tion of II, there was isolated 0.45 g. of IX, m.p. 193–195°, λ_{max}^{Nujol} 5.72 μ (17-carbonyl), 5.85 μ (11-carbonyl), 6.01, 6.14, 6.22 μ ($\Delta^{1,4}$-diene-3-one). No depression in melting point was observed when this sample was mixed with IX from X.

$\Delta^{1,4}$-Androstadiene-3,11,17-trione (IX) from X.—To a solution of 4 g. of etiocholane-3,11,17-trione in 40 ml. of glacial acetic acid was added 2 drops of 0.28 *N* hydrogen bromide in acetic acid. The reaction mixture was cooled to 15°, and a solution of 5.1 g. of bromine in 20 ml. of acetic acid was added dropwise with stirring at such a rate that no build-up of bromine in the reaction mixture resulted. This required about 10 minutes. Stirring was continued for an additional 15 minutes, and then the reaction mixture was diluted with water and extracted with methylene chloride. The extracts were washed free of acid with water, dried and concentrated to a residue.

Trituration of the residue with ether afforded 2.92 g. of crystalline dibromide, m.p. 191–192° dec. Concentration of the ethereal solution gave an additional 1.75 g. of material, m.p. 189° dec.

Three grams of the dibromide was added to 90 ml. of boiling 2,4,6-collidine and reflux was continued for 25 minutes. The reaction mixture was diluted with ether and the precipitated collidine hydrobromide was removed by filtration. The filtrate was washed free of collidine with dilute sulfuric acid and then washed neutral with water. The dried solution was concentrated to a small volume and chromatographed on Florisil. A series of crystalline fractions, m.p. 180–192°, was eluted with 25% ether in hexane. Recrystallization from ether afforded 110 mg. of IX, m.p. 192.5–195°, $[\alpha]^{25}D$ +232° (acetone).

BLOOMFIELD, NEW JERSEY

[CONTRIBUTION FROM THE MEDICINAL CHEMICAL RESEARCH SECTION, LEDERLE LABORATORIES RESEARCH DIVISION, AMERICAN CYANAMID CO.]

Steroidal Cyclic Ketals. XV.[1,2] 17,21-Oxido-steroids. Part I. Preparation

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Treatment of the ditosylate IIa of 11-*epi*-hydrocortisone bis-ethylene ketal with alkali resulted in a product which was assigned the structure, Δ^5-pregnene-11α-ol-3,20-dione-17α,21-oxide 3,20-bis-ethylene ketal (IIIa). Solvolysis without Walden inversion occurred at C-11, and the derived oxygen anion at C-17 internally displaced the 21-tosyloxy group. Hydrolysis with dilute sulfuric acid gave Δ^4-pregnene-11α-ol-3,20-dione-17α,21-oxide (IVa). Similar base-catalyzed cyclizations were performed on the 21-tosylates of the bis-ethylene ketals of Reichstein's substance S, cortisone and hydrocortisone. The cyclization also could be effected with lithium aluminum hydride as exemplified with the hydrocortisone derivative. Acid hydrolysis of these cyclized products (IIIc,d,e) afforded the desired 17α,21-oxidocompounds (IVb,c), except in the case of the cortisone analog in which only the 3-ketal group was removed, and the 20-ketal-Δ^4-3-one VIIa was obtained.

In conjunction with other work carried out in this Laboratory to determine the direction of elimination of C11-α and β-hydroxy-compounds,[3] Δ^5-pregnene-11α,17α,21-triol-3,20-dione 11α,21-di-(*p*-toluenesulfonate) 3,20-bis-ethylene ketal (IIa) was prepared in the usual fashion by tosylation of the bis-ethylene ketal Ia[4] of 11-*epi*-hydrocortisone. This compound proved to be difficult to prepare in a pure state[5]; its elemental analyses invariably were not completely satisfactory. Moreover the infrared absorption spectrum of the best sample obtained showed a weak, unexplained absorption in the carbonyl region at 1742 cm.$^{-1}$ (see Experimental). It was felt, however, that the material was of sufficient purity so that the conclusions drawn from ensuing experimentation were on a firm foundation. The ditosylate IIa was refluxed with 5% alcoholic potassium hydroxide for 4 hours to yield a new compound which contained no tosyl groups. This compound possessed *one* hydroxyl group which underwent facile acetylation.

It seemed that these facts could be accounted for best by the following reactions which are mechanistically sound. Firstly, solvolysis of the 11α-tosyl group proceeded without Walden inversion.[6] The presence of an 11α-hydroxyl group in the product was supported by the ease of acetylation. Secondly, under the basic conditions of the reaction, the derived anion at C-17 displaced the 21-tosyloxy group in the conventional manner[7] to form a 1,3-oxide as shown by the structure IIIa; the product of acetylation may be represented by the structure IIIb. Moreover, the infrared absorption spectrum of the latter showed no free hydroxyl groups. It is evident that, since the carbon–oxygen bond at C-17 was not involved in the reaction, the oxide formed may be designated as a 17α,21-oxide. To demon-

(1) Paper XIV, S. Bernstein and R. H. Lenhard, THIS JOURNAL, **77**, 2233 (1955).

