# Tracer Studies in Rearrangements of 17-Hydroxy-20-ketosteroids and Observations on the Reaction of Compound L Monoacetate with Aluminum Isopropoxide

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Reductive rearrangement of Compound L monoacetate (I) with aluminum isopropoxide in benzene solution furnishes 3β-acetoxy-17α,17aα-dihydroxy-17-methyl-D-homoandrostane (IVa). Iso-L monoacetate (XXI) rearranges without reduction under these conditions and yields 3β-acetoxy-17aβ-hydroxy-17a-methyl-D-homoandrostan-17-one (XXII). Tracer studies utilizing 17-hydroxy-20-ketosteroids labeled at C-20 with carbon-14 have demonstrated that D-homoannulation of L monoacetate with Lewis acids proceeds in a single step with migration of the 16,17-bond. Rearrangements that occur when L monoacetate and iso-L diacetate are treated with base involve rupture of the 13,17-bond in a one-stage process. Although rearrangements of iso-L monoacetate with Lewis acids have not been investigated by the tracer technique, it seems most probable that D-homoannulation in these cases is accompanied by cleavage of the 13,17-bond as well.

With regard to the D-homoannulation reaction of 17-hydroxy-20-ketosteroids, a mechanism has recently been proposed[1] that satisfactorily accounts for the stereospecificity observed in transformations of these substances promoted by the action of bases and of Lewis acids. In the course of this investigation it was noted that treatment of 3β - acetoxy - 17α - hydroxyallopregnan - 20 - one (I) with aluminum t-butoxide in benzene solution affords a mixture from which small amounts of 3β-acetoxy-17aα-hydroxy- 17a - methyl- D -homoandrostan-17-one (IIa) can be isolated by chromatography on alumina. However, the major portion of the reaction product cannot be obtained in crystalline form by this purification procedure. It was
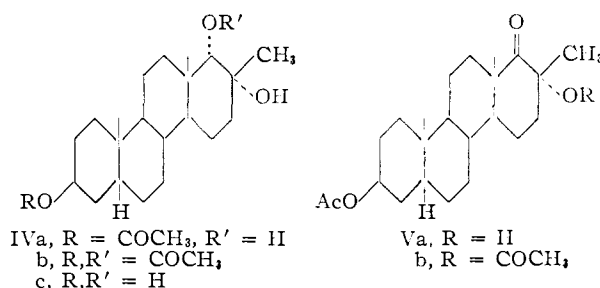


IIa, R = H   b, R = COCH₃
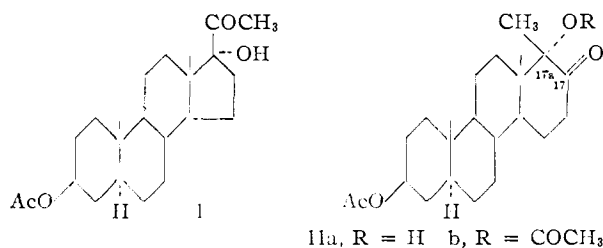
further reported[1] that reaction of I with boron trifluoride and acetic anhydride gives 3β,17aα-diacetoxy - 17a - methyl- D - homoandrostan - 17 - one (IIb) in nearly quantitative yield. These reactions were formulated as proceeding through a coördinated, cyclic intermediate with migration of the 13,17-bond as indicated in the transformation III → II.



III                    II
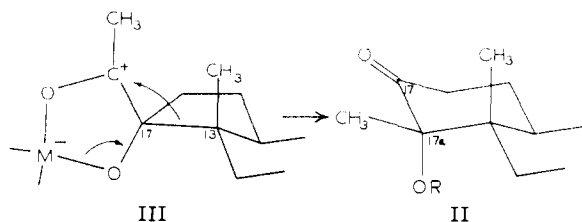
Some doubt as to the validity of conclusions regarding the course of rearrangement of I with Lewis acids arose when it was observed that treatment of this substance with aluminum *isopropoxide* furnishes, in good yield, a triol monoacetate which clearly possesses structure IVa. At about this time Dr. D. K. Fukushima kindly informed us of

(1) R. B. Turner, THIS JOURNAL, **75**, 3484 (1953).

the fact that the mixture obtained from the aluminum t-butoxide reaction can be separated by partition chromatography on silica gel. In addition to 15% of 3β-acetoxy-17aα-hydroxy-17a-methyl-D-



IVa, R = COCH₃, R′ = H          Va, R = H
b, R,R′ = COCH₃                  b, R = COCH₃
c, R,R′ = H

homoandrostan-17-one (IIa), identical with material isolated in our experiments, there is obtained 52% of a crystalline isomer (Va), *the diacetate* (Vb) *of which is identical with the BF₃–acetic anhydride rearrangement product.* The structures assigned to Va and Vb have now been fully substantiated,[2] and repetition of these experiments in this Laboratory has given results in complete accord with those of the Sloan–Kettering and Merck groups. It is therefore clear that rearrangement of 17α-hydroxy-20-ketosteroids in the presence of Lewis acids leads to the formation of 17-methyl-D-homo derivatives rather than to 17a-methyl compounds as suggested earlier. The recent results can be accommodated by the previously proposed mechanistic scheme, if cleavage of the 16,17- rather than the 13,17-bond is postulated (cf. VI → V).[2a]

In order to establish the direction of bond migration in an unambiguous manner and to exclude



VI                    V
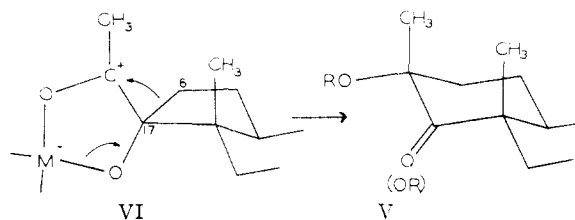
the alternate possibility of a twofold rearrangement involving secondary methyl migration of the type illustrated by the changes VII → IX and VII →

(2) (a) D. K. Fukushima, S. Dobriner, M. S. Heffler, T. H. Kritchevsky, F. Herling and G. Roberts, *ibid.*, **77**, 6585 (1955); (b) N. L. Wendler, D. Taub, D. K. Fukushima and S. Dobriner, *Chemistry & Industry*, 1259 (1955).

