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# GROUP TRANSFER AND RING CONTRACTION PHENOMENA IN THE D-HOMOSTEROID SERIES[1]

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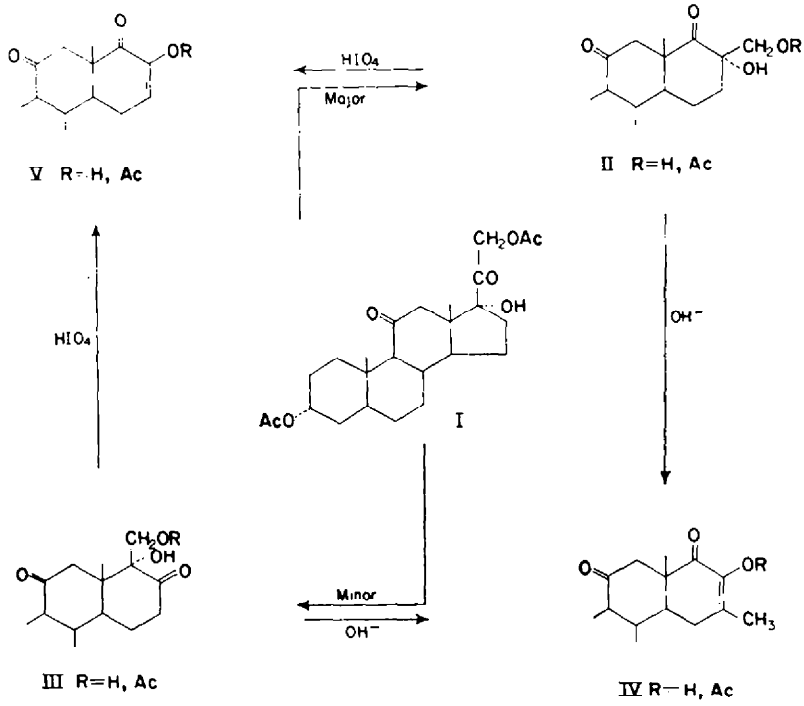
**Abstract**—The D-homoketols arising from 17,21-dihydroxy-20-ketosteroids with aluminum alkoxides were observed to undergo alkaline catalyzed rearrangement with group transfer to yield diosphenols. The latter on more vigorous alkaline treatment suffered unidirectional benzilic acid ring contraction to afford 17$\beta$-hydroxyisoetianic acids. In the presence of formaldehyde and alkali, on the other hand, these same diosphenols were initially hydroxymethylated followed by ring-contraction to lactones.

IN an earlier account the D-ring expansion of 17$\alpha$-hydroxy-21-acetoxy cortical systems with Lewis acids was shown to give 17a-ketonic systems as the major product.[2] Under these conditions 3$\alpha$,17$\alpha$,21-trihydroxypregnane-11,21-dione-3,21-diacetate (I) provided the 17a-ketone (II, R = Ac) as the major product accompanied by the 17-ketone (III, R = Ac) as the minor component. Room temperature alkaline

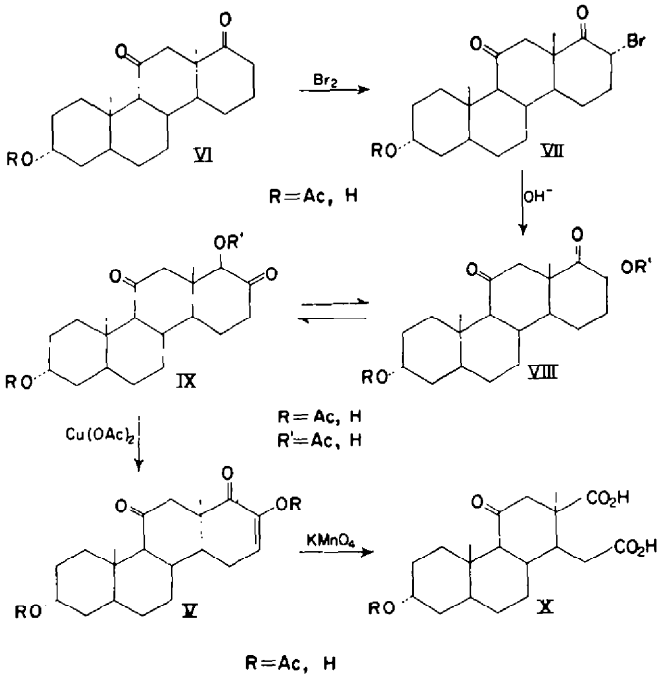



[1] A preliminary account of certain aspects of this work was communicated earlier. N. L. Wendler and D. Taub, *Chem. & Ind.* 415 (1958).

[2] N. L. Wendler and D. Taub, *Chem. & Ind.* 822 (1957); *J. Amer. Chem. Soc.* **80**, 3402 (1958).

hydrolysis of II (R = Ac) and III (R = Ac) provided the corresponding 3α,17α,21- and 3α,17aα,21-triols respectively. The latter triols on periodate cleavage both afforded the diosphenol V, in turn oxidizable by potassium permanganate to the known etiobilianic acid X.[3] The diosphenol (V) was also synthesized by an independent route emanating from the 17a-ketone (VI).[4] The latter was brominated and the bromo derivative (VII) converted with aqueous alkali in tetrahydrofuran to the ketol (VIII) and/or its positional isomer (IX, R = R′ = H). Copper acetate oxidation of the resultant ketol afforded diosphenol (V, R = H) identical with that obtained from the periodate cleavage of the D-homoketols II and III.

