonolysis of a 21-benzal steroid does not appear to have been tried.[6] Oxidation of Ia with potassium permanganate did permit the isolation of some 3α-hydroxy-11-ketoetianic acid. This was smoothly converted to III with N-bromosuccinimide in *t*-butyl alcohol and methylene chloride.

Treatment of the 3-ketoetio-acid III with ethylene glycol and selenium dioxide in methylene chloride[7] gave the 3-ethylene ketal IV in good yield. This was reduced to the 11β-hydroxyetio-acid V with sodium borohydride, and the ethylene ketal removed with aqueous acid to give VI. The sodium salt of VI was prepared, treated with oxalyl chloride and then diazomethane to give the diazo-ketone VIII. Warming with acetic acid gave 11β,-21-dihydroxypregnane-3,20-dione 21-acetate (IX), identical in all respects with an authentic sample.[8] Compound IX had been converted to corticosterone previously.[9] The over-all yield from VI to IX was 32%, indicating a fair order of stability for the 11β-hydroxyl group during the several intermediate steps.

(B) The application of protective ethylene ketal formation has been successfully applied to the synthesis of hydrocortisone from cortisone,[10] but the corresponding synthesis of corticosterone from its 11-keto analog has not been reported.

3α,21-Dihydroxypregnane-11,20-dione X was prepared by saponification of the corresponding diacetate[11] in 66% yield. Selective oxidation at C-3 with N-bromoacetamide in aqueous acetone gave a 98% yield of 21-hydroxypregnane-3,11,20-trione (XI). Neither X nor XI has been reported specifically previously, although their 21-acetates are known.

21-Hydroxypregnane-3,11,20-trione 3,20-bis-ethylene ketal (XII) was prepared from XI in 59% yield with ethylene glycol in refluxing benzene, catalyzed by *p*-toluenesulfonic acid. Reduction of XII with lithium aluminum hydride gave 11β,21-dihydroxypregnane-3,20-dione bis-ethylene ketal (XIII). This was not isolated, but was hydrolyzed directly to 11β,21-dihydroxypregnane-3,20-dione (XIV) with methanolic hydrochloric acid and then acetylated with acetic anhydride in pyridine to give 11β,21-dihydroxypregnane-3,20-dione 21-acetate (IX) in 33% yield from XII.

Experimental[12,13]

3α-Acetoxy-11-ketoetianic Acid (IIb).—A solution of 2.20 g. of 3α-hydroxy-21-benzylidenepregnan-11,20-dione 3-acetate (Ib) in 350 ml. of C.P. ethyl acetate was ozonized at −70° until the appearance of a blue color. The system was flushed with oxygen for 10 minutes longer, 2.3 g. of zinc dust and 8 ml. of acetic acid were added, the mixture allowed to warm up to room temperature and stand overnight. A starch–potassium iodide test was then negative. The mixture was filtered and the filtrate was concentrated to dryness to give 2.02 g. of a crystalline residue. Recrys-

(1) Paper XIII: H. L. Herzog, C. C. Payne, M. A. Jevnik, D. Gould, E. L. Shapiro, E. P. Oliveto and E. B. Hershberg, THIS JOURNAL, **77**, 4781 (1955).

(2) L. F. and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, p. 444.

(3) A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **37**, 443 (1954).

(4) R. B. Turner, V. R. Mattox, W. F. McGuckin and E. C. Kendall, THIS JOURNAL, **74**, 5814 (1952).

(5) J. von Euw and T. Reichstein [*Helv. Chim. Acta*, **27**, 821 (1944)] reported the conversion of an 11β-hydroxyl to an 11-ketone with ozone.

(6) In the most recent example, ozonolysis of 3β-acetoxy-16α-benzyloxy-21-benzylidenepregnan-20-one was followed immediately by oxidation with chromium trioxide before the etio-acid was isolated, J. A. Moore, *ibid.*, **37**, 659 (1954).

(7) *Cf.* E. P. Oliveto, C. Gerold and E. B. Hershberg, THIS JOURNAL, **76**, 6113 (1954).