XI,[3] we have undertaken an examination of the D-homoannulation reaction in 17-hydroxy-20-ketosteroids labeled at C-20 with carbon-14. The results of this investigation and those obtained in connection with the reaction of I with aluminum isopropoxide are reported in the present communication.

CHART I
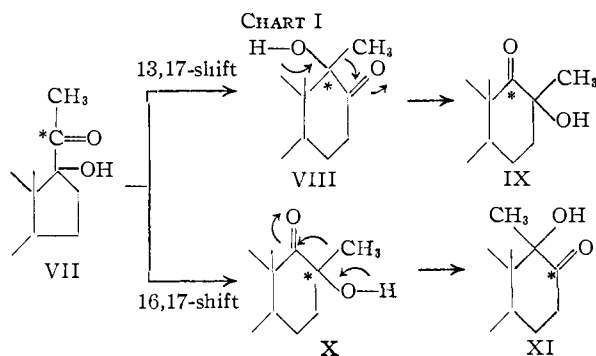


When L monoacetate (I) is treated with aluminum isopropoxide in refluxing benzene solution, there is obtained a crystalline monoacetyl derivative, $C_{23}H_{38}O_4$, melting at 183.5–184°. The infrared spectrum of this material shows strong hydroxyl and acetoxyl absorption, but no bands attributable to a ketonic carbonyl function are detectable. Acetylation of the substance under mild conditions furnishes a diacetate, m.p. 191–191.5°, and hydrolysis of both mono- and diacetyl derivatives yields a substance, $C_{21}H_{36}O_3$, m.p. 240–240.5°, which is devoid of absorption in the carbonyl region of the infrared. Although it is evident from these results that reduction of the keto group of L monoacetate has occurred, neither the triol nor its acetyl derivatives are identical with corresponding derivatives of Reichstein's Compounds J and O (XII and XIII, respectively).
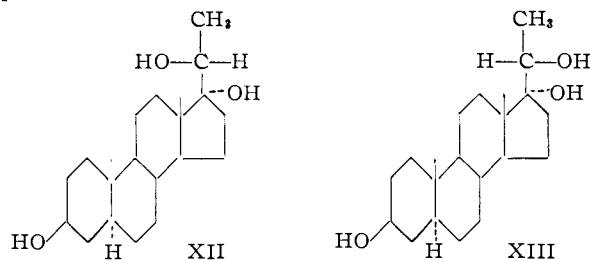


The compounds in question are likewise not identifiable with appropriate derivatives of the four known triols of the D-homo series corresponding to structure XIV, which have been obtained by reduction of the epimeric 17-keto-17a-methyl-17a-hydroxy compounds.[4] It follows, therefore, that the triol, m.p. 240°, is most probably a 17,17a-dihydroxy-17-methyl derivative, of which one epimer, IVc, is formulated above. The correctness of this conclusion was established readily.

(3) It is of some interest that all of the experimental observations, including those dealing with stereochemistry, can be accounted for on this basis. In this connection, however, it should be noted that the statement of N. L. Wendler and D. Taub, Chemistry & Industry, 505 (1955), that the transformation VIII → IX occurs in the presence of alkali and benzaldehyde has since been refuted (ref. 2b).

(4) (a) L. Ruzicka, K. Gätzi and T. Reichstein, Helv. Chim. Acta, 22, 626 (1939); (b) H. E. Stavely, THIS JOURNAL, 63, 3127 (1941).
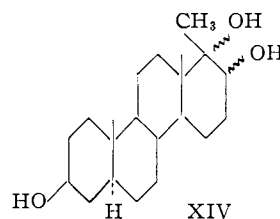


The triol rapidly consumes one equivalent of periodic acid, and chromic acid oxidation of the triol monoacetate (m.p. 184°) yields an acidic product, $C_{23}H_{36}O_5$, m. p. 147.5–148°, that is isomeric, but not identical, with the keto acid XVa obtained by similar oxidation of IIa. The corresponding
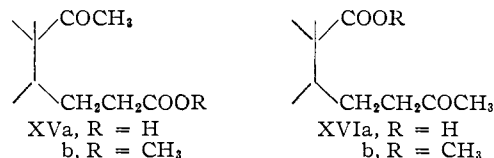


methyl esters also differ and, although methylation of the acid melting at 148° is readily accomplished with diazomethane, the substance is relatively resistant to Fischer esterification.

The presence of a methyl ketone grouping was demonstrated by hypoiodite degradation, which furnishes in addition to iodoform, a diacid convertible into an acetate dimethyl ester identical in all respects with an authentic sample of 3β-acetoxyetioallohomobilianic acid dimethyl ester (XVII).
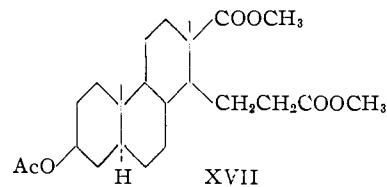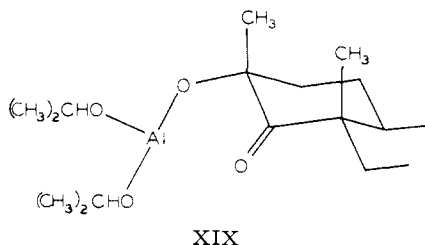


Structure XVIa is thereby established for the chromic acid oxidation product, which was further shown to be identical with keto acids obtained by degradation of the $BF_3$–acetic anhydride and aluminum t-butoxide rearrangement products of L monoacetate. It is therefore concluded that the derivatives resulting from the reaction of L monoacetate with Lewis acids belong to the 17-methyl series (cf. IV). Since it is most unlikely that the aluminum t-butoxide and aluminum isopropoxide reactions follow stereochemically different courses with respect to product configuration at C-17, the only remaining structural problem concerns the configuration of the 17a-hydroxyl group in sub stances derived by the latter procedure.

