[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE RICE INSTITUTE]

Stereospecificity in the Rearrangement of 17-Hydroxy-20-ketosteroids

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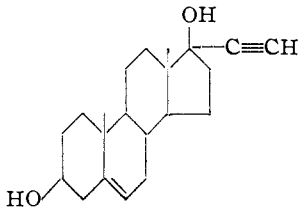
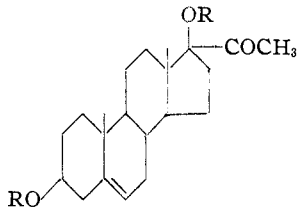
Rearrangement of 17α- and of 17β-hydroxy-20-ketosteroids into ketols of the D-homo series under the influence of bases and of Lewis acids is characterized by a high degree of stereospecificity. The nature of the products is dependent not only upon the configuration (at C-17) of the starting material, but also upon the reagent employed to effect rearrangement. The experimental results can be satisfactorily explained by consideration of the orientation of the C-20 carbonyl group with respect to the hydroxyl group at C-17 in the transition state. Although the action of boron trifluoride in acetic anhydride–acetic acid, of alumina, and of aluminum alkoxides in benzene in particular cases results in rearrangement *via* a coördinated complex, the use of aluminum chloride in acetic anhydride–acetic acid leads to acetylation of the tertiary hydroxyl group of both 17α- and 17β-hydroxy epimers. Similar results are obtained with zinc chloride in the same solvent mixture. These observations suggest that the ketols compete unfavorably with acetic anhydride for the Lewis acid when the latter reagent is larger than boron trifluoride, with the result that acetylation intervenes.

In the course of investigations directed toward the partial synthesis of 17-hydroxy-20-ketosteroids, Ruzicka and Meldahl[1] treated the ethynyl carbinol I with mercuric oxide and boron trifluoride etherate in acetic anhydride–acetic acid and obtained a diacetoxy ketone, to which structure IIa was assigned. Alkaline saponification of this material furnished a dihydroxy ketone, m.p. 276–278°,



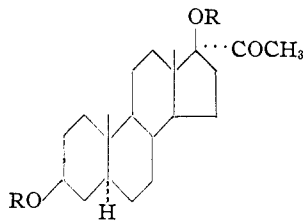
I



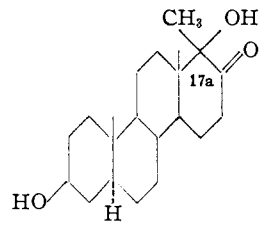
IIa, R = $COCH_3$
IIb, R = H

also obtained in small amounts by direct hydration of I,[2] which was at first regarded as 3β,17β-dihydroxy-5-pregnen-20-one (IIb). The substance, however, could not be reconverted into the diacetate IIa, even under vigorous conditions, and for this and other reasons[3] the Swiss investigators were led to consider the possibility that rearrangement had occurred. Authentic 3β,17β-dihydroxy-5-pregnen-20-one (IIb), differing from the above dihydroxy ketone, was subsequently prepared by Stavely,[4] who employed a modified hydration procedure involving the use of aniline, water and mercuric chloride. Stavely's product on acetylation with acetic anhydride and pyridine at 100° gave the diacetate IIa,[5] and on treatment with base was converted into the isomeric dihydroxy ketone of melting point 276–278°.

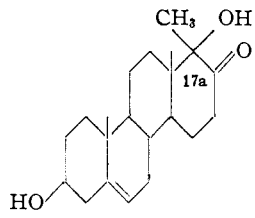
In the meantime Ruzicka and his collaborators[6,7] extended their observations to 3β,17β-diacetoxyallopregnan-20-one (IIIa) with similar results and proposed that the rearrangement involves ring enlargement with formation of D-homo derivatives (IV and V). This suggestion was supported by oxidation of IV (as the 3-monoacetate) to a *keto acid (VI) without loss of carbon*, and by degradation of V to 1-methylchrysene (VII).



