17aβ-diol-11-one.[1] The ether-soluble material (resinous) was chromatographed on 300 g. of acid-washed alumina. The fractions eluted with 40% ether–benzene through pure ether and 20% acetone–ether were combined. The material eluted with 50% acetone–ether and pure acetone gave an additional 1.8 g. of D-homoetiocholane-3α,17aβ-diol-11-one (total, 10.2 g., equivalent to a 63.7% yield of *reduction* product).

The combined earlier eluates noted above were acetylated as usual and rechromatographed on 420 g. of silica gel. The material eluted with 25–30% ether–*n*-pentane weighed 4.6 g. (23.6% yield) and had m.p. 201–209°. Recrystallization from ethyl acetate gave pure V, m.p. and mixed m.p. 210–211°. The infrared spectrum was identical with that of V. No evidence of material corresponding to VI was found in the higher eluates[27] during the chromatogram; apparently a single epimer was formed.

Dehydration Under Basic Conditions. A. Experiments with V and VI.—To a solution of 2.50 g. (0.0064 mole) of pure V in 15.0 ml. of C.P. pyridine was added 1.53 g. (0.01 mole) of C.P. phosphorus oxychloride. The solution was allowed to stand at room temperature (23–25°) for 4 days and then quenched in 500 ml. of water. The insoluble material was extracted into methylene dichloride in the usual manner and the extracts were evaporated in a tared flask. There was recovered 2.49 g. of V, m.p. 206–209°, mixed m.p. 208–210°.

From VI (2.13 g., 0.00547 mole) treated simultaneously with V under identical conditions was obtained 2.08 g. of a colorless resin (theoretical for the dehydration product 2.04 g.). The material was treated with an excess of ozone in dry acetone as outlined above. From the Raney nickel-treated ozonide was obtained 1.90 g. of crystalline product, m.p. 123–145°. Chromatography of the latter material on 200 g. of silica gel gave 1.39 g. (70.6% minimum over-all yield from VI) of pure D-homoetiocholan-3α-ol-11,17a-dione 3-acetate, m.p. and mixed m.p. 171–172°, infrared spectra identical.

B. Experiments with I and II.—To a solution of 2.00 g. of I in 15.0 ml. of dry pyridine was added 1.53 g. of C.P. phosphorus oxychloride, and the solution was allowed to stand at room temperature (23–24°) for 6 days. On working up in the above manner there was obtained 1.96 g. of recovered I, m.p. and mixed m.p. 188–190°

Treatment of 2.00 g. of II under conditions identical with those used for I above gave, on processing the same way, 2.07 g. of a red-colored resin. This material was chromatographed on 200 g. of silica gel. Two definite series of fractions were obtained on elution with 15% and with 30% ether–*n*-pentane. The first series of fractions (0.71 g. of resin) could not be obtained crystalline either by re-chromatography or by saponification and rechromatography. The material showed only end-absorption in the ultraviolet; the infrared spectrum indicated acetate (5.76, 8.05 μ) and ketone (5.84 μ), but the *absence* of ethinyl or hydroxyl groups. The second series of fractions eluted above (with 30% ether–*n*-pentane) gave 0.61 g. of recovered II on recrystallization from Skellysolve C.

RENSSELAER, NEW YORK

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

D-Homosteroids. III. The Synthesis of D-Homocortisone Acetate and Related Compounds[1]

BY R. O. CLINTON, H. C. NEUMANN, A. J. MANSON, S. C. LASKOWSKI AND R. G. CHRISTIANSEN

RECEIVED JANUARY 9, 1958

17aβ-Ethinyl-D-homoetiocholane-3α,17aα-diol-11-one has been converted to D-homopregnane-3α,17aα-diol-11,20-dione. The latter compound was subjected to the steps of 21-acetoxylation, oxidation to the 3-ketone and dehydrogenation at the 4-position to form D-homopregn-4-ene-17aα,21-diol-3,11,20-trione 21-acetate (D-homocortisone acetate). A similar procedure utilizing 17aα-ethinyl-D-homoetiocholane-3α,17aβ-diol-11-one gave the stereoisomeric D-homo-17a-isopregn-4-ene-17aβ,21-diol-3,11,20-trione 21-acetate. In addition to the outlined transformations, a number of other synthetic pathways also were examined.

The availability[1] of 17aβ-ethinyl-D-homoetiocholane-3α, 17aα-diol-11-one and its 17a-epimer afforded an opportunity to prepare both D-homopregn-4-ene-17aα,21-diol-3,11,20-trione 21-acetate (D-homocrotisone acetate) and the corresponding D-homo-17a-isopregnene isomer, and thus to shed further light upon the structural requirements for endocrinological activity of the corticoid type.

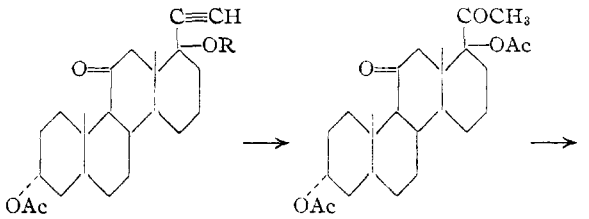
Several methods for the construction or elaboration of the dihydroxyacetone side chain were explored. The first, and most successful, approach involved the transformations shown by I–IX. A number of alternate methods to accomplish the hydration of the ethinyl side chain in Ia and Ib appeared feasible, although all of the previous synthetic work in the steroid series had been carried out on the 17α-ethinyl side chain because of the unavailability of the 17β-ethinyl epimer. Salamon and Reichstein[2] added the elements of hypobromous acid to the 17α-ethinyl side chain in steroids to form the corresponding 21,21-dibromo-20-one in high yield; the latter was then converted easily to the 17α-acetyl side chain by reductive removal of the bromine with zinc and acetic acid. When this procedure was applied to the 3,17a-diacetates IIa and IIb the 17aβ-ethinyl isomer IIa was recovered unchanged even after prolonged treatment with hypobromous acid. On the other hand, the 17aα-ethinyl isomer IIb gave a good yield of the 21,21-dibromo-20-one X. The latter compound was readily transformed to D-homo-17a-isopregnane-3α,17aβ-diol-11,20-dione 3,17a-diacetate (IIIb) by treatment with zinc dust in acetic acid. The lack of reaction with IIa can be ascribed to the large amount of steric hindrance toward approach of the positive bromine atom provided by the groups contiguous to the 17aβ-ethinyl group. These steric effects are readily apparent from models; the experiment thus adds further confirmatory evidence to the configurations already assigned[1] to the 17a-ethinyl epimers.

Stavely[3] converted a 17α-ethinyl-17β-hydroxysteroid to the corresponding 17α-acetyl-17β-hydroxy-steroid in good yield by heating the former with a mixture of aniline, water, mercuric chloride and benzene. When the Stavely procedure was applied to either Ia or IIa no reaction took place,

(1) Paper II, THIS JOURNAL, **80**, 3389 (1958).

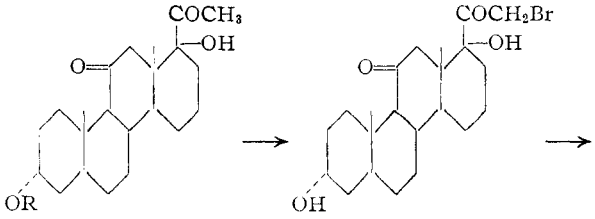
(2) I. Salamon and T. Reichstein, *Helv. Chim. Acta*, **30**, 1616 (1947).

(3) H. E. Stavely, THIS JOURNAL, **62**, 489 (1940); C. W. Shoppee and D. A. Prins, *Helv. Chim. Acta*, **26**, 201 (1943); R. B. Turner, THIS JOURNAL, **75**, 3484 (1953).