(2) Presented in part before the Organic Discussion Group at the Sixth Annual Meeting-in-miniature of the North Jersey Section, American Chemical Society, Newark, N. J., January 25, 1954.

(3) (a) S. Bernstein, R. Littell and J. H. Williams, THIS JOURNAL, **75**, 4830 (1953); (b) S. Bernstein, R. H. Lenhard and J. H. Williams, *J. Org. Chem.*, **19**, 41 (1954).

(4) (a) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell and J. H. Williams, *ibid.*, **18**, 70 (1953); (b) F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **75**, 1282 (1953); (c) S. Bernstein, R. Littell and J. H. Williams, *ibid.*, **75**, 1481 (1953); (d) W. S. Allen, S. Bernstein and R. Littell, *ibid.*, **76**, 6116 (1954).

(5) A similar experience with a compound containing an 11α-tosyloxy group has been encountered previously in this Laboratory; see reference 3b.

(6) The mother liquors of this reaction were not investigated to determine the extent of the possible $\Delta^{9(11)}$ elimination product (*cf.* reference 3b). It should be noted here that non-inversion at C-11 can be explained by a SN1 mechanism (C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 341) which would be expected to operate in preference to a possible SN2 displacement (*cf.* L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949, p. 642) since in this case the β-face of the C-11 position is sterically hindered. Non-inversion might also be explained by displacement on sulfur (R–O–Ts → R–O–H) as postulated in a number of sugar examples (R. S. Tipson, *Advances in Carbohydrate Chem.*, **8**, 167 (1953)). This suggestion apparently was based on the reductive cleavage of tosyl esters with lithium aluminum hydride which has been observed to give displacement both on carbon and on sulfur depending upon the steric situation [H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 1371 (1949)]. Furthermore, there has been reported recently an interesting transformation, in which displacement on sulfur by base was described [G. Stork, E. E. van Tamelen, L. J. Friedman and A. W. Burgstahler, THIS JOURNAL, **75**, 384 (1953)]. Summarily, however, in the present case under discussion it was not possible *a priori* to establish which mechanism was applicable.

(7) S. Winstein and R. B. Henderson, "Heterocyclic Compounds," Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 9 and 59.

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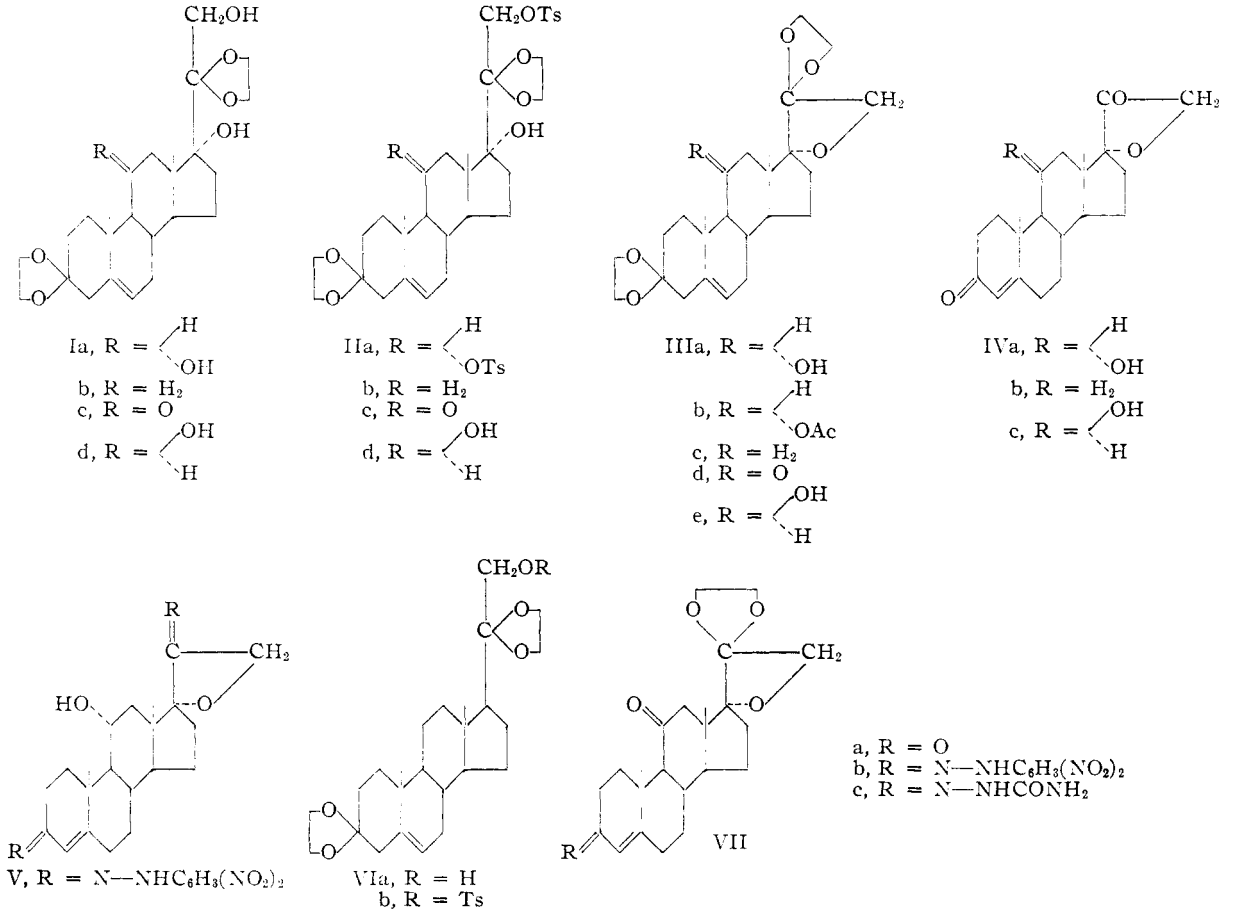


