[CONTRIBUTION FROM THE SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH, NEW YORK 21, N. Y.]

Rearrangements of Steroidal Ring D Ketols[1]

BY JACK FISHMAN

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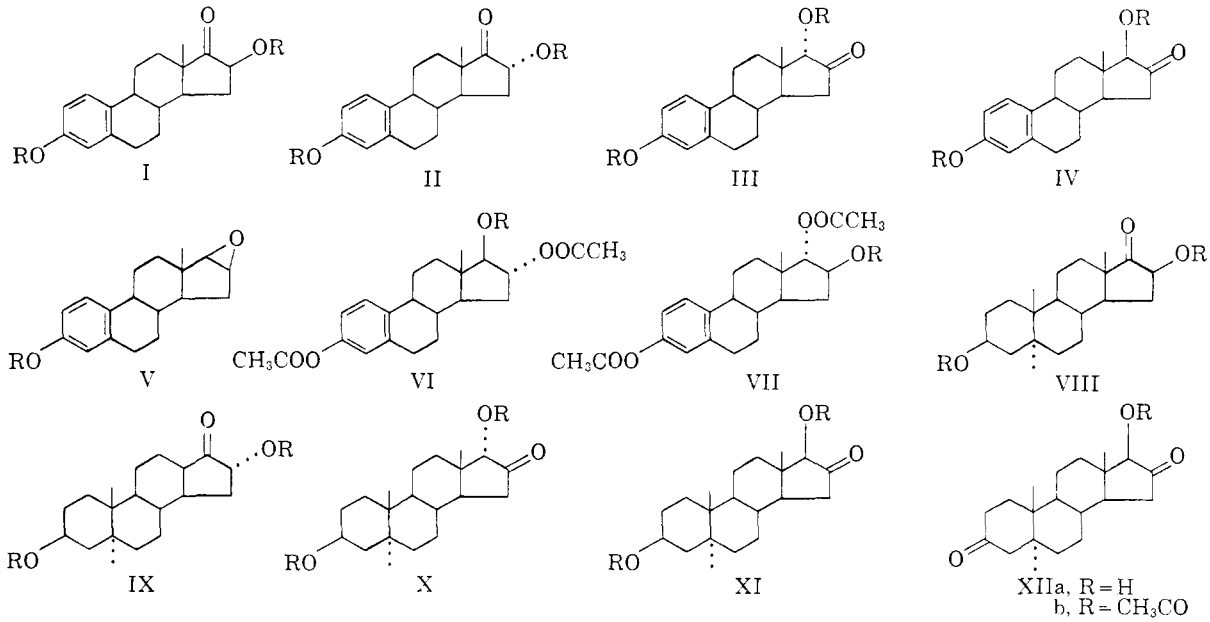
The preparation of 16-ketoestradiol-17α- and 3β,17α-dihydroxyandrostane-16-one is described. The rearrangements of the four isomeric C-16,17 ketols in the estrogen and androstane series are described and discussed. The conformation of ring D ketones is discussed in view of these rearrangements.

Recent developments in the preparation of highly active corticoids[2] have further emphasized the biological importance of ring D substitution in the steroid molecule, particularly at carbons 16 and 17. The synthesis of the new compounds has also served to generate interest in the chemistry of the five carbon ring in steroids with its unusual and sometimes unique aspects. One feature of ring D substitution of particular interest to us was the chemical reactions of the C-16,17-ketols. Of the four possible ketols of the estrogen series isomeric at C-16,17 three have already been prepared. They are 16β-hydroxyestrone (Ia),[3] 16α-hydroxyestrone (IIa)[3] and 16-ketoestradiol-17β (IVa).[4] In order to complete this series of biologically important steroids and to study the interrelationships of the four compounds we undertook the synthesis of the remaining isomer, 16-ketoestradiol-17α (IIIa).[5]

