product was dissolved in 20 ml. of acetone, filtered, concentrated to half of the original volume and diluted with ether to initiate crystallization. This procedure gave 585.5 mg. of crystals melting at 182–194°. Eighty-five mg. of this product was sublimed at 165°, at a pressure of 0.05 mm. The sublimate was recrystallized from 3 ml. of acetone–hexane to give 14α-hydroxyprogesterone, m.p. 195–200°, $[\alpha]^{23}D$ 188° (*c* 1.036 in chloroform). The infrared spectrum was identical to that of compound VI obtained by the dissimilation with *M. griseo-cyanus*.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 76.40; H, 9.15. Found: C, 77.02; H, 9.55.

3. By *H. piriforme* (A.T.C.C. 8992).—Progesterone (6 g.) was incubated with *H. piriforme* in 12 liters of medium H for 27 hours. The usual extraction of the beer with methylene chloride gave 8.313 g. of residue. This was dissolved in 600 ml. of benzene containing 10% ether and chromatographed over 300 g. of alumina. Fractions (600 ml.) were eluted with the following solvents: benzene–10% ether, ether (2 fractions each); ether–5% chloroform, ether–10% chloroform, ether–50% chloroform, chloroform (3 fractions in each instance); chloroform–5% acetone, chloroform–10% acetone, chloroform–50% acetone, acetone and methanol (2 fractions each time). Based on paper chromatographic findings the eluates of ether–50% chloroform and the first eluate of chloroform were combined (1.269 g.) and recrystallized from 15 ml. of ethyl acetate to give 680 mg. of crystalline material. A sample was repeatedly recrystallized from methanol to give 14α-hydroxyprogesterone, melting at 191–199°, $[\alpha]^{23}D$ 215° (*c* 0.693 in chloroform). The infrared spectrum was identical to that of the other two samples of compound VI described above.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.40; H, 9.15. Found: C, 76.39, 76.06; H, 9.36, 9.25.

Attempted Oxidation and Acetylation of 14α-Hydroxyprogesterone (VI).—14α-Hydroxyprogesterone (88 mg.) was dissolved in 1.6 ml. of chlorobenzene with warming. After cooling in an ice-bath a solution of 0.0532 g. of sodium dichromate dihydrate dissolved in 0.8 ml. of water and 0.135 ml. of sulfuric acid was added to the cooled steroid solution. The mixture was stirred vigorously for 2 hours in an ice-bath. The reaction mixture was diluted with water (making the acetic acid concentration less than 10%) and benzene added to bring the organic layer to the surface. The benzene layer was washed with water, 5% sodium bicarbonate solution then again with water, and was dried with anhydrous sodium sulfate. The crystalline material obtained by evaporation of the solvent was shown by infrared spectrum to be starting material.

When a sample of 14α-hydroxyprogesterone (50 mg.) was subjected to the conditions of mild acetylation with pyridine and acetic anhydride (1:1), standing overnight at room temperature, only starting material could be recovered.

Degradation of 14α-Hydroxyprogesterone (VI) to 14α-Hydroxyandrost-4-ene-3,17-dione (IV) by *P. lilacinum* (A.T.C.C. 10114).—To each of twenty erlenmeyer flasks (250-ml. capacity), each containing 100 ml. of medium E[21] were added spores of *P. lilacinum* and 10 mg. of compound VI. The flasks were closed with sterile gauze pads and then shaken for 72 hours at 25°. The fermentations were pooled and extracted with methylene chloride. Paper chromatography indicated that 20% of substrate and 20% of 14α-hydroxyandrostenedione were present in the extract (785 mg.). The extractives were dissolved in 35 ml. of benzene and chromatographed over 40 g. of alumina. The same sequence of solvents as described above was used. Fraction 24 (chloroform) weighed 103.0 mg. and consisted (by paper chromatography) of 22% of IV and 34% of substrate VI. Fraction 25 (acetone) weighing 116.5 mg. had a composition of 16% of IV and 1% of VI. This fraction was crystallized from 1 ml. of ethyl acetate by slow evaporation of the solvent. The product was then triturated with 2 ml. of ether and a few drops of acetone to give 20 mg. of crystals, m.p. 252–258°, identified by infrared spectrum as 14α-hydroxyandrostenedione (IV).

Acknowledgment.—We are grateful to Dr. J. L. Johnson and his associates for all spectrographic analyses; to W. A. Struck and associates for optical rotations and microanalyses; to Jennie M. Noteboom, Henrietta Triemstra, Hester Woltersom, Irene Pratt, G. Staffen and J. R. Heald for technical assistance.

(21) Medium E: cornsteep, 20 g.; potassium dihydrogen phosphate, 1 g.; Cerelose, 30 g.; sodium nitrate, 2 g.; magnesium sulfate, 0.5 g.; potassium chloride, 0.2 g.; ferrous sulfate, 0.01 g.; sodium acetate, 2 g.; distilled water to 1 liter.

KALAMAZOO, MICH.

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

D-Homosteroids. II. 17a-Ethinyl-D-homoetiocholane-3α,17a-diol-11-ones and Related Compounds[1]

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

RECEIVED OCTOBER 31, 1957

The Nef reaction with D-homoetiocholan-3α-ol-11,17a-dione gave a mixture of 17aα-ethinyl-D-homoetiocholane-3α,17aβ-diol-11-one and its 17a-epimer. The configuration of the two C_{17a}-epimers has been established by means of both physical and chemical evidence. Additionally, a number of compounds derived from or related to the ethinyl-epimers have been prepared; certain of these possess noteworthy endocrinological activity.