(8) Kindly supplied by Dr. T. Stoudt, Merck and Co., Inc.

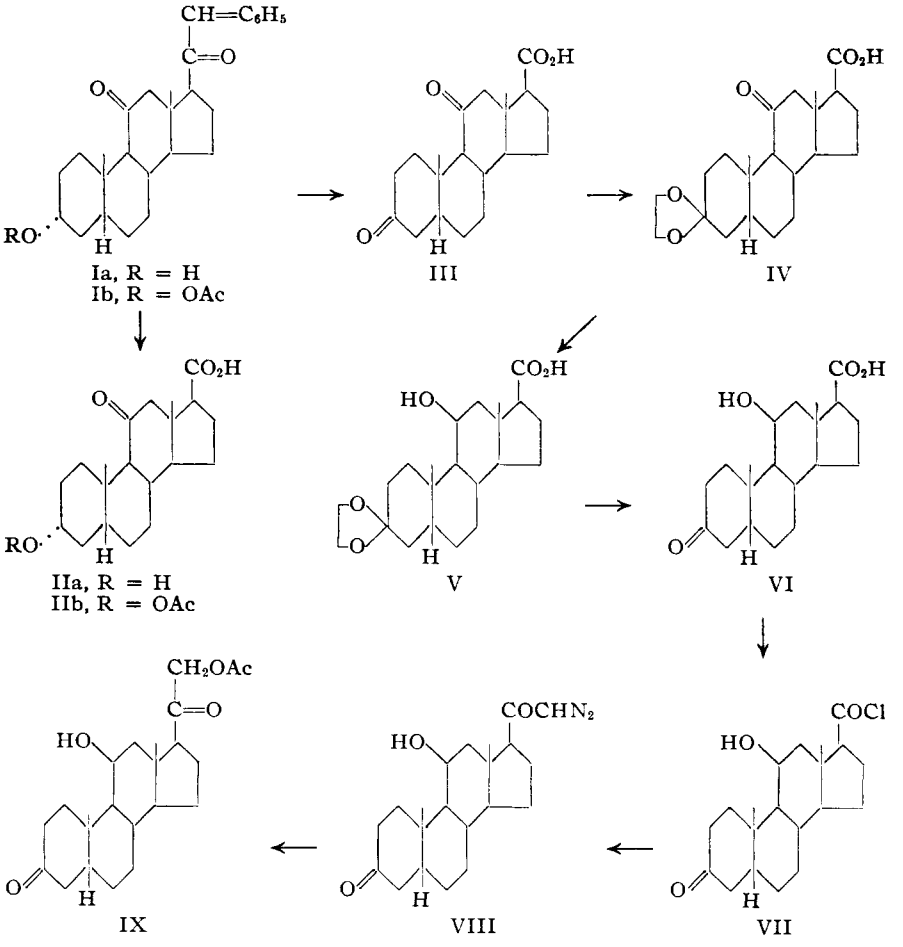
(9) J. von Euw, A. Lardon and T. Reichstein, *Helv. Chim. Acta*, **27**, 1287 (1944).

(10) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953).

(11) L. H. Sarett, THIS JOURNAL, **70**, 1456 (1948).

(12) All m.p.'s are corrected. All rotations were taken in a 1-dm. tube at a concentration of *ca.* 1%. Analyses and optical data were obtained by the Microanalytical and Physical Chemistry Department of these laboratories.

(13) We wish to acknowledge the technical assistance of Mrs. F. E. Carlon.



tallization from aqueous methanol yielded 1.24 g. of IIb, m.p. 218–220°. The analytical sample, crystallized once more, melted at 221–223°. Its infrared spectrum was identical with that of an authentic specimen.[14]

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 69.97; H, 8.88.

3,11-Diketoetianic Acid (III).—A solution of 1.00 g. of 3α-hydroxy-21-benzylidenepregnane-11,20-dione (Ia) in 150 ml. of C.P. ethyl acetate was ozonized at −70° and treated with zinc dust in the usual manner.