strate the necessity of the anion at C-17, Δ^5-pregnene-21-ol-3,20-dione 21-*p*-toluenesulfonate 3,20-bis-ethylene ketal (VIb) was prepared from the bis-ethylene ketal VIa[1] of desoxycorticosterone, and treated with potassium hydroxide. It was interesting to observe that only starting material was isolated which, incidentally, indicated an unusual stability of the 21-tosyloxy group. Thus, the driving force for the 17,21-oxide reaction was demonstrated convincingly to be involved with the C17-hydroxyl group.

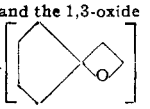
Acid hydrolysis (sulfuric acid–water–methanol) of the bis-ketal-17α,21-oxide IIIa removed the ketal groups and gave a compound best illustrated by the structure IVa, Δ^4-pregnene-11α-ol-3,20-dione-17α,21-oxide. Its infrared absorption spectrum revealed besides the expected hydroxyl and α,β-unsaturated ketone bands (at 3390 and 1682 cm.$^{-1}$, respectively) a strained carbonyl band at 1742 cm.$^{-1}$, and "C–O" stretching bands at 1087, 1075, 1039 and 1019 cm.$^{-1}$. This observation strongly supported the formulation of a 1,3-oxide ring. Parenthetically, the stability of the oxide ring to these acid conditions should be noted. The bis-(2,4-dinitrophenylhydrazone) derivative V was prepared for further characterization of the carbonyl functions.

It has been well established[8] that formation of a four-membered oxide ring (1,3-oxide) did not take place if the groups in the molecule afforded a competitive opportunity to make a smaller (1,2-oxide) or larger (1,4-oxide) ring. It has been recognized, however, that under certain favorable conditions a 1,3-oxide could be prepared easily.[9] In the case under discussion here, the structural features are such that, if ring closure is possible, only a 1,3-oxide would be formed. There would certainly appear to be adequate steric accommodation for the attack on the non-asymmetric terminal C21-carbon atom by the C17-oxygen anion.[10] Also, under the conditions set forth, the displacement reaction would not have to compete with an elimination reaction since there was obviously no β-hydrogen available next to the tosyloxy function.

To further substantiate the generality of these reactions, the bis-ethylene ketal Ib[11] of Reichstein's substance S was tosylated to form IIb which was cy-

(8) S. Peat, *Advances Carbohydrate Chem.*, **2**, 44 (1946).

(9) R. B. Clayton and H. B. Henbest, *Chemistry and Industry*, 1315 (1953).

(10) It is interesting to note that the D steroid ring and the 1,3-oxide ring form the rare 1-oxaspiro [3,4] octane ring system  of which only one previous example could be found in the literature, and that as the β-lactone [N. J. Toivonen, *Ann. acad. sci. Fennicae*, **A28**; *C. A.*, **23**, 1624[2] (1929)]. It may be further noted that the 1,3-oxide system (oxetane) with a carbonyl function on the β-carbon atom is also quite rare.

(11) R. Antonucci, S. Bernstein and R. H. Lenhard, THIS JOURNAL, **76**, 2956 (1954).

clized in the described manner to give the 17α,21-oxide IIIc. Acid hydrolysis yielded Δ⁴-pregnene-3,20-dione-17α,21-oxide (IVb), again with a strained carbonyl band at 1752 cm.$^{-1}$ and "C–O" stretching bands at 1088, 1072, 1022 and 1002 cm.$^{-1}$ in its infrared absorption spectrum.

The same series of reactions were conducted on cortisone, starting from its 3,20-bis-ethylene ketal Ic.[4a,d] Tosylation gave IIc which on cyclization under basic conditions furnished the 17α,21-oxide IIId. Hydrolysis under acidic conditions (sulfuric or acetic acid) removed only the 3-ethylene ketal group to yield Δ⁴-pregnene-3,11,20-trione-17α,21-oxide 20-ethylene ketal (VIIa). This result called to mind the stability to acetic acid[4a] of the 20-ethylene ketal group in the bis-ethylene ketal Ic of cortisone. The 20-ethylene ketal VIIa was defined further by the preparation of its 2,4-dinitrophenylhydrazone VIIb, and semicarbazone VIIc at C-3.