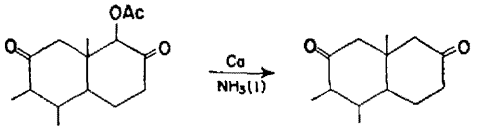
The configuration of the bromoketone VII was shown to be predominantly equatorial by bromination of the parent compound VI (R = H) and determination




of its infrared spectrum; the latter indicated not only the 11C=O at 5·83 μ but also a band at 5·76 μ of nearly the same intensity characteristic of a carbonyl group displaced in band position by an equatorial bromine.[5] The 3-monoacetate VIII and/or IX (R = Ac; R′ = H) was obtained by room temperature hydrolysis of VII (R = Ac) in tetrahydrofuran with aqueous 50 per cent potassium hydroxide in a two-phase system. This product exhibited in its infrared spectrum a single OH band at 2·84 μ characteristic of an equatorial ketol hydroxyl function. If the ketolic hydroxyl function had been axial, a double peak at 2·78 μ and 2·85–2·9 μ would have been anticipated.[3] This product, VIII and/or IX (R = Ac; R′ = H), was converted to its diacetate derivative, VIII and/or IX (R = R′ = Ac) with acetic anhydride in pyridine. The latter appeared to be an isomeric mixture inasmuch as it could not be

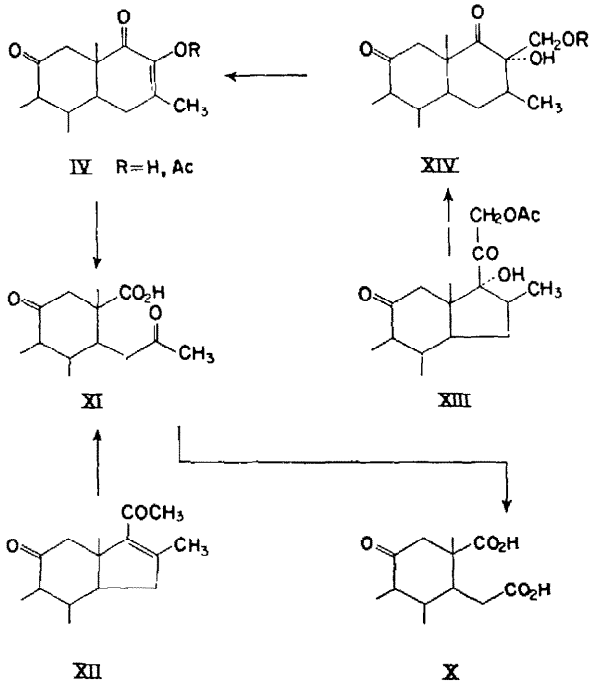
[3] N. L. Wendler, D. Taub, S. Dobriner and D. K. Fukushima, *J. Amer. Chem. Soc.*, **78**, 5027 (1956).
[4] N. L. Wendler, D. Taub and H. L. Slates, *J. Amer. Chem. Soc.* **77**, 3559 (1955).
[5] R. W. Jones, D. A. Ramsay, F. Herling and K. Dobriner, *J. Amer. Chem. Soc.* **74**, 2828 (1952).

separated by chromatography into sharp melting fractions. Reduction of the latter with calcium in liquid ammonia according to the Glaxo procedure[6] produced the 17-ketone (Xa) as the only identifiable product. The amount of Xa formed, however, was insufficient to permit a meaningful estimation of the content of its precursor IX in the original ketol equilibrium.




IX (R = R' = Ac) Xa

Treatment of both D-homo isomers II and III with hot 10 per cent methanolic potassium hydroxide evoked a unique transfer of the hydroxymethyl group leading to the diosphenol (IV). The structure of this methyl diosphenol (IV) was variously established. Oxidation, for example, of its acetate derivative with potassium permanganate afforded the methyl ketonic acid (XI) identical by infrared comparison with a sample prepared from the 16-methyl-$\Delta^{16}$-20-ketone (XII)[7] by similar oxidation. The methyl ketonic acid (XI) could be oxidized further with sodium hypoiodite to iodoform and the etiobilianic acid (X). By another approach 3α,17α-dihydroxy-21-acetoxy-16β-methylpregnane-11,20-dione (XIII)[7a] was D-homoannulated with aluminum alkoxide to the 17a-ketone (XIV). The latter on hydrolysis and cleavage with periodate yielded the methyl diosphenol (IV).




IV R=H, Ac XIV

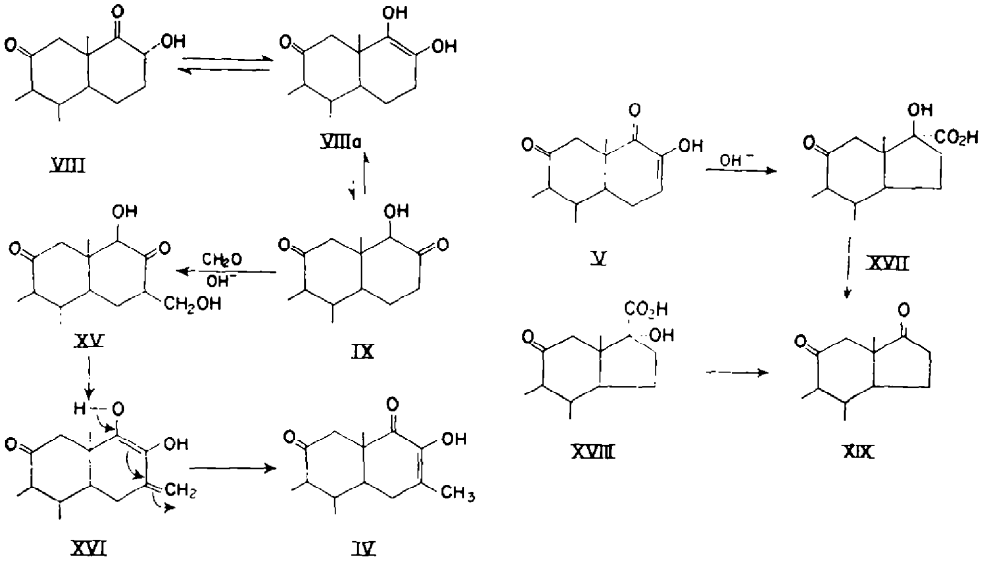
XI XIII

XII X

[6] J. H. Chapman, J. Elks, G. H. Phillips and L. J. Wyman, *J. Chem. Soc.* 4344 (1956).