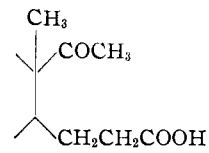
IIIa, R = $COCH_3$
IIIb, R = H



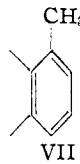
IV



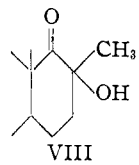
V



VI



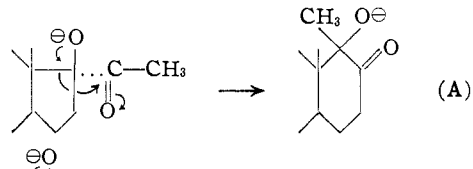
VII



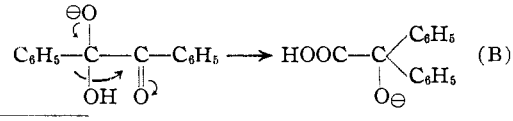
VIII

An alternate formulation, VIII, was excluded by Shoppee and Prins,[8] who provided rigorous proof for the structure indicated in IV.

The mechanism of rearrangement of these and other related products has been considered by Shoppee and Prins,[5,8,9] and is regarded as a "pinacolic" change of the type formulated in (A). In this sense the reaction is analogous to the benzilic acid rearrangement (B) and to very similar trans-

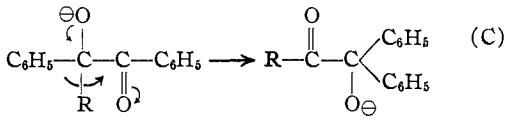


(A)



(B)

(1) L. Ruzicka and H. F. Meldahl, *Helv. Chim. Acta*, **21**, 1760 (1938).
(2) H. E. Stavely, THIS JOURNAL, **61**, 79 (1939).
(3) L. Ruzicka and H. F. Meldahl, *Helv. Chim. Acta*, **22**, 421 (1939).
(4) H. E. Stavely, THIS JOURNAL, **62**, 489 (1940).
(5) C. W. Shoppee and D. A. Prins, *Helv. Chim. Acta*, **26**, 201 (1943).
(6) L. Ruzicka, K. Gätzi and T. Reichstein, *ibid.*, **22**, 626 (1939).
(7) L. Ruzicka and H. F. Meldahl, *ibid.*, **23**, 364 (1940).
(8) C. W. Shoppee and D. A. Prins, *ibid.*, **26**, 185 (1943).
(9) C. W. Shoppee and D. A. Prins, *ibid.*, **26**, 1004 (1943).



(C)

formations (C) recently reported by Curtin and Leskowitz[10] and by Sharp and Miller.[11]

Although the general features of the rearrangement are satisfactorily represented in these terms, the most outstanding characteristic of the reaction, namely, its stereospecificity, remains unaccounted for. It is with this aspect of the problem that the present paper is primarily concerned.

Whereas the dihydroxy ketones IV and V were in each case obtained in stereochemically pure condition, the structures assigned to these substances permit existence of epimers differing in configuration at C-17a (*cf.* IX and XI). Under certain conditions such epimeric substances are encountered. Thus 3β,17β-dihydroxy-5-pregnen-20-one (IIb) when chromatographed on alumina affords in quantitative yield a dihydroxy ketone, identical neither with the starting material nor with the product of rearrangement by alkali.[12] Adsorption of 3β,17β-dihydroxyallopregnan-20-one (IIIb) on alumina gives a similar result.[5] Structural correlation of the rearranged products has been achieved by Shoppee and Prins,[5] who showed that the members of each epimeric pair, on oxidation, yield the same keto acid derivative (*cf.* VI). The fact that the alumina-promoted rearrangement is independent of the presence or absence of alkali is demonstrated by conversion of IIIb (3-monoacetate) into the same D-homo compound by samples of alumina showing basic, neutral and acidic reactions.

Assignment of configuration to the 17a-epimers can be made on the basis of Shoppee's observation[5] that whereas both substances yield acetyl derivatives (XIII and XV, respectively) on treatment with boron trifluoride–acetic anhydride–acetic acid under standardized conditions, the yields in the two cases are quite different, being 40% for the product (IX) of base-catalyzed rearrangement and 70% for the product (XI) obtained by adsorption on alumina. An equatorial (17aβ) orientation is hence assigned to the hydroxyl group of the less hindered epimer (XI) and a polar (17aα) orientation to the hydroxyl group of IX.[13]

Stereospecific rearrangement of substances possessing the part structure X[14] is also promoted by other reagents, including aluminum isopropoxide (Oppenauer conditions),[12] boron trifluoride–acetic anhydride–acetic acid,[5] and magnesium bromide.[15] It is significant that all reagents of this type furnish derivatives of XI, rather than of IX, as the sole or major products of homoannulation.