Finally, the hydrocortisone analog was prepared similarly. The 21-tosylate derivative IId of the bis-ethylene ketal Id[4a,d] of hydrocortisone on treatment with base afforded the 17α,21-oxido-alcohol IIIe. In further amplification of the general nature of the cyclization, it was found that the oxido-alcohol IIIe also was formed by treatment of the tosylate IId with lithium aluminum hydride.[12] *This experiment implies the stability of the substituted 1,3-oxide ring to lithium aluminum hydride.* This fact was substantiated further by reaction of the cortisone analog of the oxide IIId with lithium aluminum hydride to form the 11β-hydroxy-bis-ketal oxide IIIe. An attempted further reaction of IIIe with lithium aluminum hydride resulted in only recovered starting material. The stability of a substituted 1,3-oxide to lithium aluminum hydride has been noticed recently by others.[13] Treatment of IIIe with acetic anhydride–pyridine gave only starting material showing that the 11β-hydroxyl group was retained intact. It is, perhaps, well to mention here that reaction of the 11-keto-oxide-bis-ketal IIId with lithium in ammonia and alcohol yielded the 11α-hydroxy-oxide-bisketal (IIIa) as would be expected from previous publications.[4c,14]

The usual acidic hydrolysis of the bis-ethylene ketal-oxide IIIe furnished the desired Δ⁴-pregnene-11β-ol-3,20-dione-17α,21-oxide (IVc) which again had the characteristic strained carbonyl band at 1750 cm.$^{-1}$ and "C–O" stretching bands at 1079, 1070, 1041 and 1028 cm.$^{-1}$ in its infrared absorption spectrum.

Bioassay.[15]—A thymus involution assay (adrenalectomized and ovariectomized mice) of Δ⁴-pregnene-11β-ol-3,20-dione-17α,21-oxide (IVc) indicated no activity.

Infrared absorption data have been reported in the Experimental. Besides the usual hydroxyl, carbonyl and aromatic or double bond bands, we have indicated one of the principal "C–O" stretching bands of the ketal function at approximately 1100 cm.$^{-1}$, two "O-tosyl" bands consistently at 1330–1360 cm.$^{-1}$ and 1168–1171 cm.$^{-1}$, and several bands between 1000–1100 cm.$^{-1}$ which may be assigned to the 17α,21-oxide.

Acknowledgment.—We wish to thank Messrs. Louis M. Brancone, Samuel S. Modes, Arthur A. Bodden, Gerald P. McTernan, Kenneth Angyal, John Heider and Miss Phyllis McDowell for the microanalyses, and Mr. William Fulmor, Miss Joan Huffman and Miss Anne Callaghan for the infrared absorption spectra.

Experimental

Melting Points.—All melting points are uncorrected, and were determined with uncalibrated Anschütz thermometers.

Optical Rotations.—The sample was dissolved in chloroform to make a 2-ml. solution, and the rotation was determined in a 1-dm. semi-micro tube at wave length 5893 Å. (D).

Absorption Spectra.—The ultraviolet absorption spectra were determined in absolute alcohol (unless otherwise specified) with a Beckman spectrophotometer (model DU). The infrared absorption spectra (Nujol mulls) were determined with a Perkin–Elmer spectrophotometer (model 21).

Petroleum Ether.—The fraction used had a b.p. 60–70° (Skellysolve B).

All evaporations were carried out under reduced pressure.

Δ⁵-Pregnene-11α,17α,21-triol-3,20-dione 11α,21-Di-(*p*-toluenesulfonate) 3,20-Bis-ethylene Ketal (IIa).—A solution of 0.5 g. of 11-*epi*-hydrocortisone bis-ketal (Ia) in 20 ml. of pyridine cooled to 0° was mixed with 0.5 g. of *p*-toluenesulfonyl chloride, and was allowed to stand for 18 hours at room temperature. Addition of ice-water, extraction with benzene, and evaporation of the solvent gave an oil which was crystallized from ether to yield 0.58 g. (69%), m.p. 130–131° dec. Recrystallization of a small portion from ether afforded IIa, m.p. 138–140° dec.; λ_{max}^{ether} 261 mμ (ε 1,100); ν_{max} 3500, 1742, 1595, 1332, 1168, 1090 and 815 cm.$^{-1}$; $[\alpha]^{25}D$ −31° (11.1 mg., αD −0.17°), [M]D −228.

Anal. Calcd. for $C_{39}H_{50}O_{11}S_2$ (758.79): C, 61.72; H, 6.64; S, 8.43. Found: C, 61.95; H, 7.38; S, 9.16.

Δ⁵-Pregnene-11α-ol-3,20-dione-17α,21-oxide 3,20-Bis-ethylene Ketal (IIIa). A.—A solution of 100 mg. of IIa in 10 ml. of 5% ethanolic potassium hydroxide was refluxed for 4 hours. Water was added to the cooled solution, and the mixture was extracted with chloroform. The extract was dried and evaporated. Three crystallizations from acetone–petroleum ether gave 27 mg. (48%) of IIIa, m.p. 213–214°; ν_{max} 3440, 1090 and 1050 cm.$^{-1}$; $[\alpha]^{25}D$ −33° (9.8 mg., αD −0.16°), [M]D −141.