[7] [a] D. Taub, R. D. Hoffsommer, H. L. Slates and N. L. Wendler, *J. Amer. Chem. Soc.* **80**, 4435 (1958); E. P. Oliveto, R. Rausser, A. L. Nussbaum, W. Gebert, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman and M. M. Pechet, *Ibid.* **80**, 4428 (1958); [b] H. L. Slates and N. L. Wendler, *Ibid.* In press.

The formation of the methyl diosphenol (IV) ostensibly results from the loss of formaldehyde from II and III through retroaldolization, followed by recombination at position C-16 with the tautomerized ketol (IX). $\beta$-Elimination of water from the intermediate XV followed by hydrogen redistribution leads to IV. Substantiation for this mechanism was provided by the synthesis of IV through controlled condensation of the ketol (IX) with formaldehyde. In contrast to the synthesis of the methyl diosphenol from the ketol IX and formaldehyde, however, its formation from the redistribution reaction of the D-homo ketols II and III is an exceedingly efficient process. This fact is suggestive of an intramolecular transfer type reaction in the




latter case; however, an internal group transfer is lacking in a convincing route for execution. The reservation is held, nevertheless, that in the dissociation–recombination sequence, the formaldehyde residue never becomes separated to the extent that subsequent reaction is truly extramolecular in character.

When the diosphenols IV and V were heated for extended periods of time with 20 per cent methanolic potassium hydroxide[8] they suffered ring contraction to yield, in nearly quantitative yield and stereoselective manner, the corresponding 17$\beta$-hydroxy isoetianic acids.[9] The 17-iso configuration of the carboxyl function was adduced from the configuration as established in the unmethylated series. Thus, the acid (XVII) obtained from ring contraction of V was different from the known $C_{17}$-epimeric 3$\alpha$,17$\alpha$-dihydroxy-11-ketoetianic acid (XVIII)[10]; both acids, however, on esterification with diazomethane followed by successive reduction with lithium aluminum hydride and cleavage with periodate produced 3$\alpha$,11$\beta$-dihydroxy-5$\beta$-androstane-17-one. The latter on acetylation at $C_3$ followed by oxidation at $C_{11}$ gave 3$\alpha$-acetoxy-5$\beta$-androstane-11,17-dione (XIX). It follows unequivocally therefrom that the acids formed by

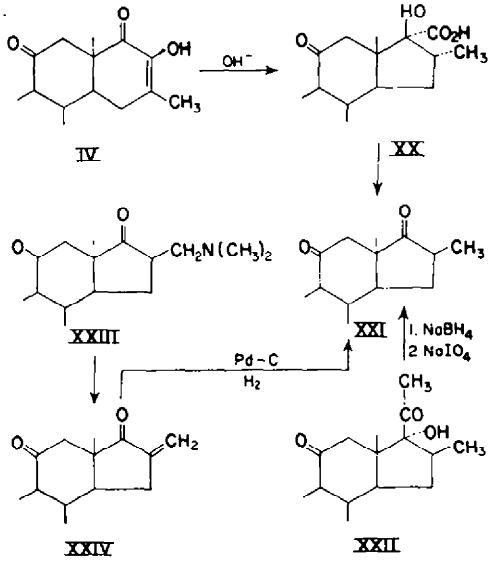
[8] Concentration of alkaline solutions of the diosphenols *in vacuo* under baking conditions at 100° also serves to produce this change.

[9] The preparation of the diosphenol (IV), under the relatively milder conditions of alkaline treatment of the D-homo ketols II and III, is always accompanied by varying amounts of the corresponding 17$\beta$ hydroxyetianic acid resulting from ring contraction of IV.

[10] L. H. Sarett, *J. Biol. Chem.* **162**, 601 (1946).

alkaline ring contraction of the D-ring diosphenols possess the 17-iso configuration of the carboxyl functions. Recently Georgian and Kundu,[11] working in another series reached the same conclusions with regard to the directional course of the ring contraction process.

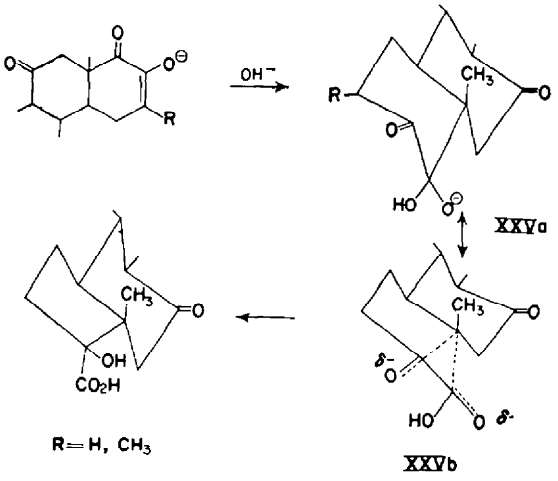
Structure proof for the acid (XX) derived from the methyl diosphenol (IV) as well as additional structural confirmation for the latter itself was provided in the following manner: The acid in the form of its methyl ester was reduced with lithium aluminum hydride followed by cleavage with periodate to 3α,11β-dihydroxy-16β-methyl-5β-androstane-17-one. Acetylation of the latter at $C_3$ followed by oxidation with chromic acid at $C_{11}$ provided the 11,17-dione (XXI). The latter was identical with a sample prepared by hydrogenation of 3α-acetoxy-16-methylene-5β-androstane-11,17-dione (XXIV). The latter was prepared in turn according to the method of Julian *et al.*[12] via the Mannich reaction on 3α-acetoxy-5β-androstane-11, 17-dione to yield XXIII; β-elimination of dimethylamine from the Mannich base afforded the methylene ketone (XXIV). The foregoing transformations establish the presence of a 16-methyl group in the diosphenol as well as its acid. Further, assuming the hydrogenation to obey the generalized rule-of-the-rear it follows that the configuration of the methyl group in the acid XX is 16β. The latter conclusion is also confirmed by the transformation of 3α,17α-dihydroxy-16β-methylpregnane-11, 20-dione (XXII)[5] by reduction and oxidative cleavage to XXI.