The synthesis of this compound was accomplished by modification of a sequence previously used in the androstane series.[6] Fission of the acetate of the β-epoxide Vb[7] with glacial acetic acid led to the two expected triol diacetates which were separated by chromatography on alumina. The minor product was shown to be 1,3,5(10)-estratrien-3,16α,17β-triol 3,16-diacetate (VIa) by chromic acid oxidation to the known 16α-hydroxyestrone diacetate (IIb).[8] The major product was 1,3,5(10)-estratrien-3,16β,17α-triol 3,17-diacetate (VIIa), which on similar chromic acid oxidation yielded the hitherto unknown 3,17α-diacetoxy-1,3,5(10)-estratrien-16-one (IIIb). 16-Ketoestradiol-17α (IIIa), was obtained by hydrolysis of the diacetate IIIb in refluxing 5% sulfuric acid in ethanol. The new compound (IIIa) was different from the other three isomers by the usual criteria (m.p., rotation, infrared spectrum) and its structure was further confirmed by reduction with lithium aluminum hydride to 3,16β,17α-estriol[7] as expected.



The stability of the new ketol to the acid conditions employed for hydrolysis was unexpected in view of the recent work of Johnson, Gastambide and Pappo.[9] These authors studied the rearrangement of 3β,16β- and 3β,16α-diacetoxyandrostan-17-one (VIIIb and IXb) with both acid and base. They showed that in base both epimers rear-

(1) This investigation was supported in part by a grant from the American Cancer Society and a research grant (CY-3207) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) L. H. Sarett, *Ann. N. Y. Acad. Sci.*, **82**, 802 (1959); E. Oliveto, *ibid.*, **82**, 808 (1959); and references cited therein.

(3) W. R. Biggerstaff and T. F. Gallagher, *J. Org. Chem.*, **22**, 1220 (1957).

(4) M. N. Huffman and M. H. Lott, *J. Biol. Chem.*, **172**, 325 (1947).

(5) Initial experiments on the *in vitro* metabolism of the new ketol have been reported; H. Breuer and L. Nocke, *Biochem. and Biophys. Acta*, **36**, 271 (1959).

(6) J. Fajkos, *Chem. Listy*, **49**, 1218 (1955); *Coll. Czechoslov. Commun.*, **20**, 1478 (1955).

(7) J. Fishman and W. R. Biggerstaff, *J. Org. Chem.*, **23**, 1190 (1958).

(8) N. S. Leeds, D. K. Fukushima and T. F. Gallagher, THIS JOURNAL, **76**, 2943 (1954).

(9) W. S. Johnson, B. Gastambide and R. Pappo, *ibid.*, **79**, 1991 (1957).

ranged to the more stable 17β-hydroxy-16-one XIa; with acid only the 16β-acetoxy compound VIIIb was isomerized while the 16α-epimer IXb was unchanged.[10] Preferring not to account for this difference by the conventional enolization mechanism, these authors suggested an alternative mechanism for the acid-catalyzed rearrangement. Their rationalization involved a reversible stereospecific hydride shift in the protonated form. It was postulated that in acidic medium the 16β-hydroxy-17-ketone VIIIa was in equilibrium with the 17β-hydroxy-16-ketone XIa, and the 16α-hydroxy-17-ketone IXa was in equilibrium with the corresponding 17α-hydroxy-16-ketone Xa. The rearrangement of the 16β-hydroxy-17-ketone VIIIa was ascribed to an equilibrium strongly in favor of the 17β-hydroxy-16-ketone XIa while the stability of the 16α-hydroxy-17-ketone IXa was similarly the result of a favored equilibrium with the 17α-hydroxy-16-ketone Xa. This reasoning, therefore, required that the then unknown 17α-hydroxy-16-ketone Xa should isomerize readily to the 16α-hydroxy-17-ketone IXa in acid solution. Since the behavior of the ketol IIIa, which has the same ring D structure, was evidently not in agreement with these conclusions, a different or modified rationale for these ketol rearrangements appeared necessary.