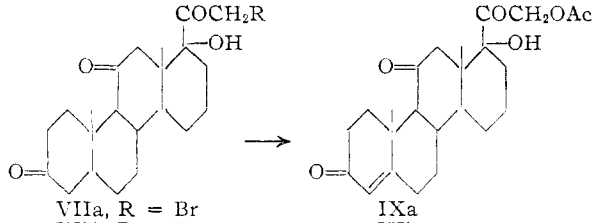
Ia, R = H
Ib, R = H
IIa, R = Ac
IIb, R = Ac

IIIa
IIIb



IVa, R = Ac
IVb, R = Ac
Va, R = H
Vb, R = H

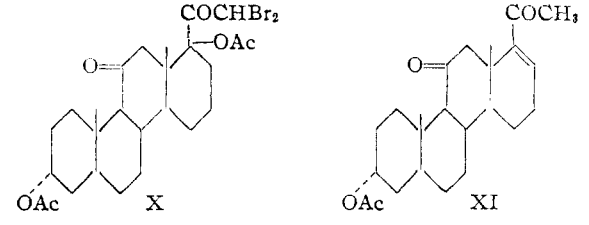
VIa
VIb



VIIa, R = Br
VIIb, R = Br
VIIIa, R = OAc
VIIIb, R = OAc

IXa
IXb

"a" series: 17aα-hydroxy
"b" series: 17aβ-hydroxy



X

XI

and the starting materials were recovered quantitatively. With Ib, on the other hand, the reaction proceeded under these conditions to give a rather complex mixture of products, in contrast to the rather smooth reaction with a 17α-ethinyl-17β-hydroxy-steroid. The major isolated product, in addition to recovered Ib, was shown to be D-homopregn-17(17a)-en-3α-ol-11,20-dione 3-acetate (XI). It seemed likely that the hydration–dehydration product XI was formed by a pathway differing from the normal mechanism involving the intermediate IVb, since it was shown that IVb was stable under the conditions of the Stavely hydration procedure. The mechanism may be similar to that suggested by Newman[4] for a related case, involving protonation of the 21-carbon followed by a 1,2-shift of the 17a-hydroxy group to the 20-carbon and subsequent loss of a proton.

In contrast to the results with Ib, the corresponding 17a-acetate IIb when treated by the Stavely hydration procedure[5] gave 90% yields of pure IVb *via* the intermediate 17a-acetate IIIb.

Successful hydration of the 17aβ-ethinyl compound was achieved by treatment of Ia with boron trifluoride and mercuric acetate[6] in aqueous acetic acid (65–70% yields of the D-homopregnane IVa after saponification and reacetylation) or better, by utilizing the 3,17a-diacetate IIa and conducting the reaction in a solvent mixture of acetic acid and acetic anhydride (75% yields of IVa).

17aα - Ethinyl - D - homoethiocholane - 3α, 17aβ-diol-11-one 3-acetate (Ib) when treated with boron trifluoride and mercuric acetate in acetic acid solution, gave no material corresponding to IVb. The diacetate IIb under similar conditions yielded a small amount of IVb, the major products appearing to be resins of lower oxygen content as judged by their elution sequence from a silica gel column.

Newman[4] found that treatment of an α-hydroxyethinyl compound with Dowex 50 resin gave a high yield of the corresponding α,β-unsaturated ketone, whereas the use of a mercurated Dowex 50 resin produced the α-hydroxyketone in equally good yield. In the present work both Ia and IIa were found to be inert toward treatment with either Dowex 50 or mercurated Dowex 50. On the other hand, while both Ib and IIb were essentially unchanged by treatment with Dowex 50, the mercurated Dowex 50 did produce a reaction with these compounds. With the former compound there was obtained a complex mixture of products, from among which XI was isolated in minor amounts. Treatment of IIb with mercurated Dowex 50 gave a smooth conversion to IIIb in 87% yield.

Since XI offered an alternative approach to the synthesis of the dihydroxyacetone side chain *via* the 17,17a-epoxide,[7] considerable additional effort was made to prepare this compound in good yield, especially from the 17aα-ethinyl-17aβ-hydroxy series. Treatment of Ib with boron trifluoride and mercuric acetate in ethylene glycol–acetic acid solution gave improved, but still low, yields of XI. In contrast to the results of Dodson, *et al.*,[8] treatment of Ib with refluxing formic acid gave several products of undetermined structure but none of the desired XI, whereas Ia gave a poor yield of XI under similar conditions. Neither IVa or IVb yielded an appreciable amount of XI when treated with phosphorus oxychloride in pyridine at room temperature for four days.

An attempt also was made to prepare XI from the intermediate 17a-cyano-D-homoetiochol-17(17a)-en-3α-ol-11-one 3-acetate (XII) by reaction of the latter compound with the methyl Grignard reagent.[9] However, the preparation of XII

(4) M. S. Newman, THIS JOURNAL, **75**, 4740 (1953).

(5) A prolonged reaction time or a subsequent acid hydrolysis was necessary to effect cleavage of the intermediate anil; *cf.* ref. 3.

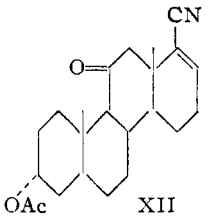
(6) A mole equivalent of mercuric acetate was found to be necessary for the attainment of good yields. In quantitative experiments it was found that when the mercuric acetate was decreased below this amount the yield of product fell abruptly.

(7) *Cf.* P. L. Julian, E. W. Meyer, W. J. Karpel and I. R. Waller, THIS JOURNAL, **72**, 5145 (1950); F. B. Colton, *et al.*, *J. Biol. Chem.*, **194**, 235, 247 (1952).

(8) R. M. Dodson, P. B. Sollman and B. Riegel, THIS JOURNAL, **75**, 5132 (1953).

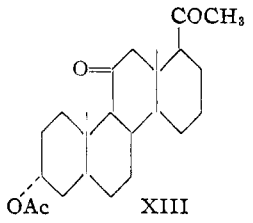
(9) A. Butenandt and J. Schmidt-Thome, *Ber.*, **71**, 1487 (1938); **72**, 182 (1939).

by dehydration of the corresponding 17a-cyanohydrin[10] offered unexpected difficulties, and in spite of considerable effort the yield of XII could not be increased above 10%. This approach was therefore not investigated further.

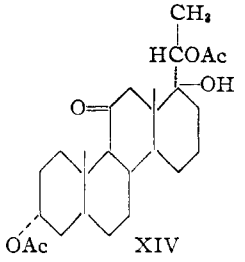


XII

The catalytic reduction of XI by means of a palladium–strontium carbonate catalyst readily afforded D-homopregnan-3α-ol-11,20-dione 3-acetate (XIII) in high yield. The same compound



XIII



XIV

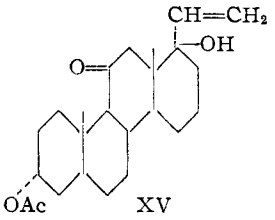
also was obtained, although in rather low yield, by the Serini rearrangement[11] of D-homo-17a-isopregnane-3α,17aβ,20-triol-11-one 3,20-diacetate (XIV). The latter compound readily was prepared by reduction of IVb or Vb with sodium borohydride followed by acetylation. The assignment of the 17aβ-configuration to the compound XIII followed from its preparation by catalytic reduction of the 17,17a-double bond[12] and was confirmed by the observation that XIII was recovered unchanged when heated with dilute acid or dilute base and re-acetylated. The formation of XIII by the Serini rearrangement of XIV serves as additional (but not conclusive[13]) evidence for the structure of XIV and, by inference, of related compounds[1]; conversely, additional weight is lent to the assigned structure of XIII.

The bromination of Va and Vb to form the corresponding 21-bromo compounds VIa and VIb, respectively, occurred readily in glacial acetic acid solution, but in contrast to results in the steroid series[14] the use of chloroform as a solvent gave much less satisfactory yields. Oxidation of VIb by means of N-bromoacetamide in *t*-butyl alcohol–methanol solution took place smoothly, if initially catalyzed by a trace of hydrogen bromide, and the crystalline 21-bromo-D-homo-17a-isopregnan-17aβ-ol-3,11,20-trione (VIIb) was isolated in good yield. However, a similar reaction with VIa gave a resinous product, and in spite of much effort VIIa could not be obtained crystalline.