The initial approach to the synthesis of D-homopregn-4-ene-17aα,21-diol-3,11,20-trione 21-acetate (D-homocortisone acetate)[2] involved the introduction of an ethinyl group into D-homoetiocholan-3α-ol-11,17a-dione at the C^{17a}-position by means of the Nef reaction, followed by suitable transformation of the ethinyl group into the desired cortical side chain.[3]

Models of the normal (five-membered D-ring) steroid and of the D-homo (six-membered D-ring) steroid indicate a greater steric hindrance toward rearward approach (α-attack) in the latter system, due primarily to the effects of the axial hydrogens on C_{12}, C_{14} and C_{16}. Chemical reduction of the C_{17a}-ketone group, involving a normal equilibration reaction, gave predominantly the expected 17aβ-hydroxy (equatorial) epimer.[1] Although the Nef reaction may also be regarded as an equilibration reaction, steric effects prevent front-side attack in the normal steroids, and the 17β-ethinyl epimer is obtained in only 0.3% yield.[4] Similar effects have been noted with ethoxyacetylene.[5] In the D-homo

(1) Paper I, THIS JOURNAL, **79**, 6475 (1957).

(2) To be published.

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

(4) T. Reichstein and C. Meystre, *Helv. Chim. Acta*, **22**, 728 (1939).

(5) H. Heusser, K. Eichenberger and P. A. Plattner, *ibid.*, **33**, 370 (1950).

series the increased steric hindrance toward rearward approach should, partially at least, balance the total steric effect, and the result should be at worst a mixture enriched in the 17$\alpha\beta$-ethinyl isomer, and perhaps even containing a preponderance of the latter.

The treatment of D-homoetiocholan-3α-ol-11,-17a-dione with a metal acetylide under various conditions gave an excellent total yield of a mixture of the two epimeric 17a-ethinyl-D-homoetiocholane-3α,17a-diol-11-ones. The epimers were readily separable in a pure form by chromatography of their 3-acetates; under the most suitable conditions found for carrying out the Nef reaction the ratio of epimers was about seven to one. With the two C_{17a}-ethinyl epimers available it thus became possible to synthesize both D-homocortisone acetate and its C_{17a}-epimer. Initially, however, it was necessary to make configurational assignments to the two C_{17a}-ethinyl epimers.

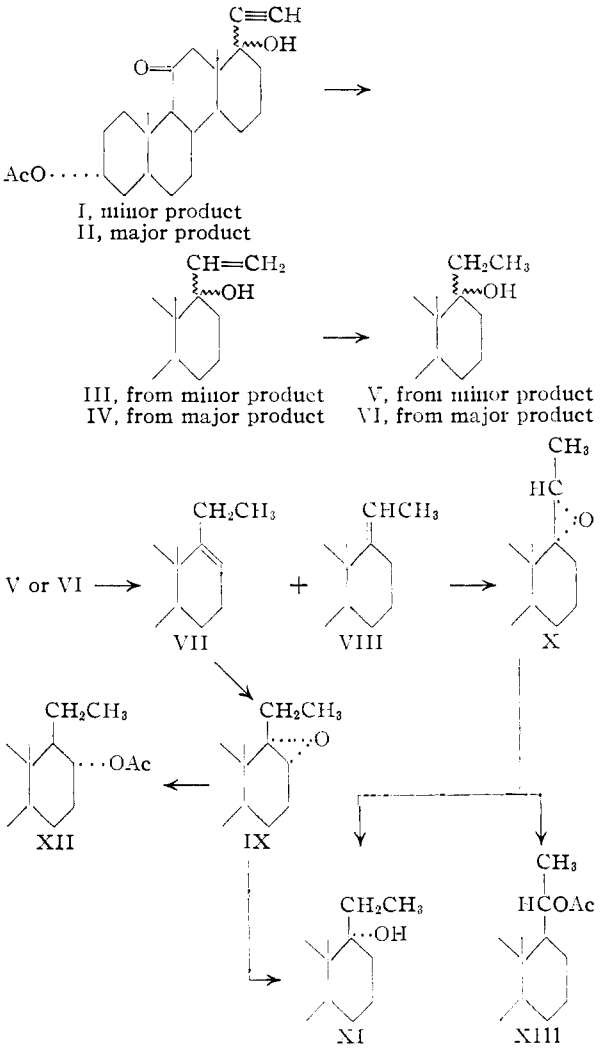
Preliminary, but inconclusive, evidence was provided by two observations: based upon analogy, the isomer eluted first from a chromatographic column should possess the 17aα-hydroxy (axial) configuration[6]; if biological activity were present, it should predominate in the 17aβ-hydroxy (equatorial) isomer.[7] The minor product (10–13%) (I) of the Nef reaction was eluted first from silica gel or acid-washed alumina columns; this compound was nearly inert endocrinologically, whereas the epimer II possessed considerable antiestrogenic activity in mice.[8] Although not determinant, the two unrelated observations were thus in agreement in predicting that the major product II possessed the 17aβ-hydroxy configuration. Further evidence was then sought in several ways, as detailed below.

Rate of Acetylation.—Initial data on the configuration of I and II were obtained by the determination of the rate of acetylation of the 17a-hydroxy groups. Accurately weighed samples of I and II were treated with a mixture of acetic anhydride, acetic acid and *p*-toluenesulfonic acid at room temperature under controlled conditions. The products were then worked up in the usual manner and quantitatively chromatographed on silica gel. The results are summarized in Table I. Since an equatorial hydroxyl group acetylates at the fastest rate, these data therefore indicate that I is the 17aβ-ethinyl-17aα-hydroxy compound and II is the 17aα-ethinyl-17aβ-hydroxy epimer.

TABLE I

Time of acetylation, hours	Yield of 17a-acetyl compound From I, %	From II, %
0.33	56.0	91.0
1.50	81.7	93.4
3.50	87.9	96.5

Epoxide Cleavage.—A second approach was based upon the observation by Barton[9] that when a steroid epoxide is cleaved by lithium aluminum hydride, both the resulting carbon–oxygen bond and the newly formed carbon–hydrogen bond are axial. Although the number of known examples is not large, no exceptions to this stereospecific reduction have been found. The two 17a-ethinyl epimers I and II were reduced to the corresponding 17a-vinyl compounds III and IV and thence to the two 17a-ethyl epimers[10,11] V and VI.