When 3β-acetoxy-17α-hydroxy-17-methyl-D-homoandrostan-17a-one (Va) is subjected to catalytic hydrogenation, a triol monoacetate (XVIII) melting at 244–246° is obtained that differs from the triol monoacetate IVa, m.p. 184°, described above. Monoacetate XVIII is also obtained from Va by sodium–alcohol reduction and subsequent reacetylation. On the basis of the principle of catalyst hindrance[5] and the generalization that sodium–alcohol reductions of ketones yield the thermodynamically more stable alcohols,

(5) R. P. Linstead, W. von E. Doering, S. B. Davis, P. Levine and R. Whetstone, THIS JOURNAL, 64, 1985 (1942).
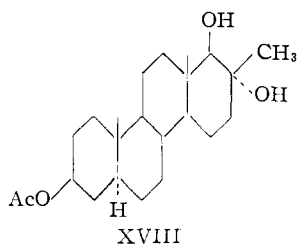
XVIII

an equatorial (17aβ) orientation is assigned to the 17a-hydroxyl group of XVIII, and the corresponding axial (17aα) configuration is deduced for this function in IVa.[6] Additional support for these assignments is derived from comparison of the specific rotations of XVIII (+2.7°) and of IVa (−7.5°) with those of 17aβ-D-homotestosterone (+125.5°) and of 17aα-D-homotestosterone (+85.4°),[7] the configurational designations of the latter compounds being those of Heusser, Herzig, Fürst and Plattner.[7] The stereospecificity observed in the aluminum isopropoxide reduction finds some rationalization in terms ·of steric effects discernible on molecular models. The hydride transfer step is clearly internal and must involve a coördinated complex of type XIX or XX, since no reduction of V, or for that matter of I, by aluminum isopropoxide occurs when the hydroxyl group of the α-ketol system is protected by an acetyl grouping. As long as ring D remains in the "chair" form, the



XIX



XX

most favorable direction of hydride transfer would appear from models to be that leading to the axial alcohol.



XXI               XXII

When 3β,17β - dihydroxyallopregnan - 20 - one 3-monoacetate (iso-L monoacetate) (XXI) is treated with aluminum isopropoxide under conditions employed for the reductive rearrangement of L monoacetate, the product obtained is 3β-acetoxy-17aβ-hydroxy-17a-methyl-D-homoandrostan-17-one (X-XII). Two points of interest emerge from this result. In the first place, in contrast to the behavior of L monoacetate, the carbonyl group of iso-L monoacetate survives the transformation without reduction and, secondly, rearrangement in this case involves apparent migration of the 13,17-bond with formation of a 17a-methyl rather than a 17-methyl derivative.

The failure of the carbonyl group of XXII to undergo reduction in the presence of aluminum isopropoxide is clearly attributable to steric factors associated with the hydride transfer process. Thus examination of molecular models indicates that hydride transfer by an internal process (cf. XIX and XX) from an isopropoxy group to the β-side of the 17-carbonyl function is severely hindered by interactions between the axial 13-methyl group and the methyl groups of the isopropyl residue. Alternatively, attack at C-17 from the α-side is restricted by interactions involving the isopropyl group and the axial methyl group at C-17a.

In order to investigate further the mechanism of the D-homoannulation reaction and, in particular, to establish unequivocally the direction of bond migration, ketols labeled with carbon-14 at C-20 were required. These substances were prepared by well-established procedures, in which 3β-acetoxyandrostan-17-one served as starting material. Treatment of this substance with ^{14}C-labeled hydrogen cyanide yields a mixture of epimeric cyanohydrins, which was dehydrated directly with phosphorus oxychloride in pyridine.[8] The resulting unsaturated nitrile was then treated with methylmagnesium bromide,[9] and the 3β-hydroxy-$\Delta^{16}$-allopregnen-20-one-20-^{14}C obtained in this way was further converted into 3β-hydroxyallopregnan-20-one-20-^{14}C by catalytic hydrogena-

(6) Arguments have recently been advanced by D. H. R. Barton, *Chemistry & Industry*, 664 (1953), in support of the contention that in 1,2,2,6,6-pentasubstituted cyclohexanes (cf. IVa and XVIII) the 1-substituent may be thermodynamically more stable in the axial than in the equatorial position. However, M. G. Ettlinger (private communication) has noted that Barton's treatment does not provide a definitive solution to the problem, since the relative stability of the axial and equatorial forms depends upon the *magnitude* of the various repulsive interactions involved. Thus, the relationships given by Barton may be expressed as

$$a + b > c + d \text{ (known)} \qquad (I)$$
$$a + 2b + e > c + 2d + f \text{ (known)} \qquad (II)$$
$$d + f > b + e \qquad (III)$$

and the fact that II + III gives the known relationship I does not establish the universal validity of III. The problem is more easily handled if the inequalities I and II are replaced by the equalities

$$a + b = c + d + x \qquad (I')$$
$$a + 2b + e = c + 2d + f + y \qquad (II')$$
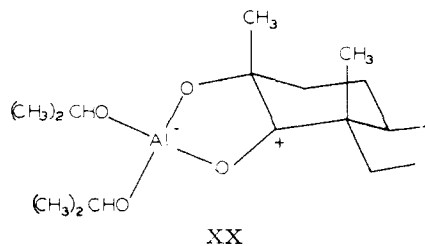
in which x and y are both positive. Subtraction of I' from II' gives
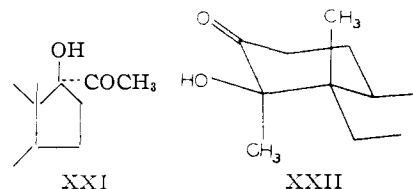
$$b + e = d + f + y - x \qquad (III')$$

and it is clear that the relationship of the quantities $b + e$ and $d + f$ is determined by the relative magnitudes of x and y.

Since the few cases in which axial preference is indicated in these systems (D. H. R. Barton, *J. Chem. Soc.*, 1027 (1953)) involve a bulky carboxyl group as the 1-substituent, we prefer to retain the original concept of equatorial stability in the present instance until evidence to the contrary is forthcoming.

(7) M. W. Goldberg, J. Sicé, H. Robert and Pl. A. Plattner, *Helv. Chim. Acta*, **30**, 1441 (1947); H. Heusser, P. Th. Herzig, A. Fürst and Pl. A. Plattner, *ibid.*, **33**, 1093 (1950).