After removal of the zinc by filtration, the filtrate was steam distilled to give 0.56 g. of III, m.p. 240–250° dec. The analytical sample, crystallized twice from acetone–hexane, melted at 254–259° dec., $[\alpha]_D$ +89.2° (chloroform). The infrared spectrum showed no free hydroxyl group.

Anal. Calcd. for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.39; H, 8.34.

3α-Hydroxy-11-ketoetianic Acid (IIa).—A solution of 1.00 g. of Ia in 35 ml. of 85% aqueous acetone at 40° was treated with a solution of 1.0 g. of potassium permanganate in 60 ml. of 85% aqueous acetone. After stirring 15 hr. at room temperature, the salts were removed by filtration, the filtrate heated to boiling and crystallized by the addition of dilute hydrochloric acid; yield 0.50 g. (62.8%), m.p. 268–276° dec. The infrared spectrum confirmed the presence of the 3-hydroxyl group and the carboxyl group.

Oxidation of IIa with N-bromosuccinimide in *t*-butyl alcohol and methylene chloride in the usual fashion gave III smoothly in 90% yield.

3,11-Diketoetianic Acid 3-Ethylene Ketal (IV).—A mixture of 1.00 g. of III, 10 ml. of ethylene glycol, 10 ml. of methylene chloride and 1.00 g. of selenium dioxide was stirred overnight at 25°. A solution of 2 g. of potassium carbonate in 15 ml. of water was then added rapidly, resulting in a *p*H of *ca.* 9. Acetic acid was added dropwise until the reaction mixture was slightly acid (*p*H 5). The layers were quickly separated and the aqueous layer extracted three times with methylene chloride. The combined extracts were washed once with water, dried and evaporated to give 1.26 g., m.p. 234–238°. Recrystallization from ether–hexane gave 0.91 g. of IV, m.p. 238–241°, $[\alpha]_D$ +70.2° (chloroform).

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.17; H, 8.80.

3-Keto-11β-hydroxyetianic Acid (VI).—A mixture of 0.60 g. of IV, 0.20 g. of sodium hydroxide, 0.60 g. of sodium borohydride and 6 ml. of water was refluxed overnight. The methanol was removed under reduced pressure, the residue acidified with acetic acid and diluted with water, and the resulting precipitate removed by filtration; yield 0.54 g., m.p. 160–165°. This was heated for 30 minutes on the steam-bath with a mixture of 10 ml. of acetic acid and 10 ml. of water. Upon further addition of water, and cooling, there was obtained 0.44 g. of VI, m.p. 252–259°. The analytical sample, crystallized from aqueous acetone, melted at 258–261°, $[\alpha]_D$ +80.8° (ethanol).

Anal. Calcd. for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 72.17; H, 9.44.

11β,21-Dihydroxypregnane-3,20-dione 21-Acetate (4,5-Dihydrocorticosterone Acetate) (IX).—With the aid of gentle heating, 5.02 g. of VI was dissolved in a solution of 603 mg. of sodium hydroxide in 50 ml. of water. The clear solution was then evaporated to dryness, and the residue dried *in vacuo* for 14 hr. This was then treated with 50 ml. of benzene, the slurry cooled to −10°, and a solution of 15 ml. of distilled oxalyl chloride in 35 ml. of benzene was added dropwise with stirring. The mixture was allowed to warm to room temperature, stirred 30 minutes longer, and the solvent then evaporated *in vacuo*. The residue was dissolved in 50 ml. of methylene chloride and any inorganic residue removed by filtration. The filtrate was cooled to −10°, and then allowed to react for two hr. at this temperature with excess diazomethane (prepared in methylene chloride and dried over sodium hydroxide pellets). The resulting yellow solution was evaporated to dryness under reduced pressure to give the crude diazo-ketone VIII. This was dissolved in 35 ml. of acetic acid, refluxed ten minutes and diluted with water to give a gummy product which crystallized upon the addition of ether; yield 1.47 g., m.p. 150–160°. Two further fractions were isolated: 0.28 g., m.p. 148–150°, and 0.37 g., m.p. 150–152°; total, 2.12 g. The three fractions were combined and crystallized from ether to give 1.87 g. (32%) of IX, m.p. 154–157°. The analytical sample, crystallized once more, had m.p. 156.5–158°, $[\alpha]_D$ +127.0° (acetone); lit.[9] m.p. 158–159°, $[\alpha]_D$ +128° (acetone).