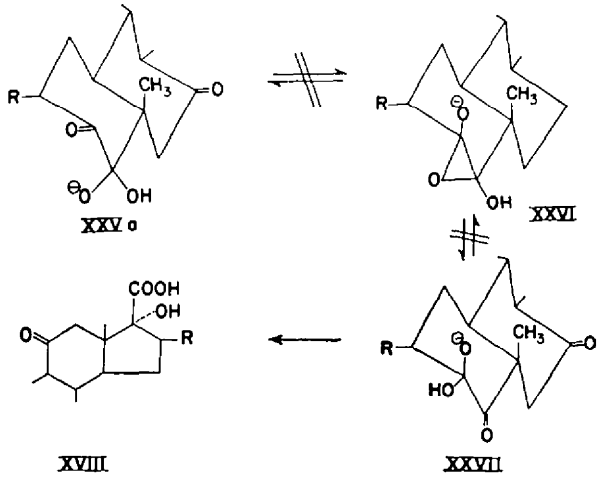

The unidirectional character and consequently the stereoselective nature of the benzilic acid contraction of the diosphenols follows logically from the fact that in alkaline solution they are largely, if not entirely, present as the $C_{17}$-oxygen anions. Consequently the $C_{17a}$-carbonyl offers the better acceptor site for hydroxide ion. With addition of hydroxide ion at $C_{17a}$, the enolization potential of the diosphenol

[11] V. Georgian and N. Kundu, *Chem. & Ind.* 1322 (1958).
[12] P. L. Julian, E. W. Meyer and H. C. Pruity, *J. Amer. Chem. Soc.* **70**, 3872 (1948); F. Newmann, O. Mancera, G. Rosenkranz and F. Sondheimer, *Ibid.* **77**, 5676 (1955).

disappears[13] and the stereochemical fate of the acid resulting from ring contraction is consequently decided. This may best be visualized from the charge distribution state indicated by XXVb.




The possibility of an interconversion of the $C_{17a}$ adduct (XXVa) with a $C_{17}$-adduct (XXVII), via a form such as XXVI for example, appears excluded by the unidirectional course of rearrangement. If the interconversion of XXVa with XXVII had been significant, a mixture of $C_{17}$-isomeric etianic acids would have resulted. In actuality the product was exclusively the 17-iso form insofar as could be determined.[14] It is

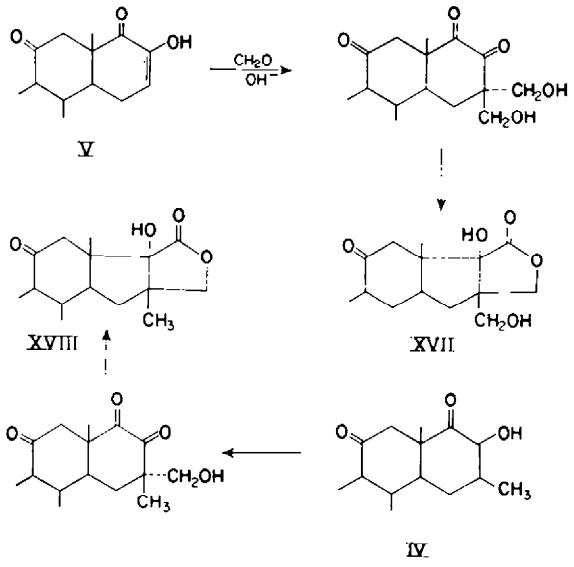



also noteworthy that in the collapse of the diosphenol enolate, consequent to OH-addition at $C_{17a}$, the methyl substituent at $C_{16}$ assumes the more stable equatorial configuration as was to be anticipated. The latter consequence has been established by the structure clarification leading to the 16$\beta$-methyl ketone (XXI).

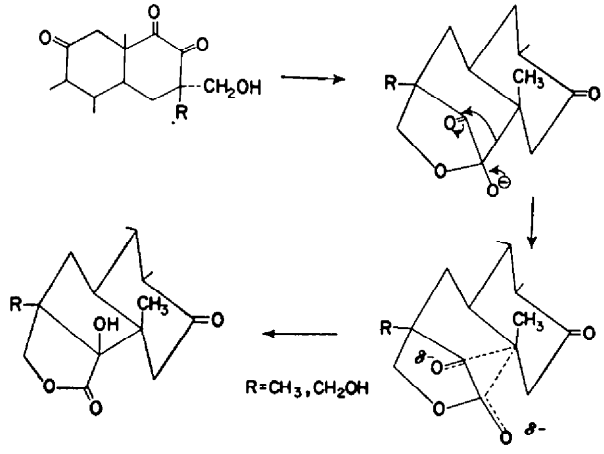
[13] The carbonyl groups in a cyclohexane 1, 2-dione face essentially in the same direction with corresponding repulsion of adjacent dipole charges. Enolization relieves both the steric instability as well as the adjacent charge repulsion. G. Baddeley, *Ann. Rep. Chem. Soc.* LII, 131 (1956).