(8) L. Ruzicka, Pl. Plattner, H. Heusser and J. Pataki, *ibid.*, **29**, 936 (1946).

(9) A. Butenandt and J. Schmidt-Thomé, *Ber.*, **72**, 182 (1939).

tion over palladium. Transformation of the latter substance into the epoxyacetate XXIII was accomplished by the method of Kritchevsky and Gallagher,[10] and hydrolysis of this material, followed by partial reacetylation, finally yielded 3β-acetoxy-
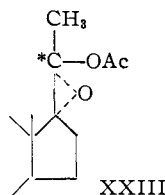


XXIII

17α-hydroxyallopregnan-20-one-20-[14]C (L monoacetate-20-^{14}C) (XXIV), m.p. 189.5–191°. Thermal isomerization of a second sample of epoxyacetate XXIII afforded 3β,17β-diacetoxyallopregnan-20-one-20-[14]C (iso-L diacetate-20-^{14}C) (XXV), m.p. 224–227°,[11] which was employed for base-catalyzed D-homoannulation. Several attempts to effect the acid-catalyzed hydrolysis of the tertiary acetate group of iso-L diacetate and of L diacetate were unsuccessful, and since iso-L diacetate cannot be hydrolyzed with base without rearrangement to the D-homo series, the free ketol was not available by this route for investigation of the reactions with Lewis acids. Both products were purified to constant activity and were fully characterized by direct comparison with authentic samples of the unlabeled compounds.

The rearrangement reactions that have been studied by the tracer technique are listed in Chart II. The position of the labeled carbon atom (17 or 17a) in the various D-homo derivatives obtained in these transformations was determined in the following way. The products were first degraded to

CHART II
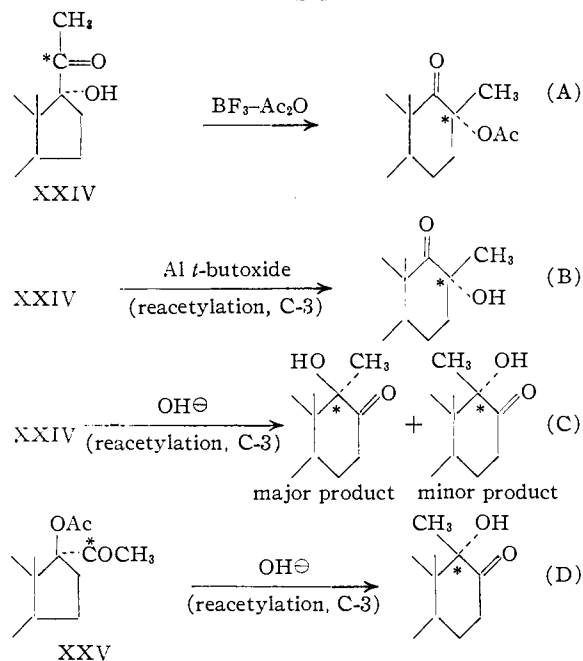


one or the other of the keto acids XXVIa and XXVIIa, which were purified as the corresponding methyl esters (XXVIb and XXVIIb, respectively). In the case of the BF₃–acetic anhydride product, hydrolysis and partial reacetylation at C-3 was carried out prior to chromic acid oxidation. Since the hydrolyzed material could be acetylated under more vigorous conditions to give a diacetate identical with the starting material, the possible occurrence of methyl migration during the hydrolysis step is excluded. 3β-Acetoxy-17aβ-hydroxy-17a-methyl-D-homoandrostan-17-one, obtained (after reacetylation at C-3) as the major product of the base-catalyzed rearrangement of XXIV, proved exceptionally resistant to direct oxidation by chromic acid.[12] This difficulty was circumvented by conversion of the compound into the corresponding glycol by catalytic hydrogenation and cleavage of the glycol with periodic acid. The cleavage product then could be oxidized readily to the keto acid XXVIIa by the action of chromic acid in acetic acid.

Perbenzoic acid oxidation of the keto esters (XXVIb and XXVIIb) furnished the acetoxy esters XXVIII and XXIX, respectively, which were finally subjected to alkaline hydrolysis in aqueous alcohol solution. At the end of the hydrolysis period, the alkaline solutions were acidified with sulfuric acid to a pH of about 3, and the acetic acid liberated was isolated by steam distillation and converted into p-phenylphenacyl acetate for radioactivity measurements. It will be noted that the activity in this fraction suffers a onefold dilution as a result of hydrolysis of the inactive 3-acetoxyl group; a dilution correction hence must be applied in the subsequent calculations. The non-volatile residues obtained after steam distillation contained crystalline material, which, after reacetylation at C-3 for convenience in purification, and recrystallization from acetone–petroleum ether, gave one or the other of the lactones XXX[13] or XXXI, melting at 168.5–170° and at 160–161.5°, respectively.

When steam distillation of the hydrolysis product of XXIX was carried out in strongly acidic solution, the lactone XXXI that was isolated was contaminated by material showing infrared absorption at 1765 cm.⁻¹ characteristic of a 5-membered lactone. Similar results were obtained when pure XXXI was subjected to the same conditions, and structure XXXII is suggested for the contaminant, which, however, has not been isolated in pure form.

The results of radioactivity measurements on various products of the degradative procedure outlined above are given in Table I. The values are expressed in terms of counts/min./mmole and were obtained in dimethylformamide solution by the method described by Schwebel, Isbell and Moyer.[14] In all cases the bulk of the activity is found in the acetate fraction, which contains the carbon atom

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

(11) A. H. Soloway, W. J. Considine, D. K. Fukushima and T. F. Gallagher, ibid., 76, 2941 (1954).

(12) C. W. Shoppee and D. A. Prins, Helv. Chim. Acta, 26, 201 (1943).

(13) H. Levy and R. P. Jacobsen, J. Biol. Chem., 171, 71 (1947); M. F. Murray, B. A. Johnson, R. L. Pederson and A. C. Ott, THIS JOURNAL, 78, 981 (1956).