The reaction of the four C-16,17-ketols derived from estrone was examined in acidic and alkaline media. The nature and approximate extent of rearrangement was most conveniently obtained by paper chromatography of the products in the system chloroform–formamide. Since, however, separation of the isomeric 17-hydroxy-16-ketones from each other in this system was only marginal, a portion of the rearrangement product was reduced with lithium aluminum hydride[11] in ether. The isomeric triols thus formed could be separated effectively on paper in the same system, and the identity of their precursors was readily recognized since the 17α-epimer IIIa yields two triols (3,16β,17α and 3,16α,17α) different from those obtained from the 17β-compound IVa (3,16α,-17β and 3,16β,17β). The results obtained from both chromatograms gave exact information as to the nature of the rearrangement products, and a good approximation of the extent of the reaction was possible from the intensity of the stain when the chromatograms were sprayed with potassium ferricyanide–ferric chloride reagent. As in the androstane series[9] on catalysis with dilute sulfuric acid in ethanol at room temperature 16β-hydroxyestrone (Ia) rearranged in about 90% yield to 16-ketoestradiol (IVa); the other three ketols, IIa, IVa and in particular the new 16-ketoestradiol-17α (IIIa), were unchanged under the same conditions. In dilute methanolic potassium hydroxide at room temperature, on the other hand, 100% of 16β-hydroxyestrone (Ia) and 90% of 16α-hydroxyestrone (IIa) rearranged to 16-ketoestradiol (IVa). Surprisingly, the new compound 16-ketoestradiol-17α (IIIa) was unchanged by this treatment and was also generated from its diacetate by this method. When, however, IIIa was refluxed for 2 hours in 4% potassium hydroxide in ethanol under a nitrogen atmosphere, it was converted essentially in entirety to 16-ketoestradiol-17β (IVa). It is thus apparent that all the isomeric ketols rearrange to 16-ketoestradiol-17β (IVa), but each compound requires different minimum conditions for rearrangement. An explanation for the sequential order of stability among the four compounds can be advantageously considered from the properties of an isolated ketone function at C-16 and at C-17 of the steroid ring D.

Estrone can be converted in essentially quantitative yield to the enol acetate,[8] whereas the corresponding compound with a ketone at C-16, estrone-16,[12] fails to react under the same conditions. Indeed, with a variety of reagents and conditions it has not been possible to prepare an enol acetate of estrone-16.[13] The reluctant enolization of estrone-16 was further confirmed by comparison experiments on the bromination of estrone acetate and estrone-16 acetate.[14] On standing with bromine in acetic acid, the 17-ketosteroid decolorized the reagent much faster than the 16-keto isomer. Since enolization is the rate-determining step in the bromination of a ketone these results were consistent with the inability to prepare an enol derivative of the 16-ketone. This result is particularly surprising since the ketone at C-16 has four α-hydrogens available in contrast to the two alpha to the 17-ketone. A possible explanation for the difference in enolization between the C-16 and C-17 ketones can be advanced on the basis of recent work on the conformation of cyclopentanones and in particular the fused cyclopentane that constitutes ring D of steroids.[15–18] The geometrical requirements of the two possible conformations the half-envelope (C s) and the half-chair (C 2), are such that ring D with a ketone at C-17 very likely exists in C s form (i) while with the ketone at C-16 the C 2 form (ii) is preferred.[19] Thus, enolization of the

(10) The conditions of rearrangement hydrolyzed the acetate groups and the products were identified following reacetylation with acetic anhydride in pyridine.

(11) This reagent was used instead of the more stereospecific sodium borohydride in order to preclude any possibility of rearrangement prior to reduction.

(12) M. N. Huffman and M. H. Lott, THIS JOURNAL, **75**, 4327 (1953).

(13) The enol acetate of 16-ketoandrostan-3β-ol can be prepared but with more difficulty and in much lower yield than the corresponding 17-keto compound.

(14) The acetates were used in order to diminish bromination of the aromatic ring. Similar results were obtained with 16-keto and 17-keto androstane compounds where the only bromine uptake is alpha to the ketone group.

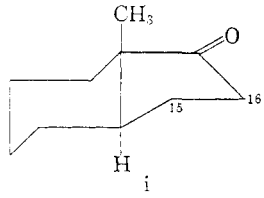
(15) J. E. Kilpatrick, K. S. Pitzer and R. Spitzer, THIS JOURNAL, **69**, 2488 (1947).