[14] This observation was also made by Georgian and Kundu.[11]

In the synthesis of the methyl diosphenol (IV) by hydroxymethylation of the ketol (IX) with alkaline formaldehyde (IX → IV), unless careful control of the formaldehyde concentration is maintained a high melting lactone results; the same lactone is also formed from the methyl diosphenol itself on treatment with alkaline




formaldehyde and the latter consequently represents an intermediate in this transformation. A related lactone arises similarly from the unsubstituted diosphenol (V) with alkaline formaldehyde. Both of these lactones are formed in consequence to hydroxymethylation of the respective diosphenols followed by benzilic acid ring




contraction. It is reasonable to assume not only that hydroxymethylation proceeds according to the generalized rule-of-the-rear but also that the subsequent benzilic acid contraction occurs internally, thereby predetermining the geometry of the products as being stereochemically the same as that of their 17-isoetianic acid counterparts.

## EXPERIMENTAL[15]

*D-Homoannulation of 3α,21-diacetoxy-17α-hydroxy pregnane-11,20-dione*

(I) *With aluminum alkoxide.* A solution of 27·5 g (I) in 300 cc dioxane and 950 cc toluene was treated with 180 cc cyclohexanone. The mixture was distilled until 100 cc distillate had been collected; 6 g aluminum isopropoxide was added and the reaction mixture refluxed for 2·5 hr in a nitrogen atmosphere. The reaction mixture was allowed to stand overnight. Water was added and the solvents were evaporated *in vacuo*, the process being repeated several times until a gum was deposited. The residue was treated with 75 cc conc. HCl in an equal vol water and the organic material extracted with ethyl acetate. The ethyl acetate extract was washed successively with dil potassium bicarbonate solution, water and saturated sodium chloride solution. The washed ethyl acetate layer was dried and concentrated *in vacuo* to an oil which partially crystallized. Separation of the crystals and recrystallization from acetone–ether afforded 8 g pure *3α-acetoxy-17α-hydroxy-17β-acetoxymethyl-5β-D-homoandrostane-11,17a-dione* II (R = Ac) m.p. 172–174°, $[\alpha]_D$ +88·1°.

Found: C, 66·73; H, 8·01. Calc. for $C_{25}H_{34}O_7$: C, 66·94; H, 8·09%)

The mother liquors from the separation of II were chromatographed on 500 g acid-washed alumina and the eluates consisting of 1–2% ether in benzene afforded an additional 4·5 g crystalline II making a total of 12·5 g of the 17a-ketone (78% of the isomer content). The eluates 5–50% ether in benzene afforded 3·5g crystalline *3α-acetoxy-17aα-hydroxy, 17aβ-acetoxy methyl, 5β-D-homandrostane-11,17-dione* (III) (R = Ac) (22% of the isomer content), m.p. 202–204°, $[\alpha]_D$ +26·5°.

(Found: C, 66·62; H, 8·02. Calc. for $C_{25}H_{36}O_7$: C, 66·94; H, 8·09%).

*Cold alkaline hydrolysis of the D-homo ketol diacetates* II *and* III (R = Ac)

A solution of 4·48 g II (R = Ac) in 150 cc methanol under nitrogen was treated at 0° with stirring with a solution of 2·25 g potassium hydroxide in 2·5 cc water and 50 cc methanol. The reaction mixture was allowed to stand at room temp for 1·5 hr followed by neutralization with 2·5 cc acetic acid and evaporation *in vacuo* to an oil. The oil was extracted with ethyl acetate and crystallized from this solvent to give 3·63 g first crop of the triol II (R = H), m.p. 202–205°.

(Found: C, 68·98; H, 8·54. Calc. for $C_{21}H_{32}O_5$: C, 69·23; H, 8·79%).

In a similar fashion 448 mg of the ketol diacetate III (R = Ac) was saponified in the cold to give 350 mg of the corresponding triol III (R = H), m.p. 167–169°.

(Found: C, 68·89; H, 9·09. Calc. for $C_{21}H_{32}O_5$: C, 69·23; H, 8·79%).

*3α, 17-Dihydroxy Δ[16]-5β-D-homoandrostene-11,17a-dione* (V) (R = H)

A solution of 2·5 g of the triol II (R = H) in 130 cc methanol was treated with 1·47 g sodium metaperiodate in 50 cc water. After 5 hr the reaction mixture was filtered from precipitated sodium iodate and evaporated to near dryness. The residue was dissolved in 5–10% $KOH_{aq}$, filtered and the filtrate acidified. The precipitated product was dissolved in ethyl acetate and the ethyl acetate extract washed several times with potassium bicarbonate solution. Acidification of the potassium bicarbonate extracts precipitated a small amount of the crystalline acid XVI, m.p. 249–253° (see below). The ethyl acetate layer was dried, and evaporated and the residue crystallized from acetone–ether to give 1·7 g of the diosphenol V (R = H), m.p. 211–215°; $\lambda_{max}$ 267 mμ, E = 16,200.

(Found: C, 72·22; H, 8·22. Calc. for $C_{20}H_{28}O_4$: C, 72·29; H, 8·43%).

Acetylation of V (R = H) with acetic anhydride in pyridine afforded the *3,17-diacetate* V (R = Ac), m.p. 211–215°; $\lambda_{max}$ 233 mμ, E = 7,500.

(Found: C, 68·94; H, 7·74. Calc. for $C_{24}H_{32}O_6$: C, 69·23; H, 7·69%).

In a similar fashion 300 mg of the ketol III in 20 cc methanol was cleaved with 176 mg sodium metaperiodate in 8 cc water to give the diosphenol V identical with material obtained from II above.

*Oxidation of diosphenol 3,17-diacetate* (V, R = Ac) *to 3α-acetoxy-11-keto-etiobilianic acid* (X)

A solution of 100 mg V (R = Ac) in 10 cc acetone was oxidized according to published procedure[3] with 130 mg $KMnO_4$ for 3–4 hr. The oxidation product was worked up in the usual manner and afforded the etiobilianic acid X m.p. 225–230° undepressed on mixed m.p. with an authentic sample.

[15] Melting points were taken on a micro hot-stage apparatus and are corrected. U.V. spectra were determined in methanol and rotation in chloroform.