(14) A. Schwebel, H. S. Isbell and J. D. Moyer, J. Research Natl. Bur. Standards, 53, 221 (1954).

XXVIa, R = H
b, R = CH₃

XXVIII

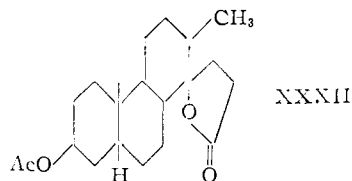XXX          + CH₃COOH

XXVIIa, R = H
b, R = CH₃

XXIX          + CH₃COOH

XXXI
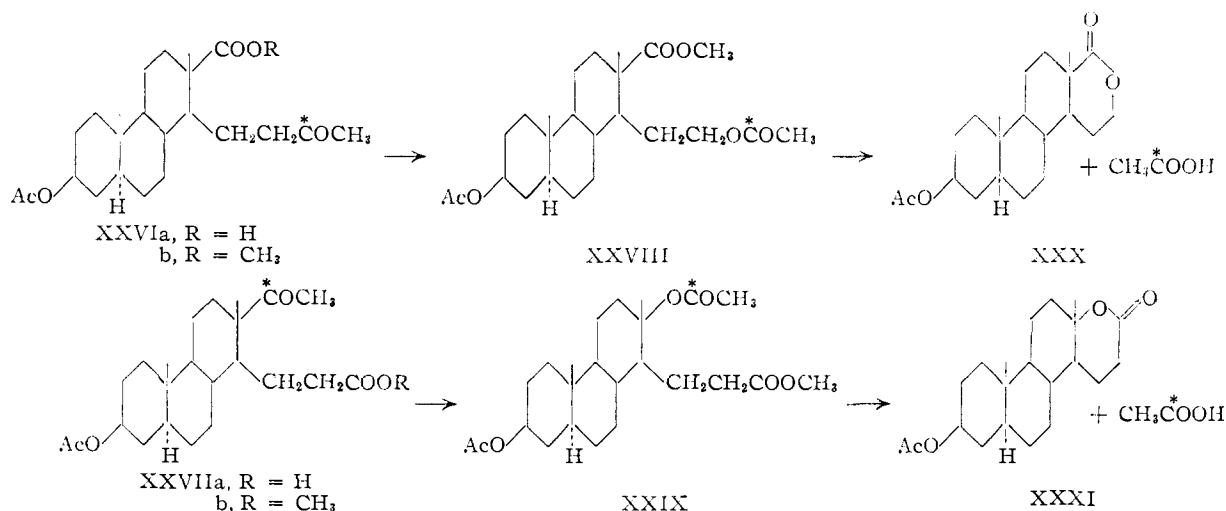
of the tertiary carbinol grouping originally present in the D-homo ketol derivatives. Only traces of residual activity appear in the lactonic degradation products, which possess the original carbonyl carbon atom.



XXXII

Since significant amounts of activity in the lactones can arise only as a result of secondary methyl migration (cf. Chart I), it is clear that within the limits of experimental error (about ±3%) the D-homo rearrangement proceeds in a single step with migration of the 13,17- or 16,17-bond as the case may be. The rather low values for total activity recovered (Table I) are attributable to the fact that the amounts of p-phenylphenacyl acetate obtained in these experiments (5–15 mg.) were in general insufficient to permit exhaustive purification prior to counting.

TABLE I

RADIOACTIVITY DATA (COUNTS/MIN./MMOLE)

| Compound | Rearrangement procedure | | | |
| | A | B | C | D |
|---|---|---|---|---|
| L monoacetate-20-¹⁴C (XXIV) | 4528 | 4528 | 4528 | .. |
| Iso-L diacetate-20-¹⁴C (XXV) | .. | .. | .. | 4620 |
| Keto ester XXVIb | 4366 | 4265 | .. | .. |
| Keto ester XXVIIb | .. | .. | 4443(4281)ᵃ | 4787 |
| Lactone XXX | 34 | 58 | .. | .. |
| Lactone XXXI | .. | .. | 114(49) | 0 |
| p-Phenylphenacyl acetateᵇ | 4120 | 4178 | 4120(4325) | 4330 |
| Activity recovered, % | 92 | 94 | 94(97) | 94 |

ᵃ Parentheses indicate values obtained in the degradation of the minor product from the reaction of L monoacetate with alkali. ᵇ Corrected for dilution with acetic acid derived from hydrolysis of the 3-acetoxy group.

With regard to the preference exhibited by 17α-hydroxy-20-ketosteroids for rearrangement into 17-methyl-D-homo derivatives in the presence of Lewis acids, as opposed to rearrangement into 17a-

methyl-D-homo compounds as observed in the other D-homoannulation reactions, the suggestion has been made that steric hindrance in the transition state favors migration of the 16,17-bond in the former case, whereas electronic factors favor migration of the 13,17-bond in the latter instances.[2a] Similar arguments have been advanced in connection with somewhat analogous rearrangements of certain 17-hydroxy-20-aminosteroids promoted by nitrous acid.[15]

## Experimental[16]

Preparation of 3β-Acetoxy-17α,17aα-dihydroxy-17-methyl-D-homoandrostane (IVa).—A solution of 1.3 g. of 3β-acetoxy-17α-hydroxyallopregnan-20-one (L monoacetate) (I) and 2.0 g. of aluminum isopropoxide in 80 ml. of dry benzene was heated under reflux for 3 hr. The mixture was cooled, acidified with dilute hydrochloric acid and extracted with ether. The ethereal solution was then washed successively with dilute hydrochloric acid, water and saturated sodium chloride solution. After drying over anhydrous sodium sulfate, the solvent was removed, and the residue was chromatographed on neutral alumina; yield 935 mg., m.p. 183.5–184°, [α]D −7.5° (c 1.16, dioxane).

Anal. Calcd. for C₂₃H₃₈O₄: C, 72.98; H, 10.12. Found: C, 73.18; H, 10.27.

A sample of the triol monoacetate IVa, on treatment with acetic anhydride and pyridine, afforded a triol diacetate IVb which crystallized from acetone–petroleum ether with one molecule of acetone of crystallization, m.p. 194–194.5°.