(16) G. C. Le Fevre and R. J. Le Fevre, *J. Chem. Soc.*, 3549 (1956).

(17) F. V. Brutcher, Jr., T. Roberts, S. J. Barr and N. Pearson, THIS JOURNAL, **81**, 4915 (1959).

(18) C. W. Shoppee, R. H. Jenkins and G. H. R. Summers, *J. Chem. Soc.*, 3048 (1958).

(19) Measurements of the infrared shifts of the appropriate bromoketones tend to confirm the assigned conformations. Although Shoppee, *et al.*,[18] reports shifts of 8 cm.$^{-1}$ for both 16-bromo-17-ketones, careful measurements in our laboratory have shown these to be 12 cm.$^{-1}$ typical of the bisectional values expected from this half-envelope form. The 17α-bromo-16-ketone, on the other hand, exhibited a shift of 8 cm.$^{-1}$ in concurrence with the quasi-axial value derived from the half-chair form; J. Fishman and C. Djerassi, *Experientia*, **16**, 138 (1960). The same shift has also been found by Brutcher, *et al.*, in the α-halo-2-hexahydroindanones.



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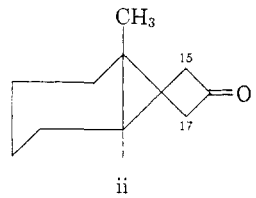

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17-ketone requires no conformational change while enolization of the 16-ketone would require a change from a more favored C-2 to the C-s conformation.[20] Similarly an equilibrium that can lead to a ketone at either C-16 or C-17 will be displaced toward the 16-ketone with its more favored conformation.

The above discussion serves to clarify the relationships in the ketol rearrangements under study. The relative ease with which the two 17-keto epimers Ia and IIa rearrange to 16-ketoestradiol-17β (IVa) is explained by the greater conformational stability of the 16-keto compound. The unusual stability of 16-ketoestradiol-17α (IIIa) is due to the reluctant enolization of the 16-ketone while the eventual preference of the 17β- over the 17α-epimer has both a kinetic as well as a thermodynamic rationalization. Kinetically there would be expected to be a steric preference for ketonization[21] of the enediol from the α-side to yield the 17β-epimer. Similarly, the quasi-equatorial 17β would be preferable to the quasi-axial 17α-hydroxy group on thermodynamic grounds. There still remains, however, the difference exhibited by the 16α- and 16β-hydroxy-17-ketones in their sensitivity to rearrangement with acid. Johnson, Gastambide and Pappo[9] felt that an enolization mechanism was weak because there appeared to be little difference in the availability for removal of the 16α- or 16β-hydrogen. While it is true that molecular models fail to indicate much distinction between the 16α- and 16β-configuration, chemical evidence supports a stereochemical difference between the two sides. Several reactions at C-16 proceed, in the absence of other stereochemical considerations, from the α-side.[22,23] Since there is no apparent conformational difference at C-16 the stereoselective reactions suggest another influence, probably a non-bonded interaction of the angular C-18 methyl group with the β-face of carbon 16. If this were accepted, the stability of the 16α-hydroxy-17-ketone in acid could then be explained on this basis. Even in the more drastic base-catalyzed rearrangement, some difference is observed in that *ca.* 10% of the 16α-hydroxy compound was unchanged as compared to the 100% rearrangement of the 16β.

Johnson, *et al.*,[9] raised another objection to the enolization mechanism in acid catalysis. They report that 3β,16β-diacetoxyandrostan-17-one (VIIIb) was recovered unchanged on standing in glacial acetic acid containing some concentrated hydrochloric acid *and acetic anhydride.*[24] Had enolization occurred, they pointed out, a mixture of the 16α- and 16β-diacetoxy compound should have resulted. In our hands, the above reaction performed as originally described yielded the isomerized product 3β,17β-diacetoxyandrostan-16-one (XIb) in 90% yield. It appears, therefore, that the same mechanism may account for both the base- as well as the acid-catalyzed rearrangements in this ketol series. The reaction under the anhydrous conditions is open to several alternative interpretations, particularly in that no free ketol is present at any time.