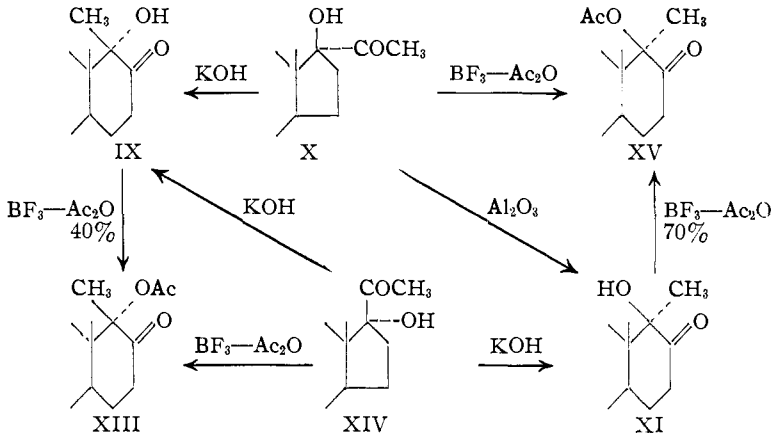
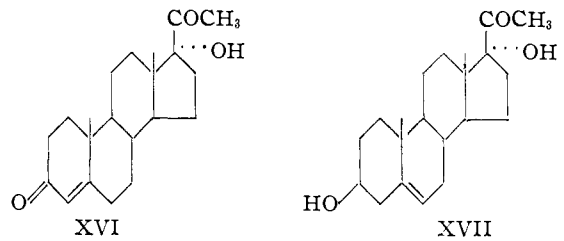


CHART I

Further information has been obtained from studies of the reactions of 17α-hydroxy-20-ketosteroids (XIV), of which the naturally occurring adrenal cortical steroids are the most common examples. Rearrangement of 17α-hydroxyprogesterone (XVI≡XIV) under the influence of hot, 3% methanolic potassium hydroxide has been reported by von Euw and Reichstein,[16] who noted that the 17α-hydroxy derivatives are considerably more resistant to isomerization by alkali than are the corresponding 17β-hydroxy epimers (X). Base-catalyzed rearrangement of XVI yields a mixture of 17a-epimers, of which about 70% of the isolated crystalline material possesses the 17aβ-hydroxy configuration (XI). This result contrasts with the



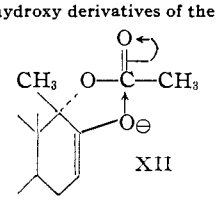
formation of 17aα-hydroxy compounds (IX) in reactions of 3β,17β-dihydroxy-5-pregnen-20-one (IIb),[4] of 3β,17β-dihydroxypregnan-20-one,[17] and of 3β,17β-dihydroxyallopregnan-20-one (IIIb) with base.

(10) D. Y. Curtin and S. Leskowitz, THIS JOURNAL, **73**, 2633 (1951).

(11) D. B. Sharp and E. L. Miller, *ibid.*, **74**, 5643 (1952).

(12) H. E. Stavely, *ibid.*, **63**, 3127 (1941).

(13) Original assignments of configuration (reference 5, p. 211) were based upon rates of saponification of the 3,17a-diacetates XIII and XV, and an analogy to 17-hydroxy derivatives of the natural series (ring D 5-membered), which, however, were incorrectly formulated at the time. In view of the small amounts of material available for the rate studies (14 mg. in the case of IX) and uncertainties regarding the mechanism of hydrolysis of ketol acetates, for example the possibility of acyl migration (XII), the results of the acetylation experiments are considered the more reliable.



XII

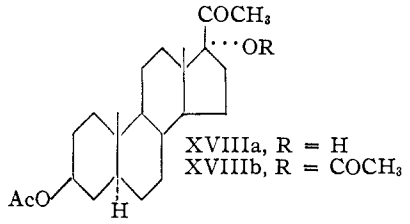
(14) Several substances differing only in the structure of the A/B ring system have been studied. These substances and the rearrangement products derived from them have all been correlated by appropriate interconversions (see reference 5).

(15) C. W. Shoppee and D. A. Prins, *Helv. Chim. Acta*, **26**, 2089 (1943).

(16) J. von Euw and T. Reichstein, *ibid.*, **24**, 879 (1941).