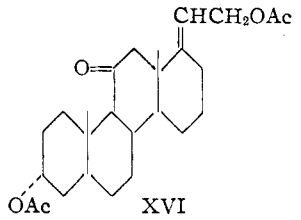
Replacement of the 21-bromine atom in VIIa or VIIb by acetate to form respectively VIIIa or VIIIb, took place only with considerable difficulty, in contrast to the ease of similar replacement in the steroid series.[15] Similar results were observed when VIb was subjected to acetolysis. This resistance to replacement of the 21-bromo atom was considered to be a further measure of the increased amount of steric hindrance affecting the 21-position in the D-homo series in contrast to the steroid series.

Bromination of VIIIa at the 4-position under buffered conditions, followed by dehydrobromination with either semicarbazide[14] or lithium chloride–dimethylformamide[16] gave D-homopregn-4-ene-17aα,21-diol-3,11,20-trione 21-acetate (D-homo-cortisone acetate) (IXa). A similar sequence of reactions employing VIIIb gave D-homo-17a-isopregn-4-ene-17aβ,21-diol-3,11,20-trione 21-acetate (IXb).

In view of the somewhat limited availability[1] of 17aβ-ethinyl-D-homoetiocholane-3α,17aα-diol-11-one 3-acetate (Ia) we also explored an additional pathway to D-homocortisone acetate. This procedure utilized as an intermediate the allylic rearrangement product XVI, prepared in high yield from 17aα-vinyl-D-homoetiocholane-3α,17aβ-diol-11-one 3-acetate (XV)[1] derived from Ib.



XV



XVI

Similar allylic rearrangement of the vinyl compound derived from Ia also gave XVI. The exocyclic position of the double bond in XVI was demonstrated by ozonolysis and reduction of the ozonide to yield D-homoetiocholan-3α-ol-11,17a-dione.

Treatment of XVI with the hydrogen peroxide–*t*-butyl alcohol–osmium tetroxide reagent of Miescher and Schmidlin[17] gave a low yield of D-homopregnane-3α,17aα,21-triol-11,20-dione 3,21-diacetate (XVII). Subsequently it was found that XVII could be prepared from XVI in improved yield by use of the phenyl iodosoacetate–osmium tetroxide reagent developed by Hogg, *et al.*[18] Saponification of XVII under nitrogen gave the corresponding 3,17aα,21-triol XVIII and the latter was converted to D-homopregnane-17aα,21-diol-3,11,20-trione (XIX) by selective oxidation of the 3-hydroxy group by means of N-bromoacetamide

(10) R. O. Clinton, R. G. Christiansen, H. C. Neumann and S. C. Laskowski, THIS JOURNAL, **79**, 6475 (1957).

(11) A. Serini, W. Logeman and W. Hildebrand, *Ber.*, **72**, 391 (1939); L. Fieser and Huang-Minlon, THIS JOURNAL, **71**, 1840 (1949); C. Djerassi and C. R. Scholz, *ibid.*, **71**, 3962 (1949).

(12) P. A. Plattner, *et al.*, *Helv. Chim. Acta*, **27**, 1177 (1944); **29**, 942 (1946); H. Heusser, N. Wahba and F. Witernitz, *ibid.*, **37**, 1052 (1954); C.W. Greenhalgh, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 1190 (1951).

(13) Heretofore the Serini rearrangement has been applied only in the steroid (5 membered D-ring) series. Regardless of the mechanism of the reaction (*cf.* Fieser and Huang-Minlon, reference 11) we cannot overlook the probable importance of steric effects in this rearrangement, and therefore we do not regard this evidence as unequivocal.

(14) T. H. Kritchesvky, D. L. Garmaise and T. F. Gallagher, THIS JOURNAL, **74**, 483 (1952).

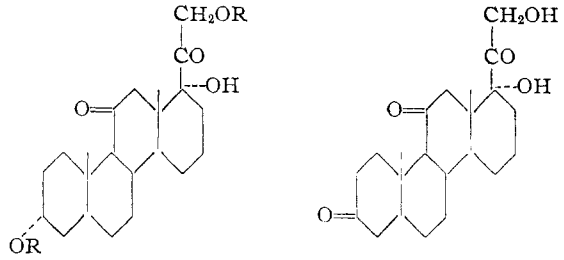
(15) E. B. Hershberg, C. Gerold and E. P. Oliveto, *ibid.*, **74**, 3849 (1952).

(16) R. P. Holysz, *ibid.*, **75**, 4432 (1953).

(17) K. Miescher and J. Schmidlin, *Helv. Chim. Acta*, **33**, 1840 (1950).

(18) J. A. Hogg, *et al.*, THIS JOURNAL, **77**, 4436 (1955).

in methanol–pyridine.[14,19] Acetylation of XIX then gave VIIIa.



XVII, R = Ac
XVIII, R = H

XIX

D-Homopregnane-3α,17aα-diol-11,20-dione (Va) was readily oxidized to D-homopregnane-17aα-ol-3,11,20-trione by N-bromoacetamide in aqueous acetone, but the use of the pyridine–chromium trioxide reagent[20] gave considerably lower yields. In direct contrast, Vb gave a high yield with the latter reagent and a lowered yield of impure product by the N-bromoacetamide procedure. A similar effect was noted previously with the corresponding 20-desoxy compounds.[1]

D - Homo - 17a - isopregnane - 17aβ - ol - 3,11,20-trione was converted to the 4-bromo compound, and the latter when subjected to treatment with lithium chloride in dimethylformamide readily afforded D-homo-17a-isopregn-4-en-17aβ-ol-3,11,-20-trione.

D - Homo - 17a - isopregnane - 3α,17aβ - diol-11,20-dione, D-homopregnane-17α,21-diol-3,11,20-trione 21-acetate and D-homopregnane-3α,17aα,-21-triol-11,20-dione 3,21-diacetate possessed no discernible hormonal or antihormonal activity.[21] D - Homo - 17a - isopregnane - 3α,17aβ,20 - triol-11-one and D-homo-17a-isopregnane-17aβ-ol-3,11,-20-trione were anti-progestational at a relatively high dose level. D-Homopregn-17a(20)-ene-3,21-diol-11-one proved to be a rather potent adrenal cortical hormone inhibitor in the liver glycogen test. The D-homopregn-4-ene-17aα,21-diol-3,11-20-trione 21-acetate (D-homocortisone acetate) possessed only one-third to one-half of the cortical hormone activity of cortisone acetate, in contrast to the previous observations[22] of increased hormonal activity in the D-homo series when compared with their steroid counterparts.

Experimental[23]

D-Homopregnane-3α,17aα-diol-11,20-dione 3-Acetate (IVa).—To a solution of 18.82 g. (0.0488 mole) of 17aβ-ethinyl-D-homoetiocholane-3α,17aα-diol-11-one 3-acetate[1] (Ia) in 500 ml. of glacial acetic acid and 100 ml. of acetic anhydride was added 25 ml. of 47% boron trifluoride etherate. The resulting clear solution was allowed to stand at room temperature for 2.5 hours to ensure complete conversion to the 3,17a-diacetate IIa and then treated with 16.08 g. (0.0504 mole) of C.P. mercuric acetate. After 4 days at room temperature the initially clear solution had set to a gel. Hydrogen sulfide gas was passed through the mixture for 0.5 hour, and after standing for 2 hours the mixture was filtered through a Filtercel pad and the pad was washed thoroughly with acetic acid. The combined filtrates were evaporated to dryness *in vacuo* and the resulting crystalline solid was ground with water, filtered off and washed thoroughly with water. The crude wet cake (IIIa) was mixed with 400 ml. of methanol and a solution of 30 g. of potassium carbonate in 75 ml. of water, and refluxed for 1.5 hours. The solution was filtered and the filtrate was concentrated *in vacuo* to remove the methanol. The solid product was filtered off, washed thoroughly with water and dried at 70°. There was obtained 17.80 g. of crude Va as a brown crystalline solid. The latter material was acetylated with a mixture of 50 ml. of acetic anhydride and 30 ml. of pyridine (0.5 hour at 90°). Recrystallization of the crude acetylated product from ethyl acetate–Skellysolve C and then from methanol gave 14.73 g. (74.5%) of pure IVa as rosettes of long slender needles of m.p. 210.5–212.4°, $[\alpha]_D$ +31.1°.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.47; H, 8.80.