In view of the recently described differences in ring D chemistry as affected by the structure of ring A,[18] it was felt necessary to confirm the rearrangement results obtained in the estrogens with those in the androstane series. An attempt was made to prepare the two as yet unknown androstane ketols, 3β,17α-dihydroxyandrostan-16-one (Xa) and 3,16β-dihydroxyandrostan-17-one (VIIIa) from their diacetates. The former was readily obtained upon acid hydrolysis of the corresponding diacetate Xb[6] and thus its stability to acid as in the estrogen series was also confirmed. An attempt, however, to hydrolyze the 3β,16β-diacetoxyandrostane-17-one (VIIIb) by microbiological means used successfully on the corresponding estrogen ketol[3] resulted in rearrangement in ring D and oxidation at C-3 to yield 17β-hydroxyandrostan-3,16-dione (XII). Another unexpected difference between the androstane and estrogen series became apparent when an attempt was made to rearrange the 3β,17α-dihydroxyandrostan-16-one (Xa) to the 17β-epimer XIa under alkali conditions similar to those used successfully in the estrogens. In this case an unidentified oil was obtained, the infrared spectrum of which showed carbonyl absorption at 1709 cm.$^{-1}$ indicative of other changes in the molecule. Similar treatment of the 17β-epimer XIa gave also an oil with an identical infrared spectrum. Thus, while the 17α-hydroxy-16-one Xa is stable to mild alkaline conditions under which the 16α-hydroxy-17-one (IXa) rearranges,[8,9] increasing the alkalinity or temperature of the reaction does not lead to the expected rearrangement, but gives unidentified products. This greater sensitivity of the androstane ketols to alkali is in contrast to the estrogens and may perhaps be rationalized from the formation of the phenoxide ion in the phenolic compounds. Alternatively the differences may be the result of long range conformational effects.

We are at present studying the effect that changes in rings A and B as well as substitution in ring D may have on the chemical behavior of that part of the steroid molecule.

Experimental[25]

16β,17β-Epoxy-$^{1,3,5(10)}$-Estratrien-3-ol Acetate (Vb).—Three grams of the epoxide Va was acetylated in the usual manner with acetic anhydride and pyridine. On work-up, the product crystallized from petroleum ether to give 2.9 g., m.p. 115–117°. The analytical sample obtained by recrys-

(20) The relative ease of isomerization of the 14α-CD-*trans* to the 14β-CD-*cis* form in the presence of a C-15 ketone is sufficiently documented in the literature. This fact indicates that the 15-ketone is similar to the C-17-ketone in the ease of enolization.

(21) H. E. Zimmerman, THIS JOURNAL, **79**, 6554 (1957).

(22) J Fajkos, *Chem. Listy*, **48**, 1800 (1954).

(23) M. N. Huffman and M. H. Lott, *J. Biol. Chem.*, **213**, 343 (1955).

(24) Professor Johnson has informed the author that the experimental conditions for this reaction were reported incorrectly.

(25) Melting points were determined on a micro hot-stage apparatus and are corrected. Analyses were performed by Spang Microanalytical Laboratories. Rotations are in chloroform unless specified otherwise.

tallization from petroleum ether melted 117–118°, $[\alpha]^{27}D$ + 103°.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.58; H, 7.65.

Acetolysis of 16β,17β-Epoxy-1,3,5(10)-estratrien-3-ol Acetate (Vb).—A solution of 2.8 g. of Vb in 100 cc. of glacial acetic acid was refluxed for 2 hours. The cooled solution was then poured slowly into cold aqueous sodium carbonate, and the basic solution was extracted three times with 100 cc. of chloroform. The organic extract was dried, the solvent was evaporated and the residue was taken up in 1:4 benzene–petroleum ether and chromatographed on 100 g. of acid-washed alumina. Elution with 1:4 benzene–petroleum ether gave 0.2 g. of starting material. With 3:10 benzene–petroleum ether there was obtained 1.3 g. of an oil the intrared spectrum of which indicated it to be primarily 3,16β, 17α-estriol triacetate VIIb[7] along with some of the isomeric 3,16α,17β-triacetoxy compound VIb. On changing the solvent to pure benzene there was obtained 400 mg. of crystalline material, m.p. 148–155°. Recrystallization from petroleum ether–ether provided the analytical sample of **1,3,5(10)-estratrien-3,16α,17β-triol 3,16-diacetate (VIa)**, m.p. 158–160°, $[\alpha]^{27}D$ +101°.