(17) C. W. Shoppee, *ibid.*, **27**, 8 (1944).

17α-Hydroxy-20-ketosteroids do not rearrange in contact with alumina. These substances are, however, sensitive to the action of aluminum alkoxides at elevated temperatures, and consequently cannot be employed in the ordinary Oppenauer and Meerwein–Pondorff–Verley procedures. Thus 17α-hydroxypregnenolone (XVII) on Oppenauer oxidation is converted into an oily mixture, of which the chief crystalline component is 17aα-hydroxy-17a-methyl-Δ⁴-D-homoandrostene-3,17-dione (*cf.* IX).[18] Treatment of 3β,17α-dihydroxyallopregnan-20-one 3-monoacetate (Reichstein's compound L monoacetate) (XVIIIa) with aluminum *t*-butoxide in refluxing benzene similarly affords 3β,17aα-dihydroxy-17a-methyl-D-homoandrostan-17-one (*cf.* IX) as the principal product.



XVIIIa, R = H
XVIIIb, R = $COCH_3$

Although XVIIIa is not rearranged by magnesium bromide, quantitative rearrangement into 3β,17aα-diacetoxy-17a-methyl-D-homoandrostan-17-one (XIII) results when the compound is treated with boron trifluoride–acetic anhydride–acetic acid. 17α-Hydroxyprogesterone (XVI) undergoes a similar reaction, although the yield is adversely affected by the presence of the conjugated ketonic grouping in ring A. These and other transformations are summarized in Chart I.

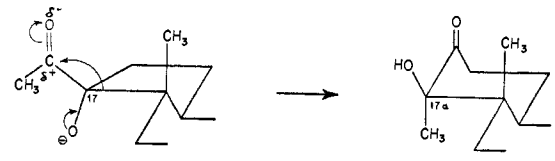
Consideration of the geometry of the system indicates that rearrangement to one or the other of the 17a-epimers is dependent upon the orientation of the C-20 carbonyl group in the transition state. A consistent explanation of the observed stereospecificity can be formulated on this basis.

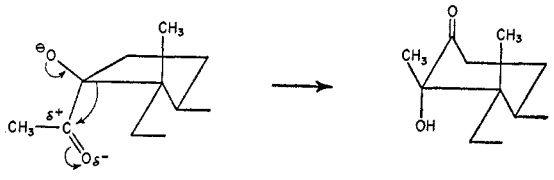
For the base-catalyzed reaction the suggestion may be made that removal of a proton from the hydroxyl group and conference of a full negative charge on oxygen will, as a consequence of electrostatic repulsion, lead to the particular orientation (*s-trans*[19]) of the carbonyl dipole indicated (for the 17α-hydroxy compounds) in XIX. Rearrangement in this case will then proceed from the 17α-hydroxy to the 17aβ-hydroxy configuration as observed. On the basis of the same arguments rearrangement of 17β-hydroxy compounds into 17aα-hydroxy-D-homo derivatives (XXI → XXII) would be anticipated, and is confirmed experimentally.

D-Homoannulation initiated by Lewis acids, on the other hand, is represented as involving a coordinated, cyclic intermediate, in which the oxygen functions bear an *s-cis*[19] relationship to each other (XXIII and XXIV). Formation of cyclic intermediates of this type insures rearrangement with reversal of the stereochemical relationships discussed above, *i.e.*, 17α → 17aα and 17β → 17aβ, in accordance with experimental observations.

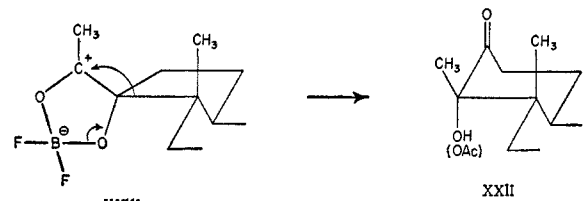
(18) P. Hegner and T. Reichstein, *Helv. Chim. Acta.*, **24**, 841 (1941).

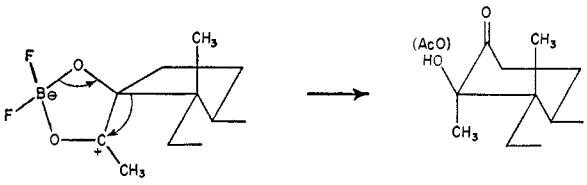
(19) The terms "*s-cis*" and "*s-trans*" [*cf.* R. S. Mulliken, *Revs. Modern Phys.*, **14**, 265 (1942)] are used in this connection to designate *cis–trans* rotational isomers about a single bond.