Anal. Calcd. for $C_{23}H_{34}O_5$. C, 70.74; H, 8.77. Found: C, 70.38; H, 9.13.

Its infrared spectrum was identical with that of an authentic sample.[8]

3α,21-Dihydroxypregnane-11,20-dione (X).—A mixture of 46.7 g. of 3α,21-dihydroxypregnane-11,20-dione diacetate (m.p. 131–132°), 1500 ml. of methanol, 31.3 g. of potassium bicarbonate and 500 ml. of water was refluxed for three hours, cooled, neutralized with acetic acid and the solvent was distilled under reduced pressure to a small volume. The

(14) Kindly supplied by Dr. R. B. Turner.

solid was filtered, washed with water and dried to give 37.9 g., m.p. 200–211°. After digestion for one hour with 350 ml. of boiling acetone, there was obtained 24.9 g. (66%) of X, m.p. 217–222°.

The analytical sample was recrystallized from ethanol and had m.p. 225.5–228.5°, $[\alpha]_D$ +110° (1% in dioxane).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.20; H, 9.42.

21-Hydroxypregnane-3,11,20-trione (XI).—A solution of 6.4 g. of I in a mixture of 224 ml. of acetone and 96 ml. of water was treated with 6.4 g. of N-bromoacetamide and 12 drops of concentrated hydrochloric acid, and allowed to stand for five hours at 5°. A solution of 9.5 g. of sodium sulfite in 135 ml. of water was added to remove the yellow color and the solution was acidified with acetic acid. The resulting mixture was steam distilled thoroughly and then distilled under reduced pressure until precipitation took place. The solid was filtered, washed with water and dried to give 5.73 g. (91.5%) of XI, m.p. 138–142°. Concentration of the mother liquor gave another 0.44 g. (7.0%), m.p. 136–139°.

The analytical sample was recrystallized from ethyl acetate–hexane, and had m.p. 142.5–143.5°, $[\alpha]_D$ +112° (1% in dioxane).

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.80: H, 8.73. Found: C, 72.88; H, 9.12.

21-Hydroxypregnane-3,11,20-trione 3,20-Bis-ethylene Ketal (XII).—A mixture of 7.0 g. of II, 165 ml. of benzene and 14 ml. of ethylene glycol was distilled to remove traces of water, and 0.70 g. of *p*-toluenesulfonic acid monohydrate was added. The mixture was refluxed with stirring for four hours and 65 ml. of distillate was removed through a Dean-Stark tube. After cooling, the mixture was neutralized with potassium hydroxide in methanol, washed with water, dried over magnesium sulfate, filtered, and evaporated to dryness under reduced pressure. Trituration of the residue with ether gave 3.75 g. (42.7%) of XII, m.p. 160–161.6°. From the mother liquor, another 1.29 g. (14.7%) was obtained, m.p. 160–161°.

The analytical sample was recrystallized from ethyl acetate–hexane and had m.p. 160–161°, $[\alpha]_D$ +59° (1% in dioxane).

Anal. Calcd. for $C_{25}H_{38}O_6$: C, 69.09; H, 8.81. Found: C, 68.97; H, 9.23.