Saponification of IVa by means of aqueous methanolic potassium carbonate solution gave **D-homopregnane-3α,-17aα-diol-11,20-dione (Va)**, prisms from ethyl acetate, m.p. 183.1–185.0°, $[\alpha]_D$ 0°.

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.95; H, 9.55.

The compound formed a solvate from aqueous methanol, m.p. 118–124°.

To a solution of 3.16 g. (7.38 mmoles) of IIa and 1.18 g. (3.7 mmoles) of C.P. mercuric acetate in 30 ml. of glacial acetic acid was added 3.0 ml. of water and 1.5 ml. of 47% boron trifluoride etherate. The mixture was allowed to stand at room temperature for 4 days, quenched in 800 ml. of water, and the insoluble material was filtered off and washed with water. The latter material (containing much bound mercury) was refluxed for 1.5 hours with aqueous methanolic potassium carbonate solution and the suspension was filtered while hot. The insoluble mercury salts were washed with hot methanol and the combined filtrates were concentrated *in vacuo* to remove the methanol. After isolation and re-acetylation of the product as outlined above, there was obtained a 68% yield of IVa. Repetition of this experiment with one-half the amount of mercuric acetate (1.85 mmoles) gave a resinous product; chromatographic purification on silica gel gave a 60% recovery of starting material (as the monoacetate Ia) and a 15% yield of IVa.

17aβ-Ethinyl-D-homoetiocholane-3α,17aα-diol-11-one 3-acetate (Ia) and the 3,17a-diacetate IIa were recovered unchanged when subjected to treatment with hypobromous acid under the conditions used with the 17a-stereoisomer (see below), or even when treated under more stringent conditions of time and temperature. Similarly, both Ia and IIa proved to be inert under the conditions of the Stavely hydration procedure used with the 17a-stereoisomer (see below).

D-Homo-17a-isopregnene-3α,17aβ-diol-11,20-dione (Vb).—A mixture of 37.43 g. (0.0873 mole) of 17aα-ethinyl-D-homoetiocholane-3α,17aβ-diol-11-one 3,17a-diacetate[1] (IIb), 52.1 g. (0.192 mole) of C.P. mercuric chloride, 11.36 g. (0.122 mole) of redistilled aniline, 635 ml. of C.P. benzene and 185 ml. of water was stirred under reflux for 24 hours.[24] The mixture was concentrated to dryness *in vacuo* and the residual material was taken up in 750 ml. of absolute alcohol. After the addition of 15 ml. of concentrated ammonium hydroxide the mixture was heated to 40° and treated with a stream of hydrogen sulfide gas for 0.5 hour at this temperature. The black mixture was filtered through a Filtercel pad and the insoluble material was washed thoroughly with absolute alcohol. The combined filtrates were concentrated *in vacuo* to 500 ml. and to the clear, yellow-colored solution was added 25 ml. of concentrated hydrochloric acid and 50 ml. of water. The mixture was refluxed for 2 hours,

(19) *Cf.* R. E. Jones and F. W. Kocher, THIS JOURNAL, **76**, 3682 (1954).

(20) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *ibid.*, **75**, 422 (1953).

(21) Private communication from Dr. A. Beyler and Dr. G. Potts of these laboratories.

(22) L. Ruzicka, N. Wahba, P. Herzig and H. Heusser, *Ber.*, **85**, 491 (1952), and references given therein.

(23) All melting points are corrected. Unless otherwise noted, the rotations were determined in chloroform solution at 25°, c ~1%. The analyses were carried out by Mr. K. D. Fleischer and staff, and the spectral determinations by Dr. F. C. Nachod and Miss Catherine Martini.

(24) If the reaction was interrupted at the end of 14 hours, the intermediate anil constituted nearly 50% of the material present. Traces of anil (m.p. *ca.* 166–178°, aniline isolated on hydrolysis) remaining at the end of 24 hours are converted to the 20-ketone by the subsequent acid hydrolysis.

50 ml. of 35% aqueous sodium hydroxide solution was carefully added and refluxing was continued for 1.5 hours. The resulting mixture was diluted with water, the alcohol was removed *in vacuo* and the suspension was filtered. After washing, and drying at 70°, the crude product (m.p. 221–226°) was recrystallized from ethyl acetate with decolorization (Darco G-60). There was thus obtained 28.45 g. (90% yield) of material melting at 224–226°. One further recrystallization from ethyl acetate furnished analytically pure material with but little loss: prisms of m.p. 225.0–226.3°, $[\alpha]_D$ +28.2°.

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.85; H, 9.69.

A mixture of 4.47 g. (10.4 mmoles) of IIb, 1.11 g. (12 mmoles) of redistilled aniline, 5.4 g. (20 mmoles) of C.P. mercuric chloride, 100 ml. of C.P. benzene and 25 ml. of water was stirred under reflux for 24 hours. The mixture was steam distilled to remove benzene and aniline and the residual insoluble material was filtered off, washed well with water and dried *in vacuo*. The semi-solid product[25] was dissolved in 100 ml. of pure acetone and the solution was treated with a slow stream of hydrogen sulfide for 0.5 hour. The heavy yellow precipitate was removed by filtration and the filtrate and washings were concentrated to dryness *in vacuo*. The residual solid (4.70 g., m.p. 159–163°) on recrystallization from methanol yielded 3.90 g. (84%) of **D-homo-17a-isopregnane-3α,17aβ-diol-11,20-dione 3,17a-diacetate (IIIb)**, slender needles of m.p. 167.1–168.6°, $[\alpha]_D$ +20.6°.

Anal. Calcd. for $C_{26}H_{38}O_6$: C, 69.93; H, 8.58. Found: C, 69.82; H, 8.83.

From five grams of Ib, treated with mercuric acetate–boron trifluoride in acetic acid–acetic anhydride under conditions similar to those used for Ia (above), was isolated 4 g. of resinous product. After saponification and re-acetylation, chromatography on 200 g. of silica gel separated 1.5 g. of pure **D-homo-17a-isopregnane-3α,17aβ-diol-11,20-dione 3-acetate (IVb)**, prisms from methanol, m.p. 196.6–199.6°, $[\alpha]_D$ +54.0°.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.02; H, 8.80.

To a solution of 4.29 g. (10 mmoles) of IIb in 200 ml. of *t*-butyl alcohol was added 10 ml. of glacial acetic acid and a solution of 5.12 g. (36 mmoles) of N-bromoacetamide and 5.14 g. (37.8 mmoles) of C.P. sodium acetate trihydrate in 50 ml. of water. The clear solution was allowed to stand at room temperature (28°) for 19 hours. The mixture was concentrated *in vacuo* (bath temperature of 30°) to a residual volume of 50 ml., diluted to 500 ml. with water, and the precipitate was filtered off and washed with water. After drying at 70° *in vacuo* there was obtained 5.75 g. of crude 21,21-dibromo-20-ketone X, m.p. 180–186° dec. The material gave consistently high bromine analyses.

The crude X (3.00 g.) was dissolved in 40 ml. of glacial acetic acid and to the solution there was added 5.0 g. of sodium acetate trihydrate and 5 g. of zinc dust. The mixture was stirred at 80° for 15 minutes, filtered, and the insoluble material was washed on the filter with acetic acid. The combined filtrates were diluted to 800 ml. with water and the precipitated product was filtered off, washed with water and dried at 70°. Recrystallization from methanol gave 2.00 g. (86% over-all from IIb) of pure IIIb, identified by mixed m.p. and a comparison of the infrared spectra. Hydrolysis with aqueous methanolic potassium carbonate solution gave a quantitative yield of Vb, m.p. and mixed m.p. 223–226°.