When either V or VI was dehydrated by means of boron trifluoride or *p*-toluenesulfonic acid in acetic acid solution, a *mixture* of the unsaturated products VII and VIII was obtained, in essentially quantitative yield.

In the case of the 17aα-ethyl-17aβ-hydroxy epimer the system 20-H, 20-C, 17a-C, 17aβ-OH (e), forms a plane suitable for normal *trans*-elimination[12] to yield the unsaturated isomer VIII. Similarly, the 17aβ-ethyl-17aα-hydroxy epimer should yield the unsaturated compound VII by *trans*-elimina-

(6) K. Savard, *J. Biol. Chem.*, **202**, 457 (1953); C. S. Barnes and A. Palmer, *Austr. J. Chem.*, **9**, 105 (1956).

(7) L. Ruzicka, N. Wahba, P. T. Herzig and H. Heusser, *Chem. Ber.*, **85**, 491 (1952).

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

(9) D. H. R. Barton, *J. Chem. Soc.*, 1033 (1953); E. J. Corey, THIS JOURNAL, **76**, 178 (footnote 20) (1954).

(10) Throughout the text and the Experimental section the compounds are named as derivatives of D-homoetiocholane rather than as D-homopregnane derivatives. The former nomenclature is used for the purpose of ensuring clarity and consistency.

(11) When a 1:1 mixture of V and VI was quantitatively chromatographed on silica gel, the compound V was eluted first, as shown by mixed m.p. and infrared spectra; *cf.* Ref. 6.

(12) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951).

tion from the coplanar system 17aα-OH (a), 17a-C, 17-C, 17-H (a). Under the highly acidic conditions used for the dehydration we would expect a certain amount of migration of the exocyclic double bond in VIII[13]; further, we cannot entirely discount the possibility of some *cis*-elimination by an ionic mechanism in either epimer.[14]

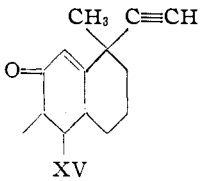
The mixture of VII and VIII could not be separated completely even by repeated chromatography.[15] An accurately weighed, chromatographically "pure" (free of 17a-hydroxy compounds) mixture of VII and VIII, derived from either V or VI, was treated with an excess of perbenzoic acid in benzene. The resulting mixture of 17,17a- and 17a,20-epoxides IX and X was purified by chromatography (separation could not be achieved). The mixed epoxides were reduced by refluxing with lithium aluminum hydride in tetrahydrofuran solution, and the crude product was acetylated and re-oxidized (at C_{11}) with chromium trioxide in acetic acid solution. Quantitative chromatography of the latter product on silica gel gave first a trace of resinous material (17- and/or 20-acetates, XII and XIII?) and then a series of crystalline fractions. Micro mixed melting points on these fractions showed no depression, and the infrared spectra were identical. The single product was shown by mixed melting point and comparison of the infrared spectra to be identical with V. The latter, therefore, should possess a 17a-axial hydroxy group and have the 17aβ-ethinyl structure.

Grignard Reaction.—The reaction of a Grignard reagent with the 17a-ketone group would take place normally by an irreversible mechanism. Since rearward approach of an alkyl group is blocked to a greater extent (by the 12 and 16-methylene groups) than front side attack, the reaction should be subject only to steric control, and the entering alkyl group should occupy the 17aβ-equatorial position.[16]

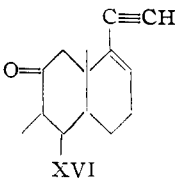
The reaction of an excess of ethylmagnesium bromide with D-homoetiocholan-3α-ol-11,17a-dione 3-acetate in tetrahydrofuran solution was shown by quantitative chromatography to yield a mixture of D-homoetiocholane-3α,17aβ-diol-11-one (63.7%)[17] and a *single* 17a-ethyl-D-homoetiocholane-3α,17a-diol-11-one (23.6%). The latter epimer was shown by mixed melting point and a comparison of the infrared spectra to be identical with V.

Dehydration Experiments.—Although dehydration of either V or VI under acidic conditions gave nearly the same equilibrium mixture of VII and VIII,[14] the equilibration should be preventable by conducting the dehydration under basic conditions. Accordingly, both V and VI were treated with phosphorus oxychloride in pyridine solution for four days at room temperature. Under these conditions V was recovered unchanged quantitatively, but VI was converted into a colorless resin. The latter material was ozonized at 0°, the ozonide was reduced by Raney nickel, and the resulting crystalline product was quantitatively chromatographed on silica gel. There was thus obtained a 70.3% over-all yield of pure D-homoetiocholan-3α-ol-11,17a-dione 3-acetate, identified by mixed melting point and a comparison of the infrared spectra. The dehydration of VI under those conditions therefore gave VIII, which could be derived by *trans* coplanar elimination only from the 17aα-ethyl-17aβ-hydroxy epimer.[18] Furthermore, the *lack* of dehydration with V under these conditions is also presumptive evidence, since a model indicates very considerable steric hindrance to the attack of phosphorus oxychloride on the 17aα-hydroxy (axial) group; in effect the latter occupies a "cup" formed by the C_{12}, C_{14} and C_{16} axial hydrogens.

Under similar conditions (phosphorus oxychloride–pyridine, six days at 25°) compound I was recovered unchanged, although here again *trans* coplanar elimination theoretically can occur if the compound has the 17aα-hydroxy configuration. The epimer, II, on the other hand, gave a highly colored resin, which was shown by chromatography to consist of a mixture of II and an unidentified resinous product. Ionic elimination in the latter case could, for example, produce a retropinacolic rearrangement to XV or formation of the ene–yne system XVI.



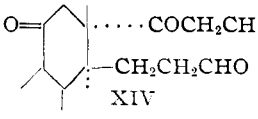
XV



XVI

The resinous product, however, showed only end absorption in the ultraviolet, and the infrared spectra gave no indication of the presence of an ethinyl group. The structure could not, therefore, be either XV or XVI.