*3α-17-Dihydroxy 5β-D-homoandrostane-11, 17a-dione or 3α, 17a-dihydroxy 5β-D-homoandrostane-11, 17-dione* (VIII or IX)

A solution of 1·38 g 3α-acetoxy 5β-D-homoandrostane-11, 17a-dione[3] in 30 cc chloroform was treated with 0·69 g bromine in 10 cc chloroform. A drop of 15% hydrogen bromide in acetic acid was employed as catalyst. The bromination product was dissolved in 50 cc tetrahydrofuran and refluxed for 1 hr with a solution of 1 g potassium hydroxide in 50 cc water. Concentration of the reaction mixture caused deposition of the product as a solid. The latter was separated and crystallized from acetone–ether, m.p. 224–230°, wt. 800 mg.

(Found: C, 71·99; H, 8·85. Calc. for $C_{20}H_{30}O_5$: C, 71·85; H, 8·98%).

*Oxidation of the ketol* VIII *or* IX *to the diosphenol* (V)

A solution of 50 mg of the ketol (VIII or IX) in 4 cc methanol was treated with 75 mg copper acetate monohydrate and refluxed for 1 hr. Separation of cuprous oxide was evident after several min. The reaction mixture was worked up by addition of 0·5 cc water followed by refluxing for 0·5 hr followed by filtration and evaporation of the filtrate *in vacuo*. The residue was acetylated with acetic anhydride in pyridine and the acetylated product crystallized from ether, m.p. 206–211°. Mixed m.p. with diosphenol diacetate (V, R = Ac) prepared by periodate cleavage of II or III (R = H) above was 208–214°. The infrared spectra of the two samples were the same.

*3α-17-Dihydroxy-16-methyl-*$\Delta^{16}$*-5β-D-homoandrostene-11,17a-dione* (IV)

(A) A solution of 3·65 g of the 17a-ketone diacetate II (R = Ac) in 150 cc methanol was treated with 30 g potassium hydroxide in 30 cc water and 150 cc methanol. The alkali was added to the steroid from a dropping funnel in a nitrogen atmosphere and the reaction mixture refluxed for 15–18 hr. At the end of this period the reaction mixture was cooled and acidified with 50 cc conc HCl diluted with an equal volume of water. The solvents were evaporated *in vacuo* and the residue dissolved in 10% $KOH_{aq}$, filtered, acidified and the precipitated product extracted with ethyl acetate. The ethyl acetate extract on washing with potassium bicarbonate solution afforded, after acidification, 300 mg of the 16β-methyl 17-isoetianic acid (XX) (see below). The washed ethyl acetate layer was dried and evaporated to the point of crystallization whereby 2·31 g of the methyl diosphenol (IV) was afforded; m.p. 238–243°, $\lambda_{max}$ 273 mμ, E = 8600.

(Found: C, 72·80; H, 8·70. Calc. for $C_{21}H_{34}O_4$: C, 72·83; H, 8·67%).

(B) In an identical manner and in equal yield the methyl diosphenol IV was prepared from the ketolic isomer III (R = Ac).

Acetylation of IV (R = H) with acetic anhydride in pyridine afforded the *3,17-diacetate* (IV, R = Ac), m.p. 220–222°, $\lambda_{max}$ 239 mμ, E = 10,850.

(Found: C, 69·93; H, 7·96. Calc. for $C_{25}H_{34}O_6$: C, 69·77; H, 7·91%).

*Oxidation of the methyl diosphenol diacetate* (IV, R = Ac) *and 3α-acetoxy-16-methyl-*$\Delta^{16}$*-pregnene-11, 20-dione* XII *to the methyl ketonic acid* (XI)

(A) A solution of 500 mg IV (R = Ac) in 50 cc acetone at 0° was treated with 650 mg potassium permanganate and allowed to stir at room temp for 2 hr. At the end of this time the acetone was evaporated in a stream of nitrogen and replaced with water; the latter was acidified with 7·5 cc 50% $H_2SO_4$ and decolorized with saturated sodium bisulfite solution. The product was taken up in ether and the organic acid extracted with bicarbonate, released from the latter by acidification and re-extracted with ether. Evaporation of the dried ether solution gave a non-crystalline acid XI identical in the infrared spectrum with the acid obtained from XII on oxidation (see Part B below). This acid gave a copious precipitate of iodoform, m.p. 120–121°, on treatment with sodium hypoiodite solution to form X.

(B) Similar oxidation of the $\Delta^{16}$*-pregnene derivative* XII[5] gave the same amorphous acid XI identical by infrared spectral comparison with the sample obtained from IV (R = Ac) *Part A.*

D-*Homoannulation of 3α, 21-diacetoxy-17α-hydroxy 16β-methyl pregnane 11,20-dione* (XIII)

A solution of 900 mg XIII[5] in 10 cc dioxane and 30 cc toluene was treated with 6 cc cyclohexanone and 200 mg aluminum isopropoxide and the reaction mixture refluxed for 2·5 hr. The product was

worked up in the same manner described for the preparation of II and III (see above). The D-homo compound (XIV, R = Ac) crystallized directly from acetone–ether to give a first crop of 500 mg m.p. 191–193°.

(Found: C, 67·22; H, 8·10. Calc. for $C_{25}H_{38}O_7$: C, 67·53; H, 8·44%).

*Conversion of* D-*homo compound* XIV *to methyl diosphenol* (IV)

A solution of 400 mg XIV (R = Ac) in 15 cc methanol was hydrolyzed to XIV (R = H) with 194 mg potassium hydroxide at room temp for 1·5 hr. The reaction product was isolated by neutralization with acetic acid and extraction with ethyl acetate. The residue (200 mg) obtained on evaporation of the solvent was dissolved in 10 cc methanol and treated with 119 mg sodium metaperiodate. The product from the cleavage reaction was worked up in the same manner as described for the preparation of V(R = H) and afforded the methyl diosphenol (IV, R = H) identical in m.p. and infrared spectrum with that obtained from the alkaline rearrangement of II and III (see above). Acetylation of this material afforded 3, 17 *diacetate* identical with (IV, R = Ac) obtained previously, m.p. and mixed m.p. 217–221°. The infrared spectra of the two samples were the same.