Anal. Calcd. for $C_{25}H_{36}O_6$ (432.54): C, 69.42; H, 8.39. Found: C, 69.41; H, 8.55.

In another run 630 mg. (69%) of IIIa, m.p. 212–214°, was obtained from 1.6 g. of IIa.

B.—To a solution of 150 mg. of the 11-one-oxide bis-ketal IIId in 5 ml. of dioxane, 2 ml. of absolute ethanol and 100 ml. of liquid ammonia was added 0.3 g. of lithium in small pieces over an hour with stirring. The ammonia was allowed to evaporate at room temperature, cold water was added, and the resultant solid filtered and washed well with water to yield 137 mg. (91%), m.p. 212–214°. Two crystallizations from acetone–petroleum ether gave 90 mg. of IIIa, m.p. 217.5–219.5°. Its infrared absorption spectrum was identical to that of the sample above.

Anal. Found: C, 69.17; H, 8.59.

Δ⁵-Pregnene-11α-ol-3,20-dione-17α,21-oxide 11-Acetate 3,20-Bis-ethylene Ketal (IIIb).—To a solution of 150 mg. of the 11-ol-oxide bis-ketal IIIa in 5 ml. of pyridine was added 2.5 ml. of acetic anhydride and the mixture allowed to stand at room temperature for 40 hours. The solvents were removed at room temperature to give a white powder, m.p. 203–205°. Two crystallizations from acetone–petroleum ether resulted in 86 mg. of IIIb, m.p. 203–205°; ν_{max} 1721, 1105 and 1025 cm.$^{-1}$; $[\alpha]^{25}D$ −37° (15.0 mg., αD −0.28°), [M]D −177.

(12) H. L. Goering and C. Serres, Jr., THIS JOURNAL, **74**, 5908 (1952), also prepared an oxide in this manner.

(13) G. Büchi, C. G. Inmen and E. S. Lipinsky, *ibid.*, **76**, 4327 (1954).

(14) F. Sondheimer, R. Yashin, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 2696 (1952).

(15) This bioassay was carried out under the direction of Dr. Ralph I. Dorfman at the Worcester Foundation for Experimental Biology, Shrewsbury, Mass. It is a pleasure to acknowledge this collaboration on the biological aspect of the work.

Anal. Calcd. for $C_{27}H_{38}O_7$ (474.57): C, 68.33; H, 8.07. Found: C, 68.56; H, 8.25.

Δ^4-Pregnene-11α-ol-3,20-dione-17α,21-oxide (IVa).—A solution of 250 mg. of IIIa in methanol (20 ml.) and 8.5% (v./v.) sulfuric acid (2.5 ml.) was refluxed for 1.25 hours, cooled, and sodium bicarbonate was added until the mixture was basic. The filtered solution was concentrated, extracted with ethyl acetate, and the extract was washed with water, dried and evaporated. Four crystallizations from acetone–petroleum ether gave 77 mg. (39%) of IVa, m.p. 175–177°, λ_{max} 239–240 mμ (ϵ 14,600); ν_{max} 3390, 1742, 1882, 1600, 1087, 1075, 1039 and 1019 cm.$^{-1}$; $[\alpha]^{25}D$ +13° (13.8 mg., αD +0.09°), [M]D +45.

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.44): C, 73.22; H, 8.19. Found: C, 73.38; H, 8.22.

A single attempted preparation of Δ^4-pregnene-11α-ol-3,20-dione-17α,21-oxide 11-*p*-toluenesulfonate exactly as conducted for IIa (isolated with benzene) yielded only the starting material IVa. The preparation was not investigated further.

Δ^4-Pregnene-11α-ol-3,20-dione-17α,21-oxide 3,20-Bis-(2,4-dinitrophenylhydrazone) (V).—This compound was prepared by the method of Djerassi.[16] The dione IVa (100 mg.) was dissolved in warm glacial acetic acid (5 ml.) and 2,4-dinitrophenylhydrazine (127 mg.) was added. After heating on the steam-bath for 5 minutes, the solution was cooled, filtered and washed with methanol to yield 62 mg. of an orange-red powder, m.p. 239–241° dec. From the mother liquor an additional 40 mg. was collected. The two fractions were combined and crystallized twice from chloroform–methanol to furnish 27 mg. of Va, m.p. 248–249° dec.; $\lambda_{max}^{chloroform}$ 257–260° (ϵ 30,000) and 372–376 mμ (ϵ 48,500); ν_{max} 3510, 3300, 1622 and 1590 cm.$^{-1}$.

Anal. Calcd. for $C_{33}H_{36}O_{10}N_8$ (704.68): C, 56.24; H, 5.14; N, 15.90. Found: C, 55.96; H, 5.31; N, 15.74.

Δ^5-Pregnene-17α,21-diol-3,20-dione 21-*p*-Toluenesulfonate 3,20-Bisethylene ketal (IIb).—A solution of 0.5 g. of substance S bis-ketal Ib in 6 ml. of pyridine at −5° was treated with 270 mg. of *p*-toluenesulfonyl chloride, and kept at −5° for 24 hours. Water was added to the solution, and the resultant mixture was filtered. Recrystallization of the residue from acetone–petroleum ether afforded 500 mg., m.p. 143–145° dec. A small portion (120 mg.) was crystallized three times from the same solvent pair to yield 48 mg. of IIb, m.p. 171.5–172° dec.; ν_{max} 3510, 1360, 1168, 1103 and 817 cm.$^{-1}$; $[\alpha]^{23}D$ −28° (14.9 mg., αD −0.21°), [M]D −166.