Anal. Calcd. for C₂₅H₄₀O₅·CH₃COCH₃: C, 70.26; H, 9.69. Found: C, 70.06; H, 9.80.

Recrystallization from methylene chloride–petroleum ether gave a solvent free product melting constantly at 191–191.5°, [α]D +29.0° (c 1.10, dioxane).

Anal. Calcd. for C₂₅H₄₀O₅: C, 71.39; H, 9.59. Found: C, 71.25; H, 9.62.

(15) F. Ramirez and S. Stafiej, THIS JOURNAL, 77, 134 (1955); 78, 644 (1956).

(16) All melting points are corrected. Microanalyses were carried out by S. M. Nagy, M.I.T.

3β,17α,17aα-Trihydroxy-17-methyl-D-homoandrostane (IVc) was obtained by hydrolysis of IVa or IVb in the presence of 1% methanolic sodium hydroxide. Three recrystallizations of the crude material from methanol gave the analytical sample, m.p. 240–240.5°, [α]D +10.5° (c 0.94, methanol).

*Anal.* Calcd. for $C_{21}H_{26}O_3$: C, 74.95; H, 10.79. Found: C, 74.68; H, 10.84.

This substance consumed one equivalent of periodic acid on microtitration and furnished the diacetate IVb on re-acetylation.

**Preparation of the Keto Acid XVIa.**—A solution of 252 mg. of $CrO_3$ in 3 ml. of acetic acid containing 3 drops of water was added dropwise to a solution of 466 mg. of the monoacetate IVa in 3 ml. of acetic acid. After standing at room temperature for 0.5 hr., the reaction mixture was diluted with water and extracted with ether. The ethereal solution was washed with dilute hydrochloric acid and then with water until the washes were neutral to litmus. The acidic product was removed by extraction with ice-cold 1% sodium hydroxide, the alkaline extracts being immediately acidified and extracted with ether. Removal of the solvent gave 429 mg. of material melting at 144–145°. Two recrystallizations from acetone–petroleum ether gave the analytical sample, m.p. 147–148°, [α]D −10.9° (c 1.12, dioxane).

*Anal.* Calcd. for $C_{23}H_{36}O_5$: C, 70.37; H, 9.25. Found: C, 70.04; H, 9.34.

The carboxyl group of XVIa could not be satisfactorily esterified with methanol and mineral acid. Treatment of XVIa with excess diazomethane, however, afforded the corresponding methyl ester, which crystallized from acetone–petroleum ether, m.p. 160–160.5°, [α]D −15.4° (c 1.00, dioxane).

*Anal.* Calcd. for $C_{24}H_{38}O_5$: C, 70.90; H, 9.42. Found: C, 71.04; H, 9.50.

**Degradation of XVIa to Dimethyl 3β-Acetoxyetioallohomobilianate (XVII).**—A potassium iodide solution containing 500 mg. of iodine was added to a solution of 100 mg. of keto acid XVIa and 600 mg. of potassium hydroxide in 5 ml. of water. After standing at room temperature for 15 minutes, the precipitated iodoform was removed by filtration, m.p. 119–121° dec. A mixed m.p. with an authentic sample showed no depression. The alkaline filtrate was acidified with dilute hydrochloric acid and extracted with ether. Removal of the ether gave 85 mg. of oil, which was esterified with diazomethane and reacetylated with acetic anhydride and pyridine. After four recrystallizations from methanol, the material melted at 156–156.8° and did not depress the melting point of an authentic sample of dimethyl 3β-acetoxyetioallohomobilianate (m.p. 159.5–160°) kindly supplied by Dr. W. S. Johnson. The infrared absorption spectra of the two samples were identical.

**Preparation of 3β-Acetoxy-17α,17aβ-dihydroxy-17-methyl-D-homoandrostane (XVIII). By Catalytic Hydrogenation.**—A solution of 60 mg. of 3β-acetoxy-17α-hydroxy-17-methyl-D-homoandrostan-17a-one (Va) in 30 ml. of ethanol was shaken in a hydrogen atmosphere with 50 mg. of platinum oxide until reduction was complete. After removal of the catalyst, the solvent was evaporated, and the residue was crystallized three times from acetone–petroleum ether. The product obtained in this way (41 mg.) melted at 244–246°, [α]D +2.7° (c 2.98, chloroform), and did not depress the melting point of a sample prepared as described in the following experiment. The infrared spectra of the two samples were identical but differed from that of 3β-acetoxy-17α,17aα-dihydroxy-17-methyl-D-homoandrostane (IVa).

*Anal.* Calcd. for $C_{23}H_{38}O_4$: C, 72.98; H, 10.12. Found: C, 72.76; H, 10.29.

**By Sodium–Alcohol Reduction.**—Six grams of sodium was added in small pieces over a period of 2 hr. to a solution of 100 mg. of 3β-acetoxy-17α-hydroxy-17-methyl-D-homoandrostan-17a-one (Va) in 35 ml. of absolute ethanol, during which time a slow stream of nitrogen was passed through the reaction vessel. The reaction mixture was then diluted with a large volume of water, acidified with dilute hydrochloric acid and extracted repeatedly with methylene chloride–ether. The combined extracts were washed with water, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was reacetylated (C-3) with acetic anhydride and pyridine at room temperature for 3 hr.,

and the crude product was chromatographed on alumina, yielding 74 mg. of material melting at 235–240°. Three recrystallizations from acetone–petroleum ether gave 48 mg. of XVIII, m.p. 244–246°.

**Rearrangement of Iso-L Monoacetate (XXI) with Aluminum Isopropoxide.**—A solution of 150 mg. of iso-L monoacetate and 265 mg. of aluminum isopropoxide in 15 ml. of dry benzene was heated under reflux for 8 hr. The mixture was cooled, acidified with dilute hydrochloric acid and extracted with ether. The ether extracts were combined and washed successively with dilute hydrochloric acid, water, dilute alkali, water and saturated sodium chloride solution. After drying over anhydrous sodium sulfate and evaporation of the solvent, the residue was allowed to stand overnight with acetic anhydride and pyridine. The acetylation mixture was worked up in the usual way and yielded 129 mg. of crystalline material. Two recrystallizations from acetone–petroleum ether afforded 50 mg. of 3β,17aβ-dihydroxy-17a - methyl - D - homoandrostan - 17 - one (XXII), m.p. 156–157°, that did not depress the melting point of an authentic sample, m.p. 158–159.5°. By chromatography of the mother liquors an additional 49 mg. of product, m.p. 157.5–158.5°, was obtained.