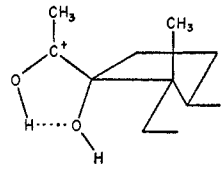




The stability of the cyclic structures XXIII and XXIV will depend to a large extent upon the size and nature of the particular Lewis acid employed. Furthermore, stereospecific rearrangement in the presence of proton donors might not be expected in view of the lesser stability of hydrogen bonded structures such as XXV.[20] Reactions of 3β,17α-dihydroxyallopregnan-20-one 3-monoacetate (L monoacetate) and of 3β,17β-dihydroxyallopregnan-20-one 3-monoacetate (iso-L monoacetate) with certain acidic reagents were investigated in order to test these hypotheses.







The initial observation[21] that treatment of both L monoacetate and iso-L monoacetate with *p*-toluenesulfonic acid in acetic anhydride and acetic acid results, not in rearrangement, but in acetylation of the 17-hydroxyl group (XVIIIb and IIIa) was surprising in that acetylation of 17α-hydroxy-20-ketosteroids had not previously been accomplished.[22] Both substances, moreover, are recovered

(20) Spectroscopic evidence for hydrogen bonding of a similar type is discussed by R. N. Jones, P. Humphries, F. Herling and K. Dobriner, THIS JOURNAL, **74**, 2820 (1952).

(21) See R. B. Turner, THIS JOURNAL, **75**, 3489 (1953).

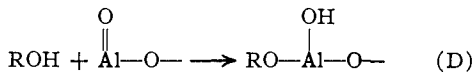
(22) *Cf.* J. von Euw and T. Reichstein, *Helv. Chim. Acta*, **30**, 205 (1947).

unchanged (except for partial cleavage of the 3-acetoxyl group) from dioxane–water mixtures containing *p*-toluenesulfonic acid. It is hence concluded that the rearrangement is not subject to general acid catalysis, but is associated with special properties of Lewis acids.

Although alumina and aluminum alkoxides promote rearrangement in instances already cited, the use of aluminum chloride in acetic anhydride–acetic acid results in acetylation of both L monoacetate and iso-L monoacetate. Acetylation rather than rearrangement also occurs in the presence of zinc chloride in the same solvent mixture. Treatment of L monoacetate (XVIIIa) with stannic chloride–acetic anhydride–acetic acid furnishes L diacetate (XVIIIb); iso-L monoacetate yields an oily mixture, from which a small amount of a crystalline substance, m.p. 181–183°, can be isolated. This substance depresses the melting point of the starting material, but has not been further characterized owing to the small amounts of material available.

Of the reagents thus far investigated, only boron trifluoride, the smallest as well as the most electronegative substance of the group, gives uniformly high yields of rearranged products in both 17α- and 17β-hydroxy series. Whereas iso-L is rearranged by alumina and by magnesium bromide, compound L is stable to the action of both reagents. Results with other aluminum derivatives are variable, and in no case has rearrangement been demonstrated for salts of heavier metals. The following explanations may be advanced in connection with these observations.

First, since substituents at C-17 (C/D *trans*) are more strongly hindered in the α-(pseudo-polar) than in the β-configuration (pseudo-equatorial), reaction of 17α-hydroxy derivatives with bulky reagents (D) will be less favored sterically than that of the corresponding 17β-hydroxy epimers.

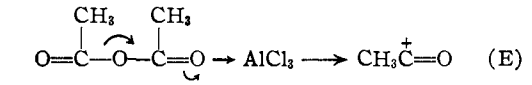


ROH + Al(=O)—O— ⟶ RO—Al(OH)—O— (D)

It should be noted that attack on the oxygen atom of the C-20 carbonyl group is presumably not subject to the same steric effects that govern reactions occurring on carbon (C-20).[23]

The second argument concerns the nature of the driving force responsible for rearrangement. This can be assigned, at least in part, to relief of strain accompanying conversion of a *trans*-fused hydrindane into a *trans*-fused decalin system.[24] It has, moreover, been established[25] that in the C/D *trans* series 17α-acetyl derivatives are thermodynamically unstable with respect to the 17β-acetyl epimers, into which they are convertible *via* a common enol. Hence, a somewhat greater gain in stabilization would be expected for homoannulation of compounds in which the relatively large 17-acetyl group is α-oriented than in cases in which this group possesses a β-configuration.