Anal. Calcd. for $C_{32}H_{44}O_5S$ (588.67): C, 65.29; H, 7.53; S, 5.44. Found: C, 65.61; H, 7.63; S, 5.64.

Δ^5-Pregnene-3,20-dione-17α,21-oxide 3,20-Bis-ethylene Ketal (IIIc).—A solution of the 21-tosylate IIb (265 mg.) in 25 ml. of 5% ethanolic potassium hydroxide was refluxed for 4 hours, cooled and water was added. The mixture was filtered to give 170 mg. (90%), m.p. *ca.* 214°. Two crystallizations from acetone–petroleum ether yielded 110 mg. of IIIc, m.p. 212–214°; ν_{max} 1092 and 1050 cm.$^{-1}$; $[\alpha]^{23}D$ −40° (16.0 mg., αD −0.32°), [M]D −166.

Anal. Calcd. for $C_{25}H_{36}O_5$ (416.54): C, 72.08; H, 8.71. Found: C, 71.90; H, 8.84.

Δ^4-Pregnene-3,20-dione-17α,21-oxide (IVb).—The oxide bis-ketal IIIc (0.70 g.) was refluxed in a mixture of methanol (55 ml.) and 8.5% (v./v.) sulfuric acid (7 ml.) for 1.25 hours, cooled, and was neutralized with sodium bicarbonate. The mixture was filtered, and concentrated to a small volume, cooled and water was added. This gave 450 mg. (81%) of a white powder, m.p. 221–225°. Recrystallization from acetone–petroleum ether furnished 360 mg. of IVb, m.p. 224–226°, λ_{max} 238–239 mμ (ϵ 15,700); ν_{max} 1752, 1668, 1618, 1088, 1072, 1022 and 1002 cm.$^{-1}$; $[\alpha]^{21}D$ +92° (21.1 mg., αD +0.97°), [M]D +302.

Anal. Calcd. for $C_{21}H_{28}O_3$ (328.44): C, 76.79; H, 8.59. Found: C, 76.60; H, 8.82.

Δ^5-Pregnene-17α,21-diol-3,11,20-trione 21-*p*-Toluenesulfonate 3,20-Bis-ethylene Ketal (IIc).—A solution of 0.5 g. of cortisone bis-ketal Ic in 7 ml. of cold pyridine was treated with 0.25 g. of *p*-toluenesulfonyl chloride exactly as in the preparation of IIb. After three crystallizations from acetone–petroleum ether, 0.26 g. of IIc was obtained, m.p. 175–178°; λ_{max} 225 mμ (ϵ 11,500) and 262 mμ (ϵ 660); ν_{max} 3500, 1697, 1595, 1350, 1171, 1104 and 810 cm.$^{-1}$; $[\alpha]^{25}D$ +10° (10 mg., αD +0.05°), [M]D +60.

Anal. Calcd. for $C_{32}H_{42}O_9S$ (602.72); C, 63.77; H, 7.02; S, 5.31. Found: C, 63.93; H, 7.02; S, 5.26.

Δ^5-Pregnene-3,11,20-trione-17α,21-oxide 3,20-Bis-ethylene Ketal (IIId).—A mixture of the tosylate IIc (180 mg.) and 5% ethanolic potassium hydroxide (10 ml.) was heated and worked up as in the fashion described for IIIc to give 123 mg. (95%), m.p. 192–195°. Three crystallizations from acetone–petroleum ether furnished 65 mg. of IIId, m.p. 184.5–187.5°; ν_{max} 1694, 1095 and 1054 cm.$^{-1}$; $[\alpha]^{25}D$ ±0° (11 mg., αD ±0°), [M]D ±0.

Anal. Calcd. for $C_{25}H_{34}O_6$ (430.52): C, 69.74; H, 7.96. Found: C, 69.48; H, 8.06.

Δ^5-Pregnene-11β,17α,21-triol-3,20-dione 21-*p*-Toluenesulfonate 3,20-Bis-ethylene Ketal (IId).—A solution of 0.62 g. of hydrocortisone bis-ketal (Id) was dissolved in 12 ml. of cold pyridine and treated with 0.4 g. of *p*-toluenesulfonyl chloride as in the synthesis of IIb. Recrystallization of the resultant solid from acetone–methanol yielded 0.65 g. (78.5%) of IId, m.p. 121–123°; λ_{max} 225 mμ (ϵ 10,700) and 262 mμ (ϵ 415); ν_{max} 3510, 1607, 1350, 1172, 1102 and 814 cm.$^{-1}$.

Anal. Calcd. for $C_{32}H_{44}O_9S$ (604.67): C, 63.72; H, 7.34; S, 5.29. Found: C, 63.04; H, 7.52; S, 5.05.

Further crystallization of IId from the same solvent pair eventually led to decomposition and finally an oil.