**Preparation of 3β-Acetoxy-17α-hydroxyallopregnan-20-one-20-14C (XXIV).**—A mixture of 500 mg. of 3β-acetoxyandrostan-17-one and 1.5 g. of potassium cyanide containing a tracer amount of carbon-14 labeled sodium cyanide (Tracerlab) in 12 ml. of 95% ethanol was cooled to 0° and treated with 1.6 ml. of glacial acetic acid. The reaction mixture was stirred for 1 hr. at 0° and for 2 hr. at room temperature, during which time all of the material dissolved. The solution was then diluted with a large volume of water, and the solid material that separated was removed by filtration, taken up in ether, washed with water and evaporated to dryness. The crude mixture of cyanohydrin epimers, m.p. 135–140°, was used in the next step without further purification. Evaporation of the aqueous filtrates after neutralization with base permitted recovery of the excess radioactive cyanide, which could then be employed in subsequent preparations.

The cyanohydrin mixture, obtained as described in the preceding paragraph, was dehydrated according to the procedure of Ruzicka, Plattner, Heusser and Pataki[8] with phosphorus oxychloride (0.7 ml.) and pyridine (4 ml.) in a sealed tube at 155°. Three recrystallizations of the crude product from ether gave 317 mg. (84%) of 3β-acetoxy-17-cyanoandrost-16-ene-20-14C, m.p. 159–160°.

Conversion of the unsaturated nitrile into 3β-hydroxy-Δ16-allopregnen-20-one-20-14C, m.p. 201–203°, was accomplished by reaction of the nitrile with methylmagnesium bromide[17] as described by Butenandt and Schmidt-Thomé[9]; yield 81%. Reduction of this material over palladium-on-calcium carbonate in 95% ethanol furnished 3β-hydroxyallopregnan-20-one-20-14C, m.p. 189–192°, in 85% yield.

Treatment of the hydroxy ketone with acetic anhydride and p-toluenesulfonic acid yielded the corresponding 17,20-enol acetate (3-acetyl derivative), which was treated directly with perbenzoic acid in benzene solution.[10] The reaction mixture was worked up in the usual way and, after removal of the solvent, the epoxyacetate XXIII was obtained as a partially crystalline residue. Direct hydrolysis[10] of the crude epoxyacetate with 0.5 N sodium hydroxide in 50% aqueous ethanol for 1 hr. at room temperature gave material, which on reacetylation (C-3) with acetic anhydride and pyridine afforded a pure sample of 3β-acetoxy-17α-hydroxyallopregnan-20-one-20-14C, m.p. 189.5–191°, radioactivity, 4528 counts/min./mmole.

**Preparation of 3β,17β-Diacetoxyallopregnan-20-one-20-14C (XXV).**—A sample of crude epoxyacetate XXIII, obtained in another run carried out as indicated in the preceding experiments, was heated at 235° in a nitrogen atmosphere for 10 minutes.[11] Chromatography of the resulting dark, viscous oil on alumina yielded 3β,17β-diacetoxyallopregnan-20-one-20-14C, m.p. 224–227°, radioactivity, 4620 counts/min./mmole.

**D-Homoannulation Reactions and Degradations to the Keto Esters XXVIb and XXVIIb.**—Rearrangements of L monoacetate-20-14C (XXIV) and of iso-L diacetate-20-14C (XXV) were carried out by procedures that are described in the literature.

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(17) Use of the *bromide* is essential to the successful outcome of this reaction (see ref. 9).

A.   A solution of 300 mg. of XXIV in 30 ml. of acetic acid containing 0.6 ml. of acetic anhydride was treated with 0.6 ml. of boron trifluoride etherate.[1]   After standing overnight at room temperature, 321 mg. of labeled $3\beta,17\alpha$-diacetoxy-17-methyl-D-homoandrostan-17a-one (Vb), m.p. 233–236.5° (the pure product melts at 240–241°) was obtained, which was hydrolyzed directly without further purification by treatment with 400 mg. of potassium hydroxide in a mixture of 40 ml. of ethanol and 14 ml. of water. After standing at room temperature in a nitrogen atmosphere for 7 hr., the steroidal material was extracted with ether–methylene chloride and was reacetylated at C-3 with acetic anhydride and pyridine (3 hr. at room temperature). This procedure afforded 284 mg. of $3\beta$-acetoxy-17$\alpha$-hydroxy-17-methyl-D-homoandrostan-17a-one (Va), m.p. 105–107°, the infrared absorption spectrum of which was identical with that of the product obtained in reaction B.

Chromic acid oxidation of this material (110 mg. of CrO$_3$, 6 ml. of 90% aqueous acetic acid, 2 hr.) furnished, after esterification with diazomethane, 217 mg. of the keto ester XXVIb, m.p. 156–158.5°.

B.   A solution of 689 mg. of XXIV and 1.1 g. of aluminum $t$-butoxide in 55 ml. of dry benzene was heated under reflux for 36 hr.[1,2a]   The mixture was then acidified with dilute hydrochloric acid and extracted with ether. Removal of the ether gave an oily product, which was dissolved in 6 ml. of pyridine and 4 ml. of acetic anhydride and allowed to stand at room temperature for 3 days.   At the end of this time the excess acetic anhydride was decomposed with ice, and the product was isolated in the usual way. Several recrystallizations from acetone–petroleum ether yielded 325 mg. of Vb, m.p. 237–239°, identical in all respects with material obtained by rearrangement of XXIV in the presence of boron trifluoride.   Hydrolysis and partial reacetylation furnished Va, m.p. 107–109°, which was degraded as described in the preceding experiment to keto ester XXVIb.   A somewhat higher yield of Va could be obtained from the aluminum $t$-butoxide reaction by limiting the reacetylation time to 3 hr. and subjecting the crude material obtained in this way to partition chromatography.