Finally, the behavior of aluminum chloride–acetic anhydride–acetic acid relative to that of boron trifluoride–acetic anhydride–acetic acid and of aluminum alkoxides in benzene may be attributed to the fact that as complexing with the steroid ketol becomes more difficult, reaction with the solvent (E) with formation of an active acetylating agent intervenes.



O=C(CH₃)—O—C(CH₃)=O → AlCl₃ ⟶ CH₃C⁺=O (E)

Materials employed in this investigation were made available through the courtesy of Dr. T. F. Gallagher, Sloan–Kettering Institute, Drs. G. Rosenkranz and F. Sondheimer, Syntex, S. A., and Drs. T. P. Carney and J. Rowe, Eli Lilly and Co.

Experimental[26]

Preparation of 3β,17α-Dihydroxyallopregnan-20-one 3-Monoacetate (L-Monoacetate) (XVIIIa).—This compound was prepared by the procedure of Kritchevsky and Gallagher.[27] The purified product melted at 190–191°.

Preparation of 3β,17β-Dihydroxyallopregnan-20-one 3-Monoacetate (Iso-L Monoacetate).—A mixture of 4.90 g. of 17α-ethynylandrostane-3β,17β-diol 3-monoacetate in 200 ml. of benzene, 9 g. of mercuric chloride, 1.5 ml. of freshly distilled aniline and 50 ml. of water was stirred at 60° for 20 hours according to the procedure of Stavely.[4] The reaction mixture was cooled, filtered and transferred to a separatory funnel. The organic phase was washed successively with water, dilute hydrochloric acid, water, dilute sodium hydroxide solution and a saturated solution of sodium chloride. After drying over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue allowed to crystallize from methanol. 17a-Anilido-3β-hydroxy-17a-methyl-D-homoandrostane-17-one, 560 mg., m.p. 227–229°, was removed in this way. The mother liquors were then evaporated to dryness, and the product crystallized from acetone–petroleum ether; yield 1.72 g., m.p. 168–173°. Two recrystallizations from acetone–petroleum ether gave material melting constantly at 173–175°. The double melting point reported by Shoppee and Prins[8] was not observed.

Reactions of 3β,17α-Dihydroxyallopregnan-20-one 3-Monoacetate (L Monoacetate) (XVIIIa). Aluminum *t*-Butoxide in Benzene.—A solution of 71.4 mg. of L monoacetate and 100 mg. of aluminum *t*-butoxide in 5 ml. of dry benzene was heated under reflux for 15 hours. The mixture was cooled, diluted with ether, and washed successively with dilute hydrochloric acid, water, dilute sodium hydroxide and saturated sodium chloride. After filtration through anhydrous sodium sulfate, the solvent was removed, and the residue was reacetylated (9 hours at room temperature) with 2 ml. of acetic anhydride and 3 ml. of pyridine. The material obtained in this way was chromatographed on alumina and yielded 22 mg. of crude 3β,17aα-dihydroxy-17a-methyl-D-homoandrostan-17-one 3-monoacetate, m.p. 210–217°, which on two recrystallizations from dilute methanol gave material melting at 234–236° that did not depress the melting point of an authentic sample.[5]

In addition, 6 mg. of the corresponding 3,17a-diacetate,[5] m.p. 238–240°, was obtained. No other crystalline material could be isolated.

(23) For a discussion of hindrance effects in the environment of C-17 see L. F. Fieser, *Experientia*, **6**, 312 (1950).

(24) W. Klyne and C. W. Shoppee, *Chemistry and Industry*, 470 (1952), have suggested that the base-catalyzed rearrangement, XXI → XXII, should be reversible, the point of equilibrium being determined by thermodynamic properties of the system. The fact that the reaction is irreversible, at least to any appreciable extent, is indicated by the observation that both XX and XXII are recovered unchanged after prolonged treatment with alkali. This result, and the poor yields obtained in experiments designed to effect ring contraction of D-homo compounds [D. A. Prins and C. W. Shoppee, *J. Chem. Soc.*, 494 (1946)], would appear to be traceable to the strain of the *trans*-hydrindane system.