To a solution of 3.0 g. of IIb in 50 ml. of glacial acetic acid was added 5.0 ml. of water and 3.0 g. of mercurated Dowex 50 resin.[4] The slurry was stirred while heating on the steam-bath for 4 hours. The resin was removed by filtration and rinsed with acetic acid; the combined filtrates were quenched in 1500 ml. of water. After filtration and washing, the dried product had m.p. 90–115°, indicating partial hydrolysis of acetate groups.[26] Hydrolysis of the crude material with aqueous methanolic potassium carbonate gave, after recrystallization from ethyl acetate, 2.35 g. of Vb (93% yield), m.p. and mixed m.p. 224–226°, infrared spectra identical.

D-Homopregn-17(17a)-en-3α-ol-11,20-dione 3-Acetate (XI).—A solution of 5.0 g. of Ib and 2.5 g. of mercuric acetate in 150 ml. of glacial acetic acid and 175 ml. of ethylene glycol was treated with 5.0 ml. of 47% boron trifluoride etherate and heated for 5 hours on the steam-bath. The resulting canary-yellow colored solution was poured into 2000 ml. of water and the mixture was extracted with methylene dichloride in the usual manner. The washed and dried methylene dichloride extract was evaporated to dryness and the residual oil (containing ethylene glycol acetate) was saponified with aqueous methanolic potassium carbonate solution. After removal of the methanol *in vacuo* the resulting suspension was filtered and the insoluble material was washed with water and dried at 70°. The granular yellow solid (4.2 g., m.p. 165–185°) was acetylated with acetic anhydride–pyridine (0.5 hour on the steam-bath) and the resulting resinous 3-acetate was chromatographed on 250 g. of silica gel. Elution with 30% ether–*n*-pentane and 40% ether–*n*-pentane gave 2.0 g. of crystalline product, m.p. 183–187°. Recrystallization from ethyl acetate afforded 1.8 g. of the title compound as rosettes of slender needles, m.p. 191.2–193.5°, $[\alpha]_D$ +149.8°; λ_{max}^{EtOH} 230 mμ, ε 10100; λ_{max}^{KBr} 5.76 (acetate), 5.84 (C=O), 5.98 (C=C–C=O), 6.18 (C=C) μ.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.56; H, 8.87. Found: C, 74.64; H, 8.75.

Further elution of the column with 50% ether–*n*-pentane gave 1.4 g. of IVb, m.p. and mixed m.p. 196.5–199°.

Saponification of XI by means of aqueous methanolic potassium carbonate solution gave **D-homopregn-17(17a)-en-3α-ol-11,20-dione**, prisms from benzene, m.p. 207.0–211.8°, $[\alpha]_D$ +141.3°.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.40; H, 9.63.

A mixture of 10.00 g. (25.9 mmoles) of Ib, 2.79 g. (30 mmoles) of redistilled aniline, 16.3 g. (60 mmoles) of mercuric acetate, 200 ml. of benzene and 50 ml. of water was stirred under reflux for 20 hours. After working up as outlined above (saponification and re-acetylation) there was obtained 13.0 g. of resin. The resin was chromatographed on 800 g. of silica gel. Preliminary elution up to 35% ether–*n*-pentane gave a series of resinous fractions. Elution with 35–40% ether–*n*-pentane gave 3.5 g. of crystalline product, m.p. and mixed m.p. with pure XI 185–190°, infrared spectrum confirmatory.

A solution of 5.0 g. of Ia in 25 ml. of 90% formic acid was refluxed for 2 hours and quenched in 750 ml. of water. The resinous product was extracted into methylene dichloride as usual and the resulting orange resin was chromatographed on 200 g. of silica gel. Elution as above gave 1.1 g. of XI, m.p. and mixed m.p. 190–192°, infrared spectra identical. When Ib was subjected to identical conditions only resinous products were obtained, and no material corresponding to XI could be isolated.

A cold solution of 2.50 g. (6.19 mmoles) of IVa in 15.0 ml. of C.P. pyridine was treated with 0.9 ml. (10 mmoles) of phosphorus oxychloride and the mixture was held at room temperature for 4 days. After the usual workup there was obtained 2.38 g. of recovered IVa, m.p. and mixed m.p. 210.5–212.0°. Similar treatment of IVb gave 2.40 g. of product of m.p. 162–172° with gas evolution, converted by saponification and recrystallization to 2.14 g. of recovered Vb, m.p. and mixed m.p. 224–226°.

A mixture of 5.38 g. (15.7 mmoles) of Ib, 100 ml. of acetic acid, 10 ml. of water and 5 g. of mercurated Dowex 50 resin[4] was stirred and heated on the steam bath for 18 hours. After the usual workup the resulting resin was chromatographed on 200 g. of silica gel. Elution with 15% ether–*n*-pentane gave a resin with λ_{max}^{KBr} 2.93, 5.83, 5.99 μ. Elution with 25% ether–*n*-pentane gave a second resinous product (λ_{max}^{KBr} 2.96, 3.05, 5.75, 5.83, 5.97 μ), followed by 1.2 g. of crystalline XI. After additional resinous fractions, 45% ether–*n*-pentane eluted crystalline material of m.p. 167–172° (from ether) with λ_{max}^{KBr} 5.75, 5.85, 5.95 μ. Finally, pure ether eluted crystalline material of m.p. 235–240° (from ether) with λ_{max}^{KBr} 5.83, 5.86 μ. Products of similar complexity were obtained when 17aα-ethinyl-D-homoetiocholane-3α,17aβ-diol-11-one was subjected to the same reaction conditions. On the other hand, when either IVa or IVb

(25) The material weighed 8.60 g. corresponding to combination with two atoms of mercury.

(26) Chromatography of a duplicate experiment at this point on 200 g. of silica gel gave 2.7 g. (87% yield) of pure IIIb, identified by mixed m.p. and a comparison of infrared spectra.

was treated with mercurated Dowex 50 resin under the above conditions, both compounds were recovered unchanged.

17a-Cyano-D-homoetiochol-17(17a)-en-3α-ol-11-one 3-Acetate (XII).—To a solution of 6.40 g. of the epimeric mixture of 17a-cyano-D-homoetiocholane-3α,17a-diol-11-ones[10] in 60 ml. of C.P. pyridine was added 15 ml. of C.P. phosphorus oxychloride. The resulting mixture was refluxed for 2 hours, cooled, and poured slowly onto crushed ice. After standing overnight the precipitated solid was filtered off, washed with water and dried. Five recrystallizations from methanol gave 0.67 g. of the title compound, crystallizing in needles, m.p. 220.8–223.3°, $[\alpha]_D$ +128.8°, λ_{max}^{EtOH} 213 mμ, ε 9800.

Anal. Calcd. for $C_{23}H_{31}NO_3$: C, 74.67; H, 8.46; N, 3.79. Found: C, 74.74; H, 8.11; N, 3.58.

The use of acetic anhydride–pyridine, formic acid or toluenesulfonyl chloride–pyridine as dehydrating agents was unsuccessful.

D-Homopregnan-3α-ol-11,20-dione 3-Acetate (XIII).—D-Homopregn-17(17a)-en-3α-ol-11,20-dione 3-acetate (XI) was reduced by hydrogen in absolute alcoholic solution in the presence of a 22% palladium–strontium carbonate catalyst. The reduction, at a pressure of 40 lb., required 25 min.; the product, obtained in nearly quantitative yield, formed short, thick needles from methanol, m.p. 192.4–193.4°, $[\alpha]_D$ +92.4°. The ultraviolet and infrared spectra were confirmatory; the mixed m.p. with XI was 186–189°.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 73.80; H, 9.28.

A mixture of 3.30 g. of D-homo-17a-isopregnane-3α,17aβ,-20-triol-11-one 3,20-diacetate (XIV) (see below), 150 ml. of redistilled *p*-cymene and 75 g. of zinc dust was stirred vigorously while refluxing for 42 hours. The mixture was filtered, the zinc-pad was washed with hot benzene, and the combined filtrates were steam distilled until the distillate was clear. The still residue was extracted with ethyl acetate in the usual manner and the resinous product (3.09 g.) was chromatographed on 150 g. of silica gel. After a series of resinous fractions, 50% ether–*n*-pentane eluted crystalline material. The latter on recrystallization from Skellysolve C and from methanol weighed 642 mg. and had m.p. 192.5–193.5°. The mixed m.p. with XIII, above, was the same and the infrared spectra were identical. A substantial amount of unaltered XIV was also recovered from the chromatogram.