11β,21-Dihydroxypregnane-3,20-dione 21-Acetate (IX).—To a slurry of 6.0 g. of lithium aluminum hydride in 180 ml. of ether was added, with cooling, a solution of 6.0 g. of III in 180 ml. of dry tetrahydrofuran. The mixture was stirred for four hours at 25° and allowed to stand overnight. The excess hydride was destroyed by the addition of 45 ml. of ethyl acetate with ice-water cooling, and then 18 ml. of water was added. The insoluble inorganic material was removed by filtration and the filtrate was taken to a residue under reduced pressure, leaving a glass. This material, dissolved in a mixture of 60 ml. of chloroform and 210 ml. of methanol, was treated with a solution of 12.6 ml. of concentrated hydrochloric acid in 21 ml. of water. The mixture was allowed to stand 24 hours at 25°, then 600 ml. of water was added. Methylene chloride was added, the organic extract was washed with sodium bicarbonate solution and with water, then dried over magnesium sulfate, filtered and distilled to a residual oil. A solution of this product in 30 ml. of pyridine and 20 ml. of acetic anhydride was allowed to stand overnight at room temperature. After working up in the usual manner, the residue obtained was triturated with ether to give 1.78 g. (33% from XII) of IX, m.p. 151–153.5°. Recrystallization from ether gave m.p. 158–159°, $[\alpha]_D$ +128.5° (1% in acetone); lit.[9] m.p. 158°, $[\alpha]_D$ +128° (acetone). This material was identical in its infrared spectrum with an authentic sample.[8]

BLOOMFIELD, NEW JERSEY

[CONTRIBUTION FROM THE RESEARCH LABORATORY ATTACHED TO TAKEDA PHARMACEUTICAL INDUSTRIES, LTD.]

Santonin. II.[1] The Synthesis of New Stereoisomers of Santonin[2]

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The resolution of santonin A as well as the synthesis of new stereoisomers of santonin (designated as santonin C and santonin D) are described. The stereochemistry of the natural santonins and their synthetic isomers is discussed.

The synthesis of the racemic stereoisomers of santonin (santonin A and B) has been reported.[3] In recent years Barton[4] has shown conformational analysis to be an effective method for the elucidation of stereochemistry. We have used this method to obtain more detailed information on the structure of santonin and its related compounds. Since the dienone ring of santonin must be planar and a chair form is preferable for the B ring, the skeleton of santonin may be considered to correspond to the A and B rings of $\Delta^{1,4}$-3-ketosteroids, with the angular methyl group in the axial position.

The stereochemical relationships of two natural santonins (*l*-α-santonin (I[5]) and *l*-β-santonin (II)) and four optically active desmotroposantonins (III, IV, V, VI) have been investigated by Clemo,[6] Huang-Minlon,[7] Barton[8] and Mitsuhashi.[9] It has been shown that *l*-α- and *l*-β-santonins are epimeric at C-11 and in both isomers the C-5 hydrogen is *cis* to the angular methyl group at C-9, and the lactone ring is *trans*-fused to the B ring; the relation between the angular methyl and the C-6 side chain must be *cis*. Therefore in *l*-α-santonin and also in *l*-β-santonin the C-5–O bond of the lactone, as well as the C-6 side chain should be equatorial to satisfy the relationships in configuration among C-5, C-6 and C-9. Furthermore, it is likely that all the six possible racemates of santonin (XII → XVII)[10] possess the same skeleton as natural santonin. Of the eight structures which may arise from the four asymmetric carbons, X and XI are impossible since a 6-5 ring fusion cannot exist in a diaxial configuration with chair-formed cyclohexanes.

(1) This is part XI of "Studies on Anthelmintics."

(2) A preliminary report of this work was presented in *Proc. Japan Acad.*, **28**, 427 (1952); **29**, 113 (1953); **30**, 116 (1954).

(3) Y. Abe, T. Harukawa, H. Ishikawa, T. Miki, M. Sumi and T. Toga, THIS JOURNAL, **75**, 2567 (1953).

(4) D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953).

(5) *l*-α-Santonin is arbitrarily represented by I not by II, or VII. All other formulas are based on this convention.

(6) G. R. Clemo, *J. Chem. Soc.*, 1343 (1934).

(7) Huang-Minlon, THIS JOURNAL, **70**, 611 (1948).

(8) D. H. R. Barton, *J. Org. Chem.*, **15**, 467 (1950).

(9) H. Mitsuhashi, *J. Pharm. Soc. Japan*, **71**, 1115 (1951).

(10) Regarding optically active isomers, configurations in the formulae are indicated in the same way as in steroids, using full-lines and dotted lines, while for the racemates black dots are employed to show that the attached group lies above the plane of the molecule.