While no single experiment among the above may be said to provide unequivocal proof of configuration, there is an overwhelming amount of presumptive evidence, and on this basis we assigned the configuration 17aβ-ethinyl-D-homoethiocholane-3α,-17aα-diol-11-one to the minor product from the Nef



XIV

(13) O. Wallach, E. Evans, J. B. Churchill, M. Rentschler and H. Mallison, *Ann.*, **360**, 26 (1908); R. Turner and R. Garner, THIS JOURNAL, **79**, 253 (1957); B. R. Fleck, *J. Org. Chem.*, **22**, 439 (1957); H. C. Brown, *ibid.*, **22**, 439 (1957).

(14) Treatment of V or VI under identical conditions gave *ca.* 97% yields of the chromatographed mixture of VII and VIII. Ozonolysis at 0° followed by reduction with Raney nickel gave, after quantitative chromatography, a 54% yield of D-homoetiocholan-3α-ol-11,17a-dione 3-acetate from V and a 63% yield of the same product from VI. This difference in yield is indicative, but not entirely statistically significant. No attempt was made to isolate the other possible product, XIV.

(15) *Cf.* related experiments in the normal steroid series: L. H. Sarett, THIS JOURNAL, **71**, 1169, 1175 (1949).

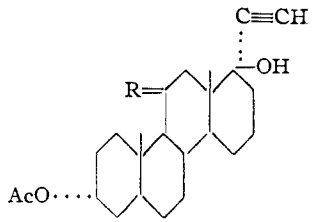
(16) This is partially a function, of course, of the size and electronegativity of the entering R group in comparison to the hydroxyl group. In the case of a methyl Grignard reagent in the D-homoandrostene series, the reaction has been shown to proceed entirely as predicted, to give exclusively the 17aβ-methyl epimer.[7]

(17) The amount of reduction occurring during the reaction could probably be decreased by adding magnesium bromide; *cf.* C. G. Swain and H. B. Boyles, THIS JOURNAL, **73**, 870 (1951).

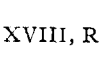
(18) A similar observation has been made with 17aα-methyl-D-homoandrost-5-ene-3β,17aβ-diol: H. Heusser, N. Wahba and F. Winternitz, *Helv. Chim. Acta*, **37**, 1052 (1954); R. B. Turner, R. Anliker, R. Helbling, J. Meier and H. Heusser, *ibid.*, **38**, 411 (1955).

reaction (I); the corresponding configurations of II–VI therefore were demonstrated also.

The observed anti-estrogenic activity of 17aα-ethinyl - D - homoetiocholane - 3α,17aβ - diol - 11-one (see above) led to the preparation of two other related 17aα-ethinyl derivatives, shown in XVII–XVIII.



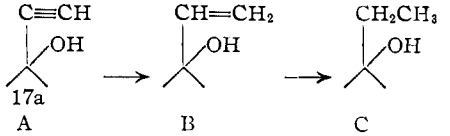
XVII, R = 

XVIII, R = 

Neither of the latter compounds was as active as 17aα-ethinyl-D-homoetiocholane-3α,17aβ-diol-11-one.[8] In the compounds XVII–XVIII the configurational assignments were made on the basis of analogy; some experimental evidence in favor of these assignments was found (*cf.* Table II).

TABLE II

ΔMD VALUES FOR THE REDUCTION OF THE 17a-ETHINYL GROUP



D-Homosteroid	M_{DA}	M_{DB}	M_{DC}	$M_{DA} - M_{DB}$	$M_{DB} - M_{DC}$
3α-Acetoxy-17aα-hydroxy-11-keto-	+265	+130	+211	+135	−81
3α-Acetoxy-17aβ-hydroxy-11-keto-	+ 3	+210	+195	−237	+45
3α-Acetoxy-11β,17aβ-dihydroxy-	+123	+247	+214	−124	+33
3α,11α-Diacetoxy-17aβ-hydroxy-	−189	− 10	− 13	−179	+ 3

Endocrinological activity also was found in several other compounds prepared in the present work.[8] The 17aα - vinyl - D - homoetiocholane-3α,17aβ-diol-11-one exhibited antiestrogenic activity and inhibited the thymolytic activity of cortisone acetate. 17aα-Ethyl-D-homoetiocholan-17aβ-ol-3,11-dione showed similar activity; again, as noted above, the related 17aα-hydroxy-epimers of these compounds were either much less active or were devoid of activity.

Experimental[19]

The Ethinylation of D-Homoetiocholan-3α-ol-11,17a-dione.—To 9 l. of *t*-butyl alcohol was added 330 g. (5.0 moles) of flake C.P. potassium hydroxide. The mixture was stirred under reflux for 0.5 hour and then distilled until a total of 1500 ml. of distillate had been collected. The resulting solution was cooled under nitrogen, and then saturated with purified acetylene[20] at room temperature (5 hours); 300 g. (0.83 mole) of D-homoetiocholan-3α-ol-11,17a-dione 3-acetate was added and the mixture was stirred for 8 hours while passing into it a slow stream of purified acetylene. The mixture was allowed to stand overnight, one liter of water was added, and the dark red colored solution was refluxed for one hour. Concentrated hydrochloric acid was then added slowly, with external cooling, until the color changed to straw-yellow, and the *t*-butyl alcohol was then distilled off *in vacuo*. The residual slurry was filtered and the insoluble material, after thorough washing with water, was dried at 70°. The *crude* product weighed 284.7 g. (99.5%) and melted at 199–214°. Fractional recrystallization from ethyl acetate gave directly 151.0 g. of **17aα-ethinyl-D-homoetiocholane-3α,17aβ-diol-11-one**, large transparent prisms, m.p. 223.5–226.0°, $[\alpha]_D$ +0.8°; λ_{max}^{KBr} 3.03, 3.12 (≡C–H); 4.79 (C≡C); 5.89 (C=O) μ.