D-Homo-17a-isopregnane-3α,17aβ,20-triol-11-one 3,20-Diacetate (XIV).—To a solution of 3.25 g. of IVb (8.05 mmoles) in 100 ml. of C.P. methanol at 20° was added a solution of 0.304 g. (8.0 mmoles) of sodium borohydride in 4 ml. of water. The solution was held at 20° for 1.5 hours and then treated slowly with 3 ml. of glacial acetic acid. The solution was evaporated to dryness *in vacuo*, the residue was triturated with water and the insoluble material was filtered off and washed with water. After drying at 70° there was obtained 3.17 g. of crude **D-homo-17a-isopregnane-3α,17aβ,20-triol-11-one 3-acetate**, m.p. 257–264°. Recrystallization from ethyl acetate and from methanol gave 2.41 g. of pure monoacetate as rosettes of short needles, m.p. 274.5–276.0°, $[\alpha]_D$ +36.1°.

Anal. Calcd. for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 71.00; H, 9.35.

Acetylation of the 3-monoacetate with acetic anhydride and pyridine (0.5 hour on the steam-bath) gave the title compound XIV, prisms from methanol, m.p. 190.3–192.5°, $[\alpha]_D$ +16.9°.

Anal. Calcd. for $C_{26}H_{40}O_6$: C, 69.61; H, 8.99. Found: C, 69.63; H, 8.83.

Hydrolysis of the 3-monoacetate, or reduction of the diol Vb by means of sodium borohydride, gave **D-homo-17a-isopregnane-3α,17aβ,20-triol-11-one**, crystallizing as prisms from ethyl acetate, m.p. 201.7–207.4°, $[\alpha]_D$ +14.4°.

Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.80; H, 10.22.

A mixture of 360 mg. of D-homo-17a-isopregnane-3α,-17aβ,20-triol-11-one 3-acetate, 350 mg. of sodium borohydride, 50 ml. of methanol and 4 ml. of 35% sodium hydroxide solution was refluxed for 18 hours. After the usual isolation there was obtained a high yield of **D-homo-17a-isopregnane-3α,11β,17aβ,20-tetrol**, prisms from methanol of m.p. 203.0–208.0°, $[\alpha]_D$ +26.4° (*c* 0.6 in methanol).

Anal. Calcd. for $C_{22}H_{38}O_4$: C, 72.09; H, 10.95. Found: C, 72.26; H, 10.38.

Acetylation of the latter compound gave the **3,20-diacetate**, feathery plates from Skellysolve C, m.p. 178.0–179.0°, $[\alpha]_D$ +19.4°.

Anal. Calcd. for $C_{26}H_{42}O_6$: C, 69.30; H, 9.40. Found: C, 69.31; H, 9.39.

D-Homopregnane-17aα-ol-3,11,20-trione.—To a cold (5°) solution of 1.1 g. of Va in 25 ml. of C.P. acetone was added 4 ml. of water and 2.0 g. of N-bromoacetamide. The solution was stirred at 5° for 4 hours (color change to deep orange and back to colorless) and then quenched in 500 ml. of water. The precipitated solid was filtered off, washed with water and dried at 50°. Recrystallization from ethyl acetate–Skellysolve C gave 1.0 g. of needles, m.p. 210.4–212.1°, $[\alpha]_D$ +10.1°.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.56; H, 8.82.

The use of pyridine–chromium trioxide for this oxidation gave only a 70% yield.

D-Homo-17a-isopregnane-17aβ-ol-3,11,20-trione.—The oxidation of 8.76 g. of Vb by means of 8.0 g. of chromium trioxide in 170 ml. of C.P. pyridine in the usual manner[20] gave 8.36 g. of pure product, crystallizing from ethyl acetate–Skellysolve C in prisms of m.p. 179.4–180.2°, $[\alpha]_D$ +36.5°.

Anal. Calcd. for $C_{22}H_{32}O_4$: C, 73.30; H, 8.95. Found: C, 73.39; H, 8.99.

When the oxidation was carried out with N-bromoacetamide under the conditions used above with the 17a-stereoisomer a product containing bromine was obtained. After zinc–acetic acid debromination, a product of m.p. 172–177° was isolated; this m.p. could not be raised by recrystallization.

4-Bromo-D-homo-17a-isopregnane-17aβ-ol-3,11,20-trione.—D-Homo-17a-isopregnane-17aβ-ol-3,11,20-trione was brominated by means of pyridinium bromide perbromide–sodium acetate.[10] The dried crude product was triturated with ether and the ether-insoluble material was recrystallized from acetone–ether. There was obtained a 77% yield of product, crystallizing in prisms of m.p. 180.8–182.0° dec.[27] (immersed at 177°), $[\alpha]_D$ +71.4°.

Anal. Calcd. for $C_{22}H_{31}BrO_4$: C, 60.13; H, 7.11; Br, 18.19. Found: C, 60.40; H, 7.28; Br, 18.10.

D-Homo-17a-isopregn-4-en-17aβ-ol-3,11,20-trione.—The above 4-bromo compound was dehydrobrominated by means of lithium chloride in dimethylformamide[16] (2 hours heating on the steam-bath under nitrogen). Recrystallization from acetone and from ethyl acetate gave a 57% yield of pure product as thick, brilliant needles of m.p. 221.1–226.5°, $[\alpha]_D$ +172.2°, λ_{max}^{EtOH} 239 mp, ε 15270.

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.46; H, 8.62.

21-Bromo-D-homopregnane-3α,17aα-diol-11,20-dione (VIa).—To a solution of 7.35 g. (0.020 mole) of Va in 200 ml. of glacial acetic acid, at room temperature, was added 4 drops of a 30% solution of hydrogen bromide in glacial acetic acid. A total of 8.15 g. of 86.4% pyridinium bromide perbromide (110 mole %) was then added to the stirred solution in small portions during 2 hours, waiting each time for the discharge of color. The solution was quenched in 3000 ml. of water, filtered, and the insoluble precipitate was washed with water and dried at 50°. Several recrystallizations from ethyl acetate gave prisms of m.p. 218.0–219.0° dec.[27] (immersed at 202°), $[\alpha]$ +74.4°.

Anal. Calcd. for $C_{22}H_{33}BrO_4$: C, 59.86; H, 7.54; Br, 18.11; O, 14.50. Found: C, 59.82; H, 7.20; Br, 17.24; O, 14.50.[28]

D-Homopregnane-17aα,21-diol-3,11,20-trione 21-Acetate (VIIIa).—The oxidation of VIa by means of N-bromoacetamide (*cf.* the preparation of VIIIb below), pyridine–chromium trioxide, Kiliani reagent or chromium trioxide in glacial acetic acid gave in all cases a resinous 3-keto compound VIIa. The resinous (but chromatographically purified) 3-ketone VIIa from 5.82 g. of VIa was added to a

(27) The melting point was dependent upon the immersion point and the rate of heating. All melting points were taken at 3° rise per minute.

(28) Direct oxygen determination.

suspension of potassium acetate in acetone, prepared by adding 4.8 ml. of glacial acetic acid to a stirred, refluxing mixture of 8.0 g. of potassium bicarbonate in 115 ml. of acetone. The resulting mixture was stirred and refluxed for 18 hours. After the addition of water, the acetone was removed *in vacuo* and the residual aqueous suspension was extracted with methylene dichloride. The methylene dichloride extracts were washed with water, dried and evaporated to dryness. The resulting resin was chromatographed on 400 g. of silica gel. Elution with 60% ether–*n*-pentane gave some recovered VIIa; elution with 100% ether gave a series of crystalline fractions. The latter on recrystallization from methanol and ethyl acetate gave 1.82 g. (27% over-all yield from VIa) of cottony needles, m.p. 198.8–201.7°, resolidified and remelted at 222.9–223.0°, $[\alpha]_D$ +63.8°.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.60; H, 8.38.