*Synthesis of methyl diosphenol* IV *by hydroxymethylation of the ketol* (VIII or IX)

A solution of 150 mg of the ketol (VIII or IX) in 10 cc methanol containing 300 mg potassium hydroxide dissolved in 1 cc water was treated dropwise under reflux and a nitrogen atmosphere with 0·04 cc 37% formaldehyde solution dissolved in 2 cc methanol. The reaction mixture was refluxed a total of 1·5 hr. At the end of this period the base was neutralized with acetic acid and the solvents evaporated *in vacuo*. The residue was dissolved in ethyl acetate and the ethyl acetate extract washed with bicarbonate, dried and concentrated to dryness. The residue was acetylated with acetic anhydride in pyridine for 15 hr at room temp and the acetylated product chromatographed on acid-washed alumina. The fractions eluted with 2–10% ether in benzene gave the methyl diosphenol diacetate (IV, R = Ac) m.p. 218–220°, mixed m.p. with IV (R = Ac) prepared from the alkaline rearrangement of the ketols II and III was not depressed (218–220°). The infrared spectra of the two samples were identical.

3α,17β-*Dihydroxy*-11-*keto* 17-*isoetianic acid* (XVII)

A solution of 200 mg of the diosphenol V (R = H) in 20 cc methanol was treated with 3 g potassium hydroxide in 3 cc water and refluxed in a nitrogen atmosphere for 15 hr. The reaction mixture was concentrated to dryness and the organic material extracted with ethyl acetate, The ethyl acetate solution was extracted with potassium bicarbonate solution and the latter on acidification deposited 210 mg crystalline acid XVII. The acid was recrystallized from acetone, m.p. 252–254° (dec).

Found: C, 68·66; H, 8·59. Calc. for $C_{20}H_{30}O_5$: C, 68·54; H, 8·63%).

The acid XVII was different from the known etianic acid XVIII and was converted to the 17-ketone XIX as follows: a 500 mg sample of XVII was esterified with diazomethane and acetylated with acetic anhydride in pyridine. The total esterified and acetylated product was dissolved in 25 cc methanol and cleaved with 600 mg sodium metaperiodate dissolved in 12 cc water for 15 hr. The cleavage product, 3α, 11β-*dihydroxy* 5β-*androstane*-11-*one* (XIX) crystallized from the concentrated reaction product, was filtered and recrystallized from acetone, m.p. 233–236°.

(Found: C, 74·30; H, 9·86. Calc. for $C_{19}H_{28}O_3$: C, 74·51; H, 9·80%).

The above sample of XIX prepared from XVII was identical with a specimen prepared from 3α, 17α-dihydroxy-11-keto etianic acid (XVIII) by the same route. The intermediate *methyl* 3α-*acetoxy*-17α-*hydroxy*-11-*keto etianate* melted at 140–142°.

(Found: C, 67·83; H, 8·27. Calc. for $C_{23}H_{34}O_6$: C, 67·98; H, 8·37%).

3α,17β-*Dihydroxy*-11-*keto*-16β-*methyl* 17-*isoetianic acid* (XX)

(A) A solution of 500 mg methyl diosphenol IV (R = H) dissolved in 25 cc methanol containing 6 g potassium hydroxide in 5 cc water was refluxed 18 hr in a nitrogen atmosphere. Concentration of the reaction mixture and dilution with water deposited 450 mg crystalline acid XX recrystallized from acetone, m.p. 277–280°.

(Found: C, 68·98; H, 8·75. Calc. for $C_{21}H_{32}O_5$: C, 69·23; H, 8·79%).

(B) A solution of 1·58 g of the ketol II (R = Ac) in 50 cc methanol containing 12 g potassium hydroxide in 12 cc water was refluxed in a nitrogen atmosphere for 15 hr. The work-up of the product afforded 400 mg methyl diosphenol IV (R = H) and the bicarbonate soluble fraction afforded 1·05 g crystalline acid XX.

*Conversion of* 3α,17β-*dihydroxy*-11-*keto*-16β-*methyl*-17-*isoetianic acid* XX *to* 3α-*acetoxy*-16β-*methyl*-5β-*androstane*-11,17-*dione* (XXI)

A 200 mg sample of XX was esterified in methanol solution with diazomethane followed by acetylation at C-3 with acetic anhydride in pyridine in the usual manner. The ester acetate was reduced with 500 mg lithium aluminum hydride in 50 cc refluxing tetrahydrofuran and the product cleaved in methanol with 2 equivalents of sodium metaperiodate to afford 3α,11β-*dihydroxy*-16β-*methyl* 5β-*androstane*-17-*one* (XXIa). The latter was crystallized as plates from acetone–ether, m.p. 186–188°.

(Found: C, 75·3; H, 10·1. Calc. for $C_{20}H_{32}O_3$: C, 75·0; H, 10·0%).

A sample of the above 17-ketone (XXIa) was acetylated with acetic anhydride in pyridine and oxidized at C-11 with chromic acid in acetic acid to give 3α-acetoxy-16β-methyl-5β-androstane-11, 17-dione (XXI) as prisms from ether, m.p. 202–205°. This material was identical by mixed m.p. and infrared comparison with a sample of XXI prepared by methylation of 3α-acetoxy-5β-androstane-11,17-dione (see below).