(25) A. Butenandt, *et al.*, *Ber.*, **68**, 1847 (1935); *ibid.*, **70**, 96 (1937); *ibid.*, **72**, 1112 (1939).

(26) All melting points are corrected. Microanalyses by S. M. Nagy, Department of Chemistry, M. I. T.

(27) T. H. Kritchevsky and T. F. Gallagher, THIS JOURNAL, **73**, 184 (1951).

Magnesium Bromide.—Anhydrous magnesium bromide prepared from 33 mg. of magnesium was taken up in a mixture of 10 ml. of anhydrous ether and 8 ml. of dry benzene. Compound L monoacetate (63 mg.) was added, the ether was removed by distillation, and the resulting mixture was heated under reflux for 3 hours. The product, isolated by ordinary procedures, melted at 175–180°. Crystallization from acetone–petroleum ether gave material, m.p. 185–187°, that did not depress the melting point of L monoacetate.

A similar result was obtained when 20 mg. of L monoacetate and 50 mg. of anhydrous magnesium bromide were heated on the steam-bath in 2 ml. of acetic acid for a period of 4 hours. Prolonged heating led to extensive decomposition and to the production of intractable oils.

Boron Trifluoride–Acetic Anhydride–Acetic Acid.—A solution of 100 mg. of L monoacetate in 10 ml. of acetic acid containing 0.2 ml. of acetic anhydride was treated with 0.2 ml. of boron trifluoride etherate. After standing at room temperature for 18 hours, the reaction mixture was diluted with water and extracted with ether. The ethereal solution was washed with water, dilute sodium hydroxide and saturated sodium chloride and filtered through anhydrous sodium sulfate. The filtrate was then concentrated to dryness, and the residue crystallized from acetone–petroleum ether. 3β,17aα-Diacetoxy-17a-methyl-D-homoandrostan-17-one, 90 mg., m.p. 240–241°, was obtained in this way.

Aluminum Chloride–Acetic Anhydride–Acetic Acid.—A solution of 37.1 mg. of L monoacetate and 75 mg. aluminum chloride in 4 ml. of acetic acid and 1 ml. of acetic anhydride was allowed to stand at room temperature for 3 days. The mixture was diluted with water, and the product was isolated by the procedure described in the preceding experiment. The total crude product melted at 193–195°. Crystallization from acetone–petroleum ether furnished 31.2 mg. of L diacetate (XVIIIb), m.p. 198–199°, that did not depress the melting point of an authentic sample.[21]

Zinc Chloride–Acetic Anhydride–Acetic Acid.—A solution of 55.4 mg. of L monoacetate and 50 mg. of anhydrous zinc chloride in 1 ml. of acetic anhydride and 1 ml. of acetic acid was allowed to stand overnight at room temperature. The crude residue, isolated as described above, melted at 194–196°. Crystallization from acetone–petroleum ether gave 48.6 mg. of pure material, m.p. 198–199°, identical with L diacetate.

Stannic Chloride–Acetic Anhydride–Acetic Acid.—A solution of 35 mg. of L monoacetate in 3 ml. of acetic acid containing 0.2 ml. of acetic anhydride was treated with 3 drops of stannic chloride. After standing at room temperature overnight, the mixture was diluted with water and worked up in the usual way. Compound L diacetate, 29.4 mg., m.p. 197–198°, identical with an authentic specimen,[21] was obtained by crystallization from acetone–petroleum ether.

***p*-Toluenesulfonic Acid in Dioxane–Water.**—A solution of 200 mg. of L monoacetate and 200 mg. of *p*-toluenesulfonic acid monohydrate in a mixture of 8 ml. of dioxane and 2 ml. of water was allowed to stand overnight at room temperature. The reaction mixture was then diluted with water and extracted with ether. The ethereal solution was washed with water, dilute sodium hydroxide and saturated sodium chloride, filtered through anhydrous sodium sulfate and concentrated to dryness. The crude product, 180 mg., m.p. 181–183°, on re-acetylation furnished 170 mg. of L monoacetate, m.p. 190–191°, identical with the starting material.