4-Bromo-D-homopregnane-17aα,21-diol-3,11,20-trione 21-Acetate.—To a stirred solution of 535 mg. of VIIIa (1.28 mmoles) in 8 ml. of glacial acetic acid was added one small drop of a 10% solution of hydrogen bromide in acetic acid followed by the dropwise addition of a solution of 482 mg. of 87.5% pyridinium bromide perbromide (1.316 mmoles) and 169 mg. of C.P. sodium acetate trihydrate (1.245 mmoles) in 6 ml. of glacial acetic acid. The addition required 15 minutes; the resulting solution was quenched in water and the product was extracted with methylene dichloride in the usual manner. The resulting resin crystallized on trituration with ether. The pure compound crystallized from methanol in thick needles of m.p. 187.2–190.4° dec.[27] (immersed at 180°), $[\alpha]_D$ +104.3° (*c* 0.5 in acetone).

Anal. Calcd. for $C_{24}H_{33}BrO_6$: C, 57.95; H, 6.69; Br, 16.07. Found: C, 57.75; H, 6.54; Br, 16.20.

D-Homopregn-4-ene-17aα,21-diol-3,11,20-trione 21-Acetate (D-Homocortisone Acetate) (IXa).—Six hundred and thirty-five milligrams of 4-bromo-D-homopregnane-17aα,-21-diol-3,11,20-trione 21-acetate was dehydrobrominated by means of 170 mg. of anhydrous lithium chloride in 15 ml. of dimethylformamide.[16] After quenching the reaction mixture in water, the product was isolated with methylene dichloride. The resin obtained by evaporation of the methylene dichloride extracts crystallized on trituration with absolute ether. Recrystallization from acetone–ether and from ethyl acetate gave pure IXa as large prisms of m.p. 234.0–236.8°, $[\alpha]_D$ +151.8° (*c* 1.0 in acetone), λ_{max}^{EtOH} 238 mμ, ε 14900; λ_{max}^{KBr} 2.89 (OH), 5.76 (acetate), 5.84 (CO), 5.95 (C=C—CO), 6.18 (C=C) μ.

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.43; H, 7.83.

21-Bromo-D-homo-17a-isopregnane-3α,17aβ-diol-11,20-dione (VIb).—To a stirred solution of 34.18 g. (0.0914 mole) of D-homo-17a-isopregnane-3α,17aβ-diol-11,20-dione (Vb) in 350 ml. of galcial acetic acid was added 3 ml. of a solution of bromine in acetic acid (74.3 mg. per ml.). When the initial color had been discharged (20 minutes) there was added dropwise an additional 201.5 ml. of the bromine–acetic acid solution (total bromine 15.18 g., 101 mole per cent.), at such a rate that each drop was decolorized before the next was added. The resulting pale yellow solution was quenched in 7 liters of water, the mixture was allowed to stand for 2 hours and the precipitated solid was filtered off and washed thoroughly with water. The dried product was recrystallized from methanol and from ethyl acetate–Skellysolve C. There was obtained 26.00 g. of pure VIb as rosettes of small, brilliant needles, m.p. 200.2–202.5° dec.[27] (immersed at 180°), $[\alpha]_D$ +25.7°.

Anal. Calcd. for $C_{22}H_{33}BrO_4$: C, 59.86; H, 7.54; Br, 18.11. Found: C, 59.60; H, 7.35; Br, 18.28.

On prolonged standing in methanolic solution, VIb was converted to a higher melting (221–223° dec.) polymorphic form.[29] Both polymorphic forms gave identical yields of the 3-ketone VIIb (see below) on oxidation.

D-Homo-17a-isopregnane-3α,17aβ,21-triol-11,20-dione 3,21-Diacetate.—To a suspension of potassium acetate in acetone (from 5.0 g. of potassium bicarbonate, 3.0 ml. of glacial acetic acid and 70 ml. of acetone) was added 50 mg. of sodium iodide and 4.41 g. of VIb. The mixture was stirred under reflux for 19 hours, diluted with water and the acetone was removed *in vacuo*. The product was extracted into methylene dichloride and the washed and dried extracts were evaporated to dryness. The residual semi-crystalline material was acetylated with acetic anhydride–pyridine (20 hours at 26°) and the resulting product was recrystallized from ethyl acetate. The pure compound formed massive prisms of m.p. 217–218°, $[\alpha]_D$ +15.9°.

Anal. Calcd. for $C_{26}H_{36}O_7$: C, 67.51; H, 8.28. Found: C, 67.36; H, 8.11.

21-Bromo-D-homo-17a-isopregnane-17aβ-ol-3,11,20-trione (VIIb).—Fifteen milliliters of commercial methanol was added to a solution of 17.85 g. of VIb in 250 ml. of *t*-butyl alcohol. After cooling to 5°, there was added 5.9 g. (105% of theory) of N-bromoacetamide and the mixture was stirred until solution of the N-bromoacetamide was complete. After the addition of 0.8 ml. of a 30% solution of hydrogen bromide in acetic acid the solution was held at 5° for 5 hours, during which period the color changed to deep orange and back again to colorless. The solution was quenched in 1500 ml. of water and the product was extracted with methylene dichloride. Recrystallization of the crude product from ether gave 13.34 g. of material melting at 222–223° dec. and suitable for the next step. Recrystallization of a small portion from acetone–Skellysolve C gave the pure compound as needles of m.p. 228.9–229.8° dec.[27] (immersed at 220°), $[\alpha]_D$ −1.5°.

Anal. Calcd. for $C_{22}H_{31}BrO_4$: C, 60.13; H, 7.11; Br, 18.19. Found: C, 59.96; H, 7.39; Br, 17.71.

D-Homo-17a-isopregnane-17aβ,21-diol-3,11,20-trione 21-Acetate (VIIIb).—The conversion of VIIb to VIIIb was carried out essentially by the procedure outlined above for D-homo-17a-isopregnane-3α,17aβ,21-triol-11,20-dione 3,21-diacetate. The resinous product was chromatographed on silica gel. After preliminary elution of a series of small resinous fractions, the product was eluted with 100% ether. Recrystallization from ethyl acetate–*n*-hexane and from dilute methanol gave about a 25% yield of VIIIb as prisms of m.p. 193.7–196.2°, $[\alpha]_D$ +1.3°.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.60; H, 8.45.

D-Homo-17a-isopregn-4-ene-17aβ,21-diol-3,11,20-trione 21-Acetate (IXb).—The bromination of VIIIb with pyridinium bromide perbromide or with bromine in acetic acid solution, under buffered conditions, gave a resinous 4-bromo compound, which resisted all efforts toward crystallization. The crude, resinous 4-bromo compound was therefore dehydrobrominated with lithium chloride in dimethylformamide[16] and the product was chromatographed on silica gel. The crystalline material eluted with 70% ether–*n*-pentane was triturated with ether and then recrystallized from acetone–*n*-hexane. There was obtained a 27.5% over-all yield of IXb from VIIIb, m.p. 180.0–181.0°, $[\alpha]_D$ +88.0° (*c* 0.5 in acetone), λ_{max}^{EtOH} 238 mμ, ε 15200.

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.14; H, 7.88.

D-Homopregn-17a(20)-ene-3α,21-diol-11-one 3,21-Diacetate (XVI).—A stirred suspension of 40.0 g. of 17aα-vinyl-D-homoetiocholane-3α,17aβ-diol-11-one 3-acetate (XV)[1] in 290 ml. of acetic anhydride was heated to 60° and there was added during 10 minutes a warm solution of 56 g. of trichloroacetic acid in 104 ml. of glacial acetic acid. After 5 minutes the XV was completely in solution; the mixture was held at 60° for 1.5 hours and then allowed to stand overnight at room temperature. The resulting clear, colorless solution was poured into 4 liters of water and, after the mixture had stood for a short while to ensure hydrolysis of the acetic anhydride, the resinous product was extracted into ether in the usual manner. The resulting resin was crystallized from *n*-hexane and recrystallized from the same solvent. There was thus obtained 39.3 g. (88.5% yield) of material melting at 109.5–113°, and suitable for the next step. One further recrystallization from *n*-hexane gave pure XVI as large rectangular crystals of m.p. 111.7–116.5°,[30] $[\alpha]_D$ −53.1°.