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.68; H, 9.26.

The combined residues from the fractional recrystallization were acetylated by heating for 0.5 hour on the steam-bath with a mixture of 300 ml. of acetic anhydride and 150 ml. of C.P. pyridine. The mixture was quenched in cold dilute sulfuric acid and the insoluble gum was extracted into methylene dichloride. The methylene dichloride extract was washed with water and with dilute sodium bicarbonate solution and, after drying over anhydrous sodium sulfate, evaporated to dryness. The residual gum was divided into four equal portions and each portion was separately chromatographed on 800 g. of silica gel (initially in 15% ether-*n*-pentane). The columns were successively eluted with 12 × 800 ml. of 15% ether-*n*-pentane, 9 × 800 ml. of 20% ether-*n*-pentane, 36 × 800 ml. of 22.5% ether-*n*-pentane and 22 × 800 ml. of 30% ether-*n*-pentane. Fractions numbered 58–78 from each column were crystalline, and after combining and recrystallizing from Skellysolve C there was obtained pure **17aα-ethinyl-D-homoetiocholane-3α,17aβ-diol-11-one 3-acetate (II)**, massive needles of m.p. 205.0–207.2°, $[\alpha]_D$ +28.9°.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.56; H, 8.87. Found: C, 74.42; H, 8.73.

The crystalline fractions numbered 30–40 from each column were combined and recrystallized from Skellysolve C: **17aβ-Ethinyl-D-homoetiocholane-3α,17aα-diol-11-one 3-acetate (I)** formed large prisms of m.p. 189.4–190.4°, $[\alpha]_D$ +69.2°. The infrared spectra of I and II differed only in the fingerprint region.

Anal. Found: C, 74.79; H, 8.71.

Rechromatography of the mother liquor material from I and II, as well as the pooled intermediate chromatographic fractions, finally furnished a total of 38.3 g. of I and 88.0 g. of II. This made the total yield of pure ethinylated products equivalent to 263.7 g. (92%) when calculated as the 3-hydroxy compound. On a relative basis the amount of I obtained corresponded to 13% of the total pure epimers. In other preparations the yield of I varied between 10–13% on a relative basis. Similar results were obtained when the Nef reaction was carried out utilizing potassium *t*-butoxide or *t*-amyl oxide in the appropriate anhydrous alcohol,[21] but the relative yield of I dropped to 4% when lithium *t*-butoxide in anhydrous *t*-butyl alcohol was used for the ethinylation.

Saponification of I by means of an aqueous methanolic potassium carbonate solution gave **17aβ-ethinyl-D-homoetiocholane-3α,17aα-diol-11-one**, thick triangular crystals from ethyl acetate, m.p. 260.7–263.0°, $[\alpha]_D$ +62.2° (acetic acid).

Anal. Found: C, 76.80; H, 9.06.

On refluxing a solution of 17aα-ethinyl-D-homoetiocholane-3α,17aβ-diol-11-one and an excess of succinic anhydride in pyridine for 3 hours there was obtained, after the usual workup, an 87% yield of **17aα-ethinyl-D-homoetiocholane-3α,17aβ-diol-11-one 3-hemisuccinate**, massive prisms from ether-*n*-hexane, m.p. 174.4–176.6°, $[\alpha]_D$ +28.2°. The compound was readily soluble in dilute sodium bicarbonate solution.

Anal. Calcd. for $C_{26}H_{36}O_6$: C, 70.24; H, 8.16; neut. equiv., 444.5. Found: C, 69.98; H, 8.24; neut. equiv., 443.0.

17aα-Ethinyl-D-homoetiocholane-3α,11α,17aβ-triol 3,11-Diacetate (XVII).—D-Homoetiocholane-3α,11α-diol-17a-one 11-acetate[1] (11.0 g.) was ethinylated by treatment with po-

(19) All melting points are corrected. Unless otherwise noted, the rotations were determined in chloroform solution at 25°, $c \sim 1\%$. 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.

(20) Tank acetylene was passed through efficient gas washing towers containing cold water (two), concentrated sulfuric acid (three) and soda-lime (two).

(21) *Cf.* C. Djerassi, R. Yashin and G. Rosenkranz, THIS JOURNAL, **72**, 5750 (1950).

tassium acetylide (from a 6-mole proportion of potassium butoxide in anhydrous *t*-butyl alcohol) and excess acetylene at room temperature for 8 hours. The reaction product was poured into a large volume of water and the mixture was allowed to stand overnight at room temperature. The crude product was isolated by filtration and saponified by refluxing for 1 hour with methanolic potassium hydroxide. After the usual workup there was obtained 10.2 g. of the crude triol, m.p. 199–214°. The material could not be purified successfully by recrystallization because of a tendency to gel, and therefore was re-acetylated by heating for 1 hour on the steam-bath with acetic anhydride–pyridine. The resulting 3,11-diacetate was chromatographed on silica gel. The fractions eluted by 40% ether–*n*-pentane[22] of m.p. above 215° were combined (9.9 g.) and recrystallized from benzene–*n*-hexane. The pure compound formed needles of m.p. 222.2–224.1°, $[\alpha]_D$ −43.8°.

Anal. Calcd. for $C_{26}H_{38}O_5$: C, 72.52; H, 8.90. Found: C, 72.39; H, 8.69.

17aα-Ethinyl-D-homoetiocholane-3α,11β,17aβ-triol 3-Acetate (XVIII).—Eleven grams of D-homoetiocholane-3α,-11β-diol-17a-one 3-acetate[1] were ethinylated as outlined above for the 11α-epimer. The crude, resinous product was acetylated (acetic anhydride–pyridine, 0.5 hour at 95°) and then chromatographed on silica gel. After preliminary elution with 10% ether–*n*-pentane and 30% ether–*n*-pentane, careful elution with 40% ether–*n*-pentane gave two distinct series of crystalline fractions, sharply separated by a series of small oily fractions. The first series of fractions were combined and recrystallized from Skellysolve C to yield 1.2 g. of recovered D-homoetiocholane-3α,11β-diol-17a-one 3-acetate.