Δ^5-Pregnene-11β-ol-3,20-dione-17α,21-oxide 3,20-Bis-ethylene Ketal (IIIe). A.—Reaction of 0.23 g. of the tosylate bis-ketal IId and 25 ml. of 5% ethanolic potassium hydroxide in the manner described previously for the preparation of IIIc furnished 0.15 g. (91%), m.p. 241–243°. After three crystallizations from methanol 0.026 g. of IIIe, m.p. 252–255°, was obtained; ν_{max} 3500, 1102 and 1055 cm.$^{-1}$; $[\alpha]^{24}D$ ±0° (7 mg., αD −0.02°), [M]D ±0.

Anal. Calcd. for $C_{25}H_{36}O_6$ (432.54): C, 69.42; H, 8.39. Found: C, 69.28; H, 8.43.

B.—To a solution of the tosylate bis-ketal IId (0.25 g.) in tetrahydrofuran (10 ml.) and absolute ether (12 ml.) was added lithium aluminum hydride (0.5 g.) and the mixture was refluxed for 3 hours. The mixture was cooled and water was added cautiously. Chloroform then was added and the entire mixture was filtered. The residue was slurried with hot chloroform, and the combined chloroform extracts washed with saturated sodium chloride and water. The dried extract was evaporated and the residual powder was crystallized twice from acetone to give 0.055 g. of IIIe, m.p. 253–256°. There was no depression of mixed melting point with the sample prepared above, and the infrared absorption spectra of the samples were identical in all respects.

C.—To a solution of 0.15 g. of the 11-one-oxide bis-ketal IIId in 30 ml. of anhydrous ether was added dropwise 4 ml. of a solution of lithium aluminum hydride in ether (0.74 mole). The mixture was refluxed one hour, cooled and the excess lithium aluminum hydride was discharged cautiously with water. The organic layer was separated and combined with two further extractions with ether of the aqueous layer, and the combined extract was dried and evaporated. Recrystallization of the solid residue from acetone–petroleum ether afforded 0.09 g. (60%) of IIIe, m.p. 252–255°. Its infrared absorption spectrum was identical with those of preparations A and B.

An attempted acetylation of the 11β-ol-oxide bis-ketal IIIe in the usual fashion (room temperature, acetic anhydrine–pyridine) gave only unchanged starting material.

Δ^4-Pregnene-11β-ol-3,20-dione-17α,21-oxide (IVc).—The bis-ethylene ketal IIIe (75 mg.) dissolved in methanol (20 ml.) was treated with 8.5% (v./v.) sulfuric acid (0.8 ml.) and worked up in the manner described for IVa. The desired product was extracted with chloroform. Two crystallizations from acetone–petroleum ether yielded 29 mg. (49%) of IVc, m.p. 198.5–201°, λ_{max} 240 mμ (ϵ 16,000); ν_{max} 3590, 3410, 1750, 1660, 1622, 1079, 1070, 1041 and 1028 cm.$^{-1}$; $[\alpha]^{24}D$ +69° (3.2 mg., αD +0.11°), [M]D +238.

Anal. Calcd. for $C_{21}H_{28}O_4$ (344.44): C, 73.22; H, 8.19. Found: C, 73.39; H, 8.40.

Δ^5-Pregnene-21-ol-3,20-dione 21-*p*-Toluenesulfonate 3,20-Bis-ethylene Ketal (VIb).—A solution of 0.5 g. of desoxycorticosterone bis-ketal (VIa) in 7 ml. of cold pyridine was treated with 0.27 g. of *p*-toluenesulfonyl chloride as de-

(16) C. Djerassi, THIS JOURNAL, **71**, 1003 (1949).

scribed for the preparation of IIb. Crystals (0.68 g.), m.p. 140–145°, were collected and crystallized five times from acetone–petroleum ether to furnish 0.33 g. (48%), m.p. 169–171°. A portion (0.2 g.) was further crystallized twice from methanol to yield 0.15 g. of VIb, m.p. 184.5–187°; λ_{max} 225.5 mμ (ε 11,600) and 262 mμ (ε 570); ν_{max} 1595, 1340, 1170, 1094 and 815 cm.$^{-1}$; $[\alpha]^{25}D$ −12° (17 mg., αD −0.10°), [M]D −69.

Anal. Calcd. for $C_{32}H_{44}O_7S$ (572.67): C, 67.11; H, 7.74; S, 5.58. Found: C, 67.36; H, 7.80; S, 5.86.

Treatment of VIb with 5% alcoholic potassium hydroxide as in the preparation of IIIc yielded only material with m.p. 184–187°. Its infrared absorption spectrum was identical to that of the starting material VIb.

Δ^4-Pregnene-3,11,20-trione-17α,21-oxide 20-Ethylene Ketal (VIIa). A.—A solution of the 11-one-oxide-bis-ethylene ketal IIId (0.15 g.) in methanol (20 ml.) was treated with 8.5% (v./v.) sulfuric acid (1.5 ml.) in the fashion described for IVb. Solid (0.103 g., 77%) was collected, m.p. 248–251°. Two crystallizations from acetone–petroleum ether afforded 0.095 g. of VIIa, m.p. 247–250°, λ_{max} 238 mμ (ε 16,600); ν_{max} 1709, 1680, 1621, 1055 and 1022 cm.$^{-1}$; $[\alpha]^{24}D$ +198° (9.9 mg., αD +0.98°), [M]D +765.