(29) Polymorphism of a similar type has been noted with 21-bromopregnane-3α,17α-diol-11,20-dione, for which the reported melting point is 178–179.5° (reference 14). Dr. S. Archer of these laboratories has isolated a higher melting (209–210°) polymorphic modification of this compound, identical in chemical properties.

(30) This material is probably a mixture of the *cis* and *trans* isomers. Separation could not be achieved by repeated recrystallization nor by chromatography.

Anal. Calcd. for $C_{26}H_{38}O_5$: C, 72.52; H, 8.90. Found: C, 72.40; H, 8.78.

The allylic rearrangement of 17aβ-vinyl-D-homoetiocholane-3α,17aα-diol-11-one 3-acetate[1] under identical conditions also gave XVI in comparable yield. Identity was confirmed by infrared analysis.

The ozonolysis of 1.50 g. of pure XVI in acetone solution at 0°, followed by reduction of the ozonide with Raney nickel gave 1.24 g. of material melting at 164–166° (theory for 17a-ketone was 1.26 g.). One recrystallization from methanol gave 1.14 g. of D-homoetiocholane-3α-ol-11,17a-dione 3-acetate, m.p. and mixed m.p. 171–172.5°, infrared spectrum confirmatory.

The saponification of XVI by means of aqueous methanolic potassium carbonate solution gave **D-homopregn-17a-(20)-ene-3α,21-diol-11-one**, rosettes of long, slender needles from methanol, m.p. 236.8–245.4°,[30] $[\alpha]D$ −24.4° (*c* 1.0 in acetic acid).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.25; H, 9.89. Found: C, 76.22; H, 9.70.

D-Homopregnane-3α,17aα,21-triol-11,20-dione 3,21-Diacetate (XVII).—To a solution of 62.0 g. of XVI (0.144 mole) in 3600 ml. of dry *t*-butyl alcohol was added 98.0 g. (0.304 mole) of phenyl iodosoacetate and 440 ml. of dry pyridine. The mixture was stirred until solution of the phenyl iodosoacetate was complete, and there was then added a solution of 720 mg. of osmium tetroxide in 18 ml. of water. After standing at room temperature for 22 hours[31] the solution was saturated with hydrogen sulfide gas and allowed to stand a further 4 hours. The black solution was steam distilled to remove *t*-butyl alcohol and iodobenzene and the residue was taken up in chloroform and water. After filtration of the chloroform–water mixture through a Filtercel pad, the chloroform layer was separated and washed with 2 *N* nitric acid, water, sodium bisulfite solution, water and sodium bicarbonate solution. Evaporation of the chloroform solution yielded a light brown colored solid. The material was chromatographed on 1800 g. of silica gel. Preliminary elution gave traces of resins; elution with 35–40% ether–*n*-pentane gave 7.74 g. (12.5%) of recovered XVI. Further elution with the same eluate gave 15.13 g. (28.6%) of the side-chain cleavage product, D-homoetiocholane-3α-ol-11,17a-dione 3-acetate. Further elution removed a series of resinous fractions, followed by a series of crystalline fractions on elution with 100% ether. The latter fractions gave, on recrystallization from acetone and from ethyl acetate, 21.0 g. (31.6% yield) of XVII as short, blunt needles, m.p. 224.6–226.0°, $[\alpha]D$ +78.3°.

Anal. Calcd. for $C_{26}H_{38}O_7$: C, 67.51; H, 8.28. Found: C, 67.46; H, 8.12.

D-Homopregnane-3α,17aα,21-triol-11,20-dione (XVIII).—To a stirred suspension of 18.70 g. (0.0404 mole) of finely powdered XVII in 1600 ml. of C.P. methanol, in an atmosphere of nitrogen, was added a solution of 23.80 g. (0.238 mole) of potassium bicarbonate in 150 ml. of water. The mixture was heated to 45° and stirred at this temperature until solution of the XVII was complete (1 hour). After standing overnight at room temperature the solution, still under nitrogen, was treated with excess glacial acetic acid and concentrated *in vacuo* to remove the methanol. The residual slurry was diluted with water, filtered, and the insoluble solid was washed thoroughly with water. After drying at 70° there was obtained 15.83 g. of a highly solvated form of XVIII, m.p. 121–129°, $[\alpha]D$ +50.6°. The material could not be obtained crystalline in the anhydrous form, nor could satisfactory analyses of the solvate be obtained. However, the solvate gave pure XVII on reacetylation with acetic anhydride–pyridine.

Methanolysis of XVII by means of 0.27 *N* perchloric acid in methanolic solution[32] failed to quantitatively remove the 3-acetate group.

D-Homopregnane-17aα,21-diol-3,11,20-trione (XIX).—To a solution of 2.00 g. of XVIII (solvate) in 10 ml. of acetone was added a solution of 1.09 g. of N-bromoacetamide, 0.4 ml. of pyridine and 1.5 ml. of water in 25 ml. of methanol. The mixture was allowed to stand in the dark overnight at room temperature. To the resulting deep orange-colored solution was added 10 ml. of glacial acetic acid and 0.4 g. of zinc dust, the mixture was stirred at room temperature for one hour, filtered and the zinc pad was washed with acetone. Concentration of the combined filtrates to dryness *in vacuo* gave a yellow resin, which crystallized when triturated with ethyl acetate. Recrystallization from methanol gave 0.62 g. of XIX as slender needles of m.p. 218.6–225.2°, $[\alpha]D$ +63.2° (*c* 0.2 in acetic acid).

Anal. Calcd. for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57. Found: C, 70.24; H, 8.33.

Acetylation of XIX with acetic anhydride–pyridine (18 hr. at 25°) gave a quantitative yield of D-homopregnane-17aα,21-diol-3,11,20-trione 21-acetate (VIIIa), identified by mixed m.p. and a comparison of the infrared spectra.

(31) The consumption of the phenyl iodosoacetate was followed titrimetrically with sodium thiosulfate. The reaction was essentially complete in 8–10 hours.

(32) *Cf.* J. Fried, *et al.*, *Chemistry & Industry*, 1232 (1956).

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[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES]

D-Homo Rearrangement of Cortical Steroids. Interrelationship of D-Homo Derivatives in the 11-Oxygenated Pregnane Series[1]

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Chemical proof is provided to substantiate the 17a-keto structure for D-homo systems arising from cortical steroids through the agency of Lewis acids.

The structure and stereochemistry of the four D-homo systems derivable from 17-hydroxy-20-keto steroids have been established recently by partial synthesis.[2] From this work it was observed that 3α-acetoxy-17α-hydroxypregnane-11,20-dione (VIII) on D-homoannulation with Lewis acids produced 3α-acetoxy,17α-hydroxy-17β-methyl-D-homoetiocholane-11,17a-dione (V-II) as the major product. Consequently, it was inferred[3] that Lewis acid-catalyzed D-homoannulation products of 17α-hydroxy-21-acetoxy-20-keto systems should correspondingly possess the 17a-ketone structure. The present account describes the chemical confirmation of this structural assignment and with it a complete correlation of the D-homo steroids in the 11-oxygenated pregnane series.

D-Homoannulation of 17α-hydroxy-21-acetoxy-pregnane-3,11,20-trione (III) with aluminum alkoxide yielded the 17a-ketone IV. Bromination

(1) A preliminary account of this work was reported in *Chemistry & Industry*, 822 (1957).

(2) N. L. Wendler, D. Taub, S. Dobriner and D. K. Fukushima, THIS JOURNAL, **78**, 5027 (1956).

(3) Reference 2, footnote 22.