The second series of crystalline fractions from the chromatogram were combined and recrystallized from benzene. There was thus obtained 5.3 g. of the title compound, XVIII, as white needles of m.p. 202.7–205.2°, $[\alpha]_D$ +31.7°.

Anal. Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.31; H, 9.60.

Preparation of the 17a-Vinyl-D-homoetiocholanes.—All of the 17a-vinyl compounds were prepared by the catalytic reduction of the corresponding 17a-ethinyl compound in pyridine solution at 25° and 3 atm. pressure, utilizing a 2% palladium hydroxide–strontium carbonate catalyst. The reductions were rapid (usually after a 4–10 minute lag) and gave the pure 17a-vinyl compound in 90–100% yield.

17aα-Vinyl-D-homoetiocholane-3α,17aβ-diol-11-one, large rectangular plates from ethyl acetate, m.p. 204.8–206.6°, $[\alpha]_D$ +30.2°; λ_{max}^{KBr} 2.98 (OH), 5.42 (CH=CH), 5.93 (C=O) μ.

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.25; H, 9.89. Found: C, 76.20; H, 9.80.

The 3-acetate IV formed long slender rods from methanol, m.p. 218.6–223.0°, $[\alpha]_D$ +61.7°. *Anal.* Calcd. for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.24; H, 9.42.

17aβ-Vinyl-D-homoetiocholane-3α,17aα-diol-11-one, large brilliant prisms from ethyl acetate, m.p. 223.0–226.1°, $[\alpha]_D$ −1.7°. *Anal.* Found: C, 75.93; H, 9.71.

The 3-acetate III crystallized from ethyl acetate in small prisms, m.p. 200.4–202.6°, $[\alpha]_D$ +33.5°. *Anal.* Found: C, 74.01; H, 8.90.

17aα-Vinyl-D-homoetiocholane-3α,11α,17aβ-triol 3,11-diacetate, rosettes of needles from Skellysolve C, m.p. 170.8–175.0°, $[\alpha]_D$ −2.2°. *Anal.* Calcd. for $C_{28}H_{40}O_5$: C, 72.19; H, 9.32. Found: C, 71.81; H, 9.31.

17aα-Vinyl-D-homoetiocholane-3α,11β,17aβ-triol 3-acetate, colorless prisms from ethyl acetate, m.p. 165.7–168.0°, $[\alpha]_D$ +63.3°. *Anal.* Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.75; H, 9.74.

Preparation of the 17a-Ethyl-D-homoetiocholanes.—The 17a-ethyl-D-homoetiocholanes were prepared by the catalytic reduction at 25° and about 3 atm. pressure of the corresponding 17a-ethinyl- or 17a-vinyl-D-homoetiocholanes in ethanol solution, using platinum oxide as catalyst. The yields were high in all cases.

17aα-Ethyl-D-homoetiocholane-3α,17aβ-diol-11-one, thick prisms from ethyl acetate, m.p. 185.7–187.5°, $[\alpha]_D$ +32.4°. *Anal.* Calcd. for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 76.12; H, 10.38.

(22) A small amount of material (insufficient for characterization) of m.p. 161–165° was eluted first. This material may correspond to the 17aβ-ethinyl isomer.

The 3-acetate VI crystallized from methanol in silky needles, m.p. 207.3–209.8°, $[\alpha]_D$ +56.0°. *Anal.* Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 74.20; H, 9.50.

17aβ-Ethyl-D-homoetiocholane-3α,17a-α-diol-11-one, prisms from ethyl acetate–Skellysolve C, m.p. 148.9–150.6°, $[\alpha]_D$ +30.1°. *Anal.* Found: C, 76.02; H, 10.10.

The 3-acetate V formed diamond-shaped laminae from Skellysolve C, m.p. 207.5–211.2°, $[\alpha]_D$ +53.9°. The mixed m.p. of V and VI was 172–183°; additionally the infrared spectra of the compounds differed only in the fingerprint region. *Anal.* Found: C, 73.78; H, 9.97.

17aα-Ethyl-D-homoetiocholane-3α,11α,17aβ-triol 3,11-diacetate, prisms from Skellysolve C, m.p. 197.0–199.8°, $[\alpha]_D$ −3.0°. *Anal.* Calcd. for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74. Found: C, 72.12; H, 9.65.

17aα-Ethyl-D-homoetiocholane-3α,11β,17aβ-triol 3-acetate, needles from benzene, m.p. 194.2–197.3°, $[\alpha]_D$ +54.5°. *Anal.* Calcd. for $C_{24}H_{40}O_4$: C, 73.43; H, 10.27. Found: C, 73.30; H, 10.26.

17aα-Ethinyl-D-homoetiocholan-17aβ-ol-3,11-dione.—To a mixture of 500 ml. of dry toluene, 50 ml. of redistilled cyclohexanone and 6.0 g. of aluminum isopropoxide was added 5.0 g. of 17aα-ethinyl-D-homoetiocholane-3α,17aβ-diol-11-one. The resulting solution was distilled slowly at atmospheric pressure until a total of 200 ml. of distillate had been collected (2 hours); water was then added and the mixture was steam distilled for 3.5 hours. To the still residue was added 50 ml. of 6 *N* sulfuric acid and 200 ml. of ethyl acetate and, after mixing well, the ethyl acetate layer was separated, washed with water and with sodium bicarbonate solution, and dried over anhydrous sodium sulfate. Evaporation to a small volume and dilution of the residual solution with *n*-pentane gave 4.2 g. of crude product, m.p. 189–206°. Recrystallization did not effect purification; the crude product was therefore chromatographed on silica gel. Elution with 40% ether–*n*-pentane gave a series of crystalline fractions,[23] which were combined and recrystallized from ethyl acetate. The product formed prisms of m.p. 221.2–225.0°, $[\alpha]_D$ +12°. The compound gave a mixed m.p. depression with the starting 3α-ol.