C.   L monoacetate-20-[14]C (XXIV), 400 mg., and 4.0 g. of potassium hydroxide were dissolved in 40 ml. of ethanol, and the resulting solution was heated under reflux in a nitrogen atmosphere for 4 hr.[18]   The crude product, after reacetylation at C-3 and chromatography on alumina, furnished 264 mg. of labeled $3\beta$-acetoxy-17a$\beta$-hydroxy-17a-methyl-D-homoandrostan-17-one, m.p. 152–154°, which was identified by direct comparison with a sample obtained from the rearrangement of iso-L monoacetate on alumina.[1] Later eluates afforded 74 mg. of $3\beta$-acetoxy-17a$\alpha$-hydroxy-17a-methyl-D-homoandrostan-17-one melting at 229–233°, which was converted by chromic acid oxidation and subsequent esterification into the keto ester XXVIIb, m.p. 102–104°.

Degradation of the major product (264 mg.) of base-catalyzed rearrangement to XXVIIb was accomplished by the following indirect method.   Hydrogenation carried out in ethanol solution in the presence of a platinum catalyst afforded a crude glycol, which was dissolved in 15 ml. of methanol and treated with a solution of 450 mg. of periodic acid in 5 ml. of water.   After standing overnight at room temperature, the reaction mixture was diluted with water and extracted with ether and ethyl acetate.   Removal of the solvents and oxidation of the residual material with chromic acid gave 128 mg. of an acidic product, which was esterified with diazomethane and reacetylated at C-3 to ensure complete recovery of material that might have undergone hydrolysis during the isolation procedure.   Chromatography on alumina furnished 104 mg. of keto ester XXVIIb, which melted at 103–105° after one recrystallization from acetone–petroleum ether.

(18) J. von Euw and T. Reichstein, Helv. Chim. Acta, **24**, 879 (1941).

D.   A solution of 152 mg. of iso-L diacetate-20-[14]C (XXV) and 0.75 g. of potassium hydroxide in 18 ml. of methanol was heated under reflux in a nitrogen atmosphere for 1 hr.   Reacetylation of the crude product gave 140 mg. of $3\beta$-acetoxy-17a$\alpha$-hydroxy-17a-methyl-D-homoandrostan-17-one, m.p. 235–237°,[12] which was converted in the usual way into keto ester XXVIIb.

**Further Degradative Procedures.**—Degradation of the keto esters XXVIb and XXVIIb, obtained in the preceding experiments, to acetic acid and lactones XXX and XXI, respectively, was carried out by the following typical procedure.

The keto ester XXVIIb, 89 mg., was dissolved in a benzene solution containing an excess of 1.2 $M$ perbenzoic acid and was allowed to stand in the dark at room temperature for 8 days.   The reaction mixture was then diluted with ether and washed with dilute alkali and water.   After drying over anhydrous sodium sulfate, the solvent was removed, and the crude product was purified by chromatography on alumina.   Recrystallization from acetone–petroleum ether gave 54 mg. of the acetoxy ester XXIX, m.p. 165–167°. A sample prepared for analysis from material obtained in a pilot experiment melted at 168.5–170°.

*Anal.*   Calcd. for C$_{24}$H$_{38}$O$_6$: C, 68.22; H, 9.07.   Found: C, 68.26; H, 9.09.

The acetoxy ester XXIX, 54 mg., obtained as described in the previous experiment was dissolved in 4 ml. of methanol and 1 ml. of water containing 290 mg. of potassium hydroxide.   The resulting solution was then heated under reflux for 2 hr., at the end of which time the reaction mixture was cooled and made just acid to congo red by the careful addition of 1 $N$ sulfuric acid.   The acetic acid liberated in the hydrolysis step was removed by steam distillation and collected in a receiver containing 0.5 mmole of sodium hydroxide.   Distillation was continued until approximately 200 ml. of distillate had been collected, and the contents of the receiver were then concentrated under reduced pressure to a volume of about 5 ml. and titrated with hydrochloric acid until an acidic reaction with litmus was just detectable. A solution of 82 mg. of $p$-phenylphenacyl bromide in 10 ml. of ethanol was then added, and the mixture was heated under reflux overnight.   Dilution with water and extraction with ether furnished 78 mg. of semi-crystalline material, which was chromatographed on alumina.   After elution of considerable quantities of $p$-phenylphenacyl bromide, 13 mg. of $p$-phenylphenacyl acetate, m.p. 94–98°, was obtained. Two recrystallizations from aqueous ethanol gave 9.2 mg. of material, m.p. 107–110°, which was employed for radioactivity measurements.

The residue obtained from the steam distillation procedure was extracted with ether–methylene chloride, and the organic layer was washed with dilute sodium bicarbonate solution and with water.   Removal of the solvents gave 40 mg. of $3\beta$-acetoxy-13$\alpha$-hydroxy-13,17-secoandrostan-17-oic acid lactone (XXXI), m.p. 160–161.5°, [$\alpha$]D −40° ($c$ 1.56, chloroform).   A mixed m.p. determination with an authentic sample of XXXI prepared by perbenzoic acid oxidation of $3\beta$-acetoxyandrostan-17-one showed no depression.

Application of this procedure to the degradation of keto ester XXVIb furnished the acetoxy ester XXVIII, m.p. 107–108°.

*Anal.*   Calcd. for C$_{24}$H$_{38}$O$_6$: C, 68.22; H, 9.07.   Found: C, 68.49; H, 9.20.

Hydrolysis of XXVIII gave acetic acid, isolated as $p$-phenylphenacyl acetate and, after reacetylation, $3\beta$-acetoxy-16-hydroxy-16,17-secoandrostan-17-oic acid lactone (XXX), m.p. 168.5–170°, [$\alpha$]D +12.9° ($c$ 1.65, chloroform).

*Anal.*   Calcd. for C$_{21}$H$_{32}$O$_4$: C, 72.38; H, 9.26.   Found: C, 72.59; H, 9.42.

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