Anal. Calcd. for $C_{23}H_{30}O_5$ (386.47): C, 71.48; H, 7.82. Found: C, 71.75; H, 7.90.

B.—A solution of 0.1 g. of IIId in 4 ml. of 75% acetic acid was heated 20 minutes on a steam-bath, cooled and added slowly to a saturated solution of sodium bicarbonate. Water was added, and the solid was filtered and washed well with water. Four crystallizations from acetone–petroleum ether gave 0.055 g. of VIIa, m.p. 247–250°. There was no depression of mixed melting point with the sample above, and the infrared absorption spectra were identical.

Δ^4-Pregnene-3,11,20-trione-17α,21-oxide 3-(2,4-Dinitrophenylhydrazone) 20-Ethylene Ketal (VIIb).—A solution of 75 mg. of the 20-ketal VIIa in 6 ml. of acetic acid was treated with 100 mg. of 2,4-dinitrophenylhydrazine, and was heated for 10 minutes on the steam-bath. The mixture was cooled, and crystallization was induced by scratching. The solid was collected and was washed with cold methanol to give 63 mg., m.p. 290–291°. This material was adsorbed on an alumina column with benzene–petroleum ether (1:1), and was eluted with benzene. Recrystallization with chloroform–methanol furnished 39 mg. of VIIb, m.p. 293–294°; $\lambda_{max}^{1\%\ CHCl_3\ in\ abs.\ EtOH}$ 256–257 mμ (ε 19,200) and 384–386 mμ (ε 31,400); ν_{max} 3330, 1707, 1625, 1595, 1116 and 1056 cm.$^{-1}$.

Anal. Calcd. for $C_{29}H_{36}O_8N_4$ (568.61): N, 9.85. Found: N, 9.23.

Δ^4-Pregnene-3,11,20-trione-17α,21-oxide 3-Semicarbazone 20-Ethylene Ketal (VIIc).—To a solution of 50 mg. of the 20-ketal VIIa in 10 ml. of warm methanol, water was added to the point of turbidity. Semicarbazide hydrochloride (40 mg.) and sodium acetate (60 mg.) were added and the mixture was heated on the steam-bath for one-half hour. The mixture was cooled and filtered to afford 37 mg. of crystals, m.p. 159–160°. Crystallization from dilute methanol and from acetone–chloroform–petroleum ether yielded 10 mg. of VIIc, m.p. 269–271°.

Anal. Calcd. for $C_{24}H_{33}O_5N_3$ (443.53): N, 9.47. Found: N, 9.52.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

The Synthesis of Some Steroidal Amines

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A variety of new steroidal 21-tertiary aminoalcohols and aminoketones have been prepared for biological experiments. The method of incorporating the nitrogen function involved the reaction of a haloketone or haloalcohol with an amine. The steroidal ring systems included the 5-pregnene, 5,16-pregnadiene and allopregnane-17-α-ol. In addition, a 21-amino derivative of desoxycorticosterone has been prepared.

The partial synthesis of steroidal alkaloids from non-nitrogenous naturally occurring steroids has been reported in several cases.[3,4] Some related steroidal amines[5,6,a,b] have been synthesized for testing as hypotensive agents, and a number of mono- and diamino derivatives of cholesterol and cholestanol have been reported to exhibit high antibacterial activity.[7–9] The amebacidal activity of conessine[10] has prompted the synthesis of amino derivatives of androstane,[11] allopregnane[9,12] and trihydroxynorcholane.[11]

It was considered of interest to make available certain 21-aminosteroids for biological testing. A simple displacement type reaction appeared to be most suitable for the initial introduction of the nitrogen function.

$$R'COCH_2X + R_2NH \longrightarrow R'COCH_2NR_2 + HX$$
$$+ R_3N \longrightarrow R'COCH_2N^+R_3$$

The two iodoketones, 21-iodo-5-pregnene-3β-ol-20-one acetate (Ia)[13] and 21-iodo-5,16-pregnadiene-3β-ol-20-one acetate (IIa),[14] were used for the preparation of the majority of the amino compounds. With dimethylamine these afforded 3β-acetoxy-21-dimethylamino-5-pregnene-20-one (Ib) and the corresponding 5,16-pregnadiene compound (IIb).[15] Similarly, the new quaternary salts (Ic, IIc) were obtained directly from gaseous trimethylamine or indirectly *via* the corresponding amine hydrochlorides. Reaction of morpholine with the two iodoketones (Ia, IIa) to give the 21-morpholino series (Ie, IId) was also quite successful. Hydrogenation of the pregnadiene amines to the pregnene analogs interrelated the two series.

During the synthesis of the methiodides (Ic, IIc,

(1) Taken in part from the thesis submitted by Robert A. Micheli in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Duke University, 1954.

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(15) The iodoketone Ia afforded a nice crystalline phthalimido derivative Id. Attempts to convert Id to the free base were unsuccessful.