Anal. Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.42; H, 8.57.

17aβ-Ethyl-D-homoetiocholan-17aα-ol-3,11-dione.—To a solution of 1.66 g. of 17aβ-ethyl-D-homoetiocholane-3α,-17aα-diol-11-one in 120 ml. of pure acetone was added 20 ml. of water and one small drop of a 30% solution of hydrogen bromide in glacial acetic acid. The solution was cooled to 10° and treated with 1.0 g. (1.5-mole proportion) of N-bromoacetamide; when solution of the latter was complete the mixture was stored at 5° for 17 hours. The resulting colorless solution was treated with zinc dust and acetic acid and worked up in the usual manner.[1] The crude product weighed 1.58 g. and melted at 137–140°. Recrystallization from dilute methanol and from an ethyl acetate–Skellysolve C mixture gave pure material: leaflets of m.p. 142.0–143.4°, $[\alpha]_D$ +36.9°.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.25; H, 9.89. Found: C, 76.33; H, 9.95.

17aα-Ethyl-D-homoetiocholan-17aβ-ol-3,11-dione.—The oxidation of 17aα-ethyl-D-homoetiocholane-3α,17aβ-diol-11-one by means of N-bromoacetamide, as outlined above for the epimer, gave a 71% yield of pure product. Utilization of the chromium trioxide–pyridine reagent of Sarett[24] gave a nearly quantitative yield of pure product: rosettes of cottony needles from ethyl acetate–Skellysolve C, m.p. 183.7–186.5°, $[\alpha]_D$ +41.2°.

Anal. Found: C, 76.00; H, 9.60.

17a-Ethyl-D-homoetiochol-17(17a)-en-3α-ol-11-one and 17a-Ethylidene-D-homoetiocholan-3α-ol-11-one. A. The Formic Acid Dehydrations.—A solution of 1.5 g. of 17aα-ethyl-D-homoetiocholane-3α,17aβ-diol-11-one in 25 ml. of 98–100% formic acid was refluxed for 2.25 hours. The resulting dark green, opaque mixture was diluted with water and extracted with ether in the usual manner. The ethereal residue was an orange-colored resin. The resinous product was chromatographed on silica gel and after preliminary

(23) Elution with 50% ether–*n*-pentane gave a small amount of recovered 3α-ol.

(24) G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, THIS JOURNAL, **75**, 422 (1953).

elution with 5% ether–*n*-pentane the fractions eluted with 10% ether–*n*-pentane were combined and saponified with aqueous-methanolic potassium carbonate solution. After recrystallization from Skellysolve C there was obtained 0.79 g. of product, m.p. 128–150°, $[\alpha]_D$ +21.4°. A second experiment, using a 1.5-hour reflux period, gave material with m.p. 107–136°, $[\alpha]_D$ +33°.

Anal. Calcd. for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.50, 79.55; H, 10.12, 10.35.

B. Boron Trifluoride or *p*-Toluenesulfonic Acid.—To a solution of 2.00 g. of the pure 17a-ethyl-D-homoetiocholane-3α,17a-diol-11-one 3-acetate epimer (either V or VI) in 100 ml. of C.P. glacial acetic acid and 20 ml. of C.P. acetic anhydride was added 2.0 ml. of 47% boron trifluoride etherate or 2.00 g. of *p*-toluenesulfonic acid monohydrate. The solution was held at room temperature for 4–8 hours and then quenched in 800 ml. of water. The precipitated gummy product was extracted by methylene dichloride in the usual manner, and the resulting resinous material obtained by evaporation of the extracts was chromatographed on 200 g. of silica gel. After preliminary elution with 5–7.5% ether–*n*-pentane, the products were eluted with 10% ether–*n*-pentane. From either epimer V or VI, utilizing either dehydration catalyst, there was obtained a 94–97% yield of analytically pure semi-crystalline product (a mixture of VII and VIII). Separation of the mixture into the components could not be achieved.

C. Constitution of the Dehydration Products.—Two-gram samples of V and VI were separately dehydrated by means of *p*-toluenesulfonic acid monohydrate as outlined above (4 hours standing). The resulting products (96–97% yields of the chromatically purified dehydration products) were separately dissolved in 100 ml. of C.P. acetone and treated with an excess of ozone at 0°. To the cold acetone solution of the ozonide was added *ca.* 20 g. (wet weight) of Raney nickel (prewashed with water, absolute alcohol and acetone) and the mixture was stirred at room temperature for 18 hours. The mixture was filtered and the catalyst was washed thoroughly with dry acetone. Evaporation of the combined filtrates gave a semi-crystalline product in each case. This material was quantitatively chromatographed on silica gel. From V there was obtained a 54.5% (over-all) yield of D-homoetiocholane-3α-ol-11,17a-dione 3-acetate and from VI a 63% yield of the same compound; in each case identification was made by mixed m.p. and infrared spectra comparison. No attempt was made to isolate or identify cleavage product(s) arising from the 17,17a-double bond (*cf.* XIV).

Configurational Experiments

Rate of Acetylation.—To a solution of 2.00 g. of pure *p*-toluenesulfonic acid monohydrate in 100.0 ml. of C.P. glacial acetic acid and 20.0 ml. of C.P. acetic anhydride was added in one portion 2.000 g. of pure 17a-ethinyl-D-homoetiocholane-3α,17a-diol-11-one 3-acetate epimer (I or II). The mixture was shaken until solution was complete (very rapid solution) and then allowed to stand at room temperature (23–24°). At the expiration of a definite period of time (measured from the time of addition of I or II) the clear solution was quenched in 2 liters of water and the resulting mixture was allowed to stand for 15 minutes to ensure hydrolysis of all acetic anhydride. The mixture was extracted with four 50-ml. portions of methylene dichloride and the extracts were washed with water and with dilute sodium bicarbonate solution. After drying, the combined extracts were evaporated to dryness. The resulting crystalline material was quantitatively chromatographed on 200 g. of silica gel, initially in 10% ether–*n*-pentane. The 3,17a-diacetates were eluted with 22.5% ether–*n*-pentane, followed by the 3-monoacetates on elution with 25% ether–*n*-pentane. The yield of the 3,17a-diacetates as a function of time and configuration are summarized in Table I.