Reactions of 3β,17β-Dihydroxyallopregnan-20-one 3-Monoacetate (Iso-L Monoacetate). Methanolic Potassium Hydroxide.—A mixture of 200 mg. of iso-L monoacetate and 1 g. of potassium hydroxide in 25 ml. of methanol was refluxed for 1 hour. Re-acetylation of the crude hydrolysis product gave 3β,17aα-dihydroxy-17a-methyl-D-homoandrostan-17-one 3-monoacetate, m.p. 235–237°.[5]

Aluminum Chloride–Acetic Anhydride–Acetic Acid.—A solution of 6.2 mg. of iso-L monoacetate and 30 mg. of aluminum chloride in 3 ml. of acetic acid and 1 ml. of acetic anhydride was allowed to stand at room temperature for 2 days. The reaction mixture was then diluted with water and extracted with ether. The ethereal solution was washed with water, dilute sodium hydroxide, saturated sodium chloride, filtered through anhydrous sodium sulfate and concentrated to dryness. Crystallization of the residual material from acetone–petroleum ether afforded 5.4 mg. of 3β,17β-diacetoxyallopregnan-20-one (IIa), m.p. 222–224°, that did not depress the melting point of an authentic sample. A mixed melting point with 3β,17aβ-diacetoxy-17a-methyl-D-homoandrostan-17-one (m.p. 220–221°)[5] was 190–202°.

Zinc Chloride–Acetic Anhydride–Acetic Acid.—A solution of 25.6 mg. of iso-L monoacetate and 50 mg. of anhydrous zinc chloride in 1 ml. of acetic anhydride and 1 ml. of acetic acid was allowed to stand at room temperature overnight. The product, isolated as described above, weighed 21.0 mg. and melted at 227–228°. The material did not depress the melting point of an authentic specimen of iso-L diacetate.

Stannic Chloride–Acetic Anhydride–Acetic Acid.—A solution of 36 mg. of iso-L monoacetate in 3 ml. of acetic acid containing 0.2 ml. of acetic anhydride was allowed to stand at room temperature overnight. The reaction product was isolated in the usual way and crystallized from ether–petroleum ether; yield 10.8 mg., m.p. 181–183°. A mixed melting point determination with the starting material showed a depression.

***p*-Toluenesulfonic Acid in Dioxane–Water.**—A small sample of iso-L monoacetate was added to a solution of 200 mg. of *p*-toluenesulfonic acid monohydrate in 8 ml. of dioxane and 2 ml. of water. After standing overnight at room temperature, the mixture was diluted with water and extracted with ether. The ethereal solution was washed, dried and evaporated on the steam-bath. The crystalline residue, after re-acetylation, gave starting material, m.p. 174–175°.

Alumina.—Iso-L monoacetate (100 mg.) was chromatographed on 4 g. of neutral alumina. The ether–methanol eluates after crystallization from ether–petroleum ether gave 92 mg. of 3β,17aβ-dihydroxy-17a-methyl-D-homoandrostan-17-one 3-monoacetate m.p. 156.5–158°.[5] Recrystallization from ether–petroleum ether gave a pure sample, m.p. 158–159.5°.

Similar results were obtained when acid-washed alumina was employed.

Reaction of 17α-Hydroxyprogesterone (XVI) with Boron Trifluoride–Acetic Anhydride–Acetic Acid.—A solution of 200 mg. of 17α-hydroxyprogesterone (XVI) in 10 ml. of acetic acid containing 1 ml. of acetic anhydride was treated with 0.3 ml. of boron trifluoride etherate and allowed to stand overnight at room temperature. The solution was then diluted with water and extracted with ether. The ether extracts were combined, washed with water, dilute sodium hydroxide, saturated sodium chloride, and filtered through anhydrous sodium sulfate. The oily residue obtained by evaporation of the solvent was chromatographed on alumina. 17aα-Acetoxy-17a-methyl-Δ^4-D-homoandrostene-3,17-dione, 59 mg., m.p. 179–182°, was obtained. Several recrystallizations from acetone–petroleum ether gave the analytical sample, m.p. 184–185°,[28] $[\alpha]_D$ +132° (*c* 0.56, dioxane). The substance showed characteristic absorption bands in the infrared (CS_2) at 1736 and 1243 cm.$^{-1}$ (acetate), 1720 cm.$^{-1}$ (carbonyl) and 1677 cm.$^{-1}$ (conjugated carbonyl).

Anal. Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.94; H, 8.66.

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(28) This substance is evidently identical with a product obtained in crude form, (m.p. about 170°) from the same reaction by Shoppee (private communication). The amounts of material available to Shoppee did not permit further identification.