3α-*Acetoxy* 16-*methylene* 5β-*androstane*-11,17-*dione* (XXIV)

A 3·46 g sample of 3α-acetoxy-5β-androstane-11,17-dione in 25 cc isoamyl alcohol was treated with 1·5 g paraformaldehyde and 6·1 g dimethylamine hydrochloride and heated under reflux for 2 hr.[12] After standing overnight in the ice box the reaction mixture was treated with 40 cc 1:9 conc HCl–water and extracted with ether. The aqueous layer was treated with saturated sodium carbonate solution and extracted with ether. The residue obtained after evaporation of the ether was steam distilled and the residue from the steam distillation was crystallized from acetone–ether to give XXIV, m.p. 234–239°, $\lambda_{max}$ 228 mμ, E = 8,800.

(Found: C, 73·36; H, 8·38. Calc. for $C_{22}H_{30}O_4$: C, 73·74; H, 8·41%).

*Hydrogenation of* 3α-*acetoxy*-16-*methylene*-5β-*androstane* 11,17-*dione* (XXIV to XXI)

A 100 mg sample of XXIV in 25 cc methanol and 50 mg 50% palladium on charcoal was hydrogenated. Uptake of 1 mole of hydrogen was complete in 3–4 min. The product was filtered, evaporated and crystallized from acetone–ether, m.p. 202–205°. A mixed m.p. of XXI obtained by the above route was undepressed on admixture with a sample prepared from degradation of the acid XX and the ketol XXII (see below). The infrared spectra of these samples were identical.

*Reductive cleavage of* 3α,17α-*dihydroxy*-16β-*methyl-pregnane*-11, 20-*dione* (XXII *to* XXI)

To a stirred solution of 2·00 g of the diol-dione XXII in 60 ml tetrahydrofuran was added 1·00 g sodium borohydride in 10 ml water and the mixture refluxed for 50 min. It was then cooled and the remaining reducing agent destroyed by addition of dilute acetic acid. Following concentration on the water pump, water was added and the mixture extracted with ethyl acetate. To the residue (1·97 g mainly 3α,17α,20-*trihydroxy*-16β-*methylpregnane*-11-*one*) in 60 ml methanol was added 2·00 g sodium metaperiodate in 25 ml water with stirring and cooling. After 18 hr at 25° the precipitated sodium iodate was removed by filtration and washed with ethyl acetate. Water was added to the filtrate which was then concentrated on the water pump until the organic solvents were removed and the product had precipitated. The crystalline product, 3α-*hydroxy*-16β-*methyl*-5β-*androstane*-11, 17-*dione*[16] was washed with water and dried in air; 1·32 g m.p. 235–245° raised to 242–250° on crystallization from acetone $\lambda_{max}^{Nujol}$ 2·86, 2·89 μ (OH); 5·78 μ (17 C=O); 5·86 μ (11 C=O).

Acetylation at 25° in acetic anhydride–pyridine gave 3α-acetoxy-16β-methyl-5β-androstane-11 17-dione (XXI) prismatic needles from ether m.p. 203–206°.

(Found: C, 73·26; H, 8·82. Calc. for $C_{22}H_{32}O_4$: C, 73·30; H, 8·95%).

[16] It is noteworthy that under the above reduction conditions which suffice to completely reduce the 11-keto group in the pregnane series, the 11-keto group in the 16β-methyl-pregnane series remains essentially unchanged. Only a few mg of crude 3α,11β-dihydroxy-16β-methyl-5β-androstane-17-one XXIa were obtained by extraction of the aqueous mother liquors and fractional crystallization.

Lithium aluminum hydride reduction of XXII in refluxing anhydrous tetrahydrofuran followed by periodate cleavage gave 3α,11β-dihydroxy-16β-methyl-5β-androstane-17-one XXIa, m.p. 187–188° identical with material obtained from the isoetianic acid XX by melting point and infrared spectral comparisons.

*3α-17β-Dihydroxy-11-keto-16, 16-bis-hydroxymethyl-17-isoetianic acid lactone* (XVII)

A solution of 350 mg of the diosphenol (V) in 10 cc isopropanol containing 0·5 g potassium hydroxide and 1 cc formaldehyde (37%) was refluxed for 2 hr. After 15–20 min of reflux two layers formed. At the conclusion of the reflux period the reaction mixture was acidified and concentrated *in vacuo*. The residue was dissolved in 5% KOH and upon acidification there was a delayed precipitation of the product. The latter was extracted with ethyl acetate and the ethyl acetate layer washed several times with potassium bicarbonate solution. Evaporation of the dried ethyl acetate solution induced crystallization of the lactone XVII, m.p. 270–273°, wt. 300 mg, $\lambda_{max}^{Nujol}$ 2·8, 3·0 and 3·14 μ (OH), 5·68 μ (5-ring lactone) and 5·86 μ (11C=O).

(Found: C, 67·37; H, 8·21. Calc. for $C_{22}H_{32}O_6$: C, 67·35; H, 8·16%).

A 200 mg sample of the lactone (XVII) was reduced in refluxing tetrahydrofuran with 1 g lithium aluminum hydride followed by cleavage of the reduced product with sodium metaperiodate. The non-crystalline oxidation product exhibited in the infrared in addition to OH absorption a band at 5·79 μ.

*3α,17β-Dihydroxy-11-keto-16β-methyl-16α-hydroxymethyl-17-isoetianic acid lactone* (XVIII)

A 200 mg sample of the methyl diosphenol (IV) in 10 cc methanol containing 0·5 g potassium hydroxide in 1 cc water and 1 cc 37% formaldehyde solution was refluxed for 2 hr. The product was worked up as in the preparation of XVII to give 100 mg lactone XVIII from ethyl acetate, m.p. 257–259°, $\lambda_{max}^{Nujol}$ 2·8–2·95 and 3·12 μ (OH), 5·69 μ (5-ring lactone) 5·95 μ (11 C=O); $\lambda_{max}^{Chf}$ 2·83 μ (OH), 5·69 μ (5-ring C=O), 5·84 μ (11C=O).

(Found: C, 70·24; H, 8·44. Calc. for $C_{22}H_{32}O_6$: C, 70·21; H, 8·51%).

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