17aα-Ethinyl-D-homoetiocholane-3α,17aβ-diol-11-one 3,17a-diacetate, large prisms from Skellysolve C or from methanol, m.p. 205.6–207.7°, resolidified and remelted at 214.4–217.6°, $[\alpha]_D$ +56.0°. *Anal.* Calcd. for $C_{26}H_{36}O_5$: C, 72.86; H, 8.47. Found: C, 72.71; H, 8.19.

17aβ-Ethinyl-D-homoetiocholane-3α,17aα-diol-11-one 3,17a-diacetate, cottony needles from methanol, m.p. 204.6–205.4°, $[\alpha]_D$ +69.9°. *Anal.* Found: C, 72.64; H, 8.34.

Epoxide Cleavage.—A solution of 3.52 g. (0.00947 mole) of the analytically pure mixture of VII and VIII[25] in 35 ml. of C.P. benzene was cooled to 10° and there was added 50 ml. of a solution of perbenzoic acid in benzene (55 mg./ml., 0.02 mole). The resulting solution, after standing at 5° for 20 hours, was washed with sodium bicarbonate solution and with sodium bisulfite solution. After drying, the benzene was removed *in vacuo* and the residual resin was chromatographed on 220 g. of silica gel. After preliminary elution with 5, 7.5, 10 and 15% ether–*n*-pentane mixture, a series of crystalline fractions (m.p. in the range 92–120°) was eluted with 20% ether–*n*-pentane. The combined fractions (3.10 g., theoretical 3.67 g.) were refluxed with 1.50 g. of lithium aluminum hydride in 375 ml. of pure tetrahydrofuran for 1.5 hours and then allowed to stand overnight at room temperature. The excess lithium aluminum hydride was destroyed by the addition of ethyl acetate, 100 ml. of saturated Rochelle salt solution was added, and the organic solvents were removed *in vacuo*. The residue was diluted with water and the gummy product was extracted into methylene dichloride in the usual manner. Evaporation of the washed and dried methylene dichloride extracts gave 2.60 g. (theoretical 2.80 g. based upon the weight of epoxide taken) of a colorless resin. The latter product was acetylated at room temperature overnight by means of an acetic anhydride–pyridine mixture and then worked up in the usual manner to give 2.92 g. of resinous product (theoretical for mono-acetylation 2.91 g., for diacetylation 3.23 g.). Re-oxidation to the 11-one was carried out by treatment of a solution of the acetylated product in 20 ml. of glacial acetic acid with a solution of chromium trioxide in 5 ml. of water and 15 ml. of glacial acetic acid, at room temperature for 1 hour. The resulting mixture was quenched in water containing a slight excess of sodium bisulfite and extracted with methylene dichloride. After washing and drying, the methylene dichloride extracts were evaporated *in vacuo*. There was obtained 2.82 g. (theoretical 2.89 g. for a mono-acetate) of product as a colorless glass. This material was quantitatively chromatographed on 200 g. of silica gel. Elution with 10% ether–*n*-pentane (6 × 400 ml.), 15% ether–*n*-pentane (12 × 400 ml.) and 20% ether–*n*-pentane (9 × 400 ml.) removed only traces of material from the column. Elution with 25% ether–*n*-pentane (10 × 400 ml.) gave a total of 0.62 g. of resinous material.[26] Elution with 30% ether–*n*-pentane (16 × 400 ml.) gave a series of crystalline fractions (1.29 g.) which appeared to be uniform in composition by mixed m.p. and infrared determinations. Recrystallization from ethyl acetate gave 1.19 g. of pure 17aβ-ethyl-D-homoetiocholane-3α,17aα-diol-11-one 3-acetate (XI ≡ V), m.p. and mixed m.p. 208.0–210.5°, infrared spectra identical.

Continued elution of the chromatographic column gave no material corresponding to the epimer,[27] although traces of more highly polar materials were eluted at high ether concentrations. It must therefore be concluded that V was the only 17a-hydroxy epimer formed during the reactions.

Grignard Synthesis.—To a solution of 1.0 mole of ethylmagnesium bromide in 1000 ml. of tetrahydrofuran was added slowly, with stirring, a solution of 18.0 g. (0.05 mole) of D-homoetiocholan-3α-ol-11,17a-dione 3-acetate in 250 ml. of tetrahydrofuran. The resulting solution was refluxed for 18 hours, cooled in an ice-bath, and treated slowly with 250 ml. of a saturated aqueous solution of ammonium chloride. The tetrahydrofuran was removed *in vacuo* and the product was isolated with methylene dichloride. The crystalline residue obtained by evaporation of the methylene dichloride extract was triturated with 75 ml. of absolute ether, the mixture was filtered, and the insoluble material was washed with absolute ether. The ether-insoluble material weighed 8.4 g.; the latter was identified by mixed m.p. and by chemical evidence as D-homoetiocholane-3α,-

(25) The mixture was composed of 1.759-g. and 1.763-g. portions, derived respectively from V and VI, dehydrated by means of boron trifluoride.

(26) This material could not be obtained crystalline even on re-chromatography, or hydrolysis and re-chromatography. All of the evidence indicated that this mixture consisted essentially of XII and/or XIII plus traces of XI.

(27) It was found experimentally that chromatography of a mixture consisting of equal weights of V and VI on silica gel, under conditions identical with the above, gave a sharp separation of V and VI. Further, V came off the column *first*.

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]

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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).