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.96; H, 7.72.

Further elution with benzene gave 1.2 g. of the isomeric **1,3,5(10)-estratrien-3,16β,17α-triol 3,17-diacetate (VIIa).** The analytical sample was obtained from petroleum ether–ether and melted 154–156°, $[\alpha]^{27}D$ +20°.

Anal. Calcd. for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found. C, 71.30; H, 7.63.

Oxidation of 1,3,5(10)-Estratrien-3,16α,17β-triol 3,16-Diacetate (VIa).—A small amount of VIa was dissolved in acetone and oxidized with 8 *N* chromic acid. Dilution with water and extraction with ether gave, after drying, evaporation and crystallization from petroleum ether, 16α-hydroxyestrone diacetate (IIb), m.p. 168–171°, identical by infrared spectra comparison and mixed melting point with the authentic material.[8]

16-Ketoestradiol-17α-Diacetate (IIIb).—A solution of 200 mg. of VIIa in 20 cc. of acetone was cooled to 0° and oxidized by the dropwise addition of 8 *N* chromic acid. After 10 minutes at room temperature the solution was diluted with water and extracted with ether. The organic layer was washed with sodium bicarbonate solution and then water. After drying and evaporating, the residue crystallized from petroleum ether to give 134 mg. of product, m.p. 108–111°. The analytical sample was obtained from the same solvent and melted 112–114°, $[\alpha]^{27}D$ −160°.

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.63; H, 7.50.

16-Ketoestradiol-17α (IIIa).—A solution of 120 mg. of the diacetate IIIb in 15 cc. of ethanol and 15 cc. of 0.1 *N* sodium hydroxide was allowed to stand overnight. Dilution with excess 5% sulfuric acid was followed by extraction with chloroform which was washed with sodium bicarbonate solution, dried and evaporated. The crystalline residue weighed 90 mg. and was recrystallized from methylene chloride to give 65 mg. of IIIa, m.p. 246–250°. The analytical sample was obtained from acetone–petroleum ether and melted at 247–252°, $[\alpha]^{27}D$ −140° (ethanol).

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.05; H, 7.65.

The same compound could also be obtained by refluxing the diacetate IIIb in 5% ethanolic sulfuric acid for 12 hours, or permitting it to stand at room temperature in the same reagent for 4 days.

3β,17α-Dihydroxyandrostan-16-one (Xa).—A solution of 50 mg. of the diacetate Xb in 20 ml. of 5% sulfuric acid in ethanol was refluxed for 5 hours. On cooling, the solution was diluted with water and extracted with chloroform. The organic layer was washed with water, dried and evaporated. The residue was crystallized from acetone–petroleum ether to give plates, m.p. 220–224°. A mixture with 3β,17β-dihydroxyandrostane-16-one (XIa) melted 195–215°.

The analytical sample was obtained from acetone–petroleum ether and melted 222–224°, changing from plates to prisms in the process; $[\alpha]^{23}D$ −205° (dioxane).

Anal. Calcd. for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.67; H, 10.11.

17β-Hydroxyandrostane-3,16-dione (XII).—One gram of the diacetate VIIIb[9] was subjected to hydrolysis by *Flavobacterium dehydrogenans* var *hydrolyticum*.[26,27]

The chloroform extract of the reaction was dried and evaporated and the residue chromatographed on 100 g. of Florisil. Elution with chloroform afforded 200 mg. of crystalline material, which was recrystallized from acetone–petroleum ether and melted 195–201°. The infrared spectrum in carbon tetrachloride showed absorption at 1752 (C-16-ketone), 1718 (C-3-ketone), 1415 $cm.^{-1}$ (C-15-methylene group). The analytical sample was obtained from acetone–petroleum ether and melted at 198–202°.

Anal. Calcd. for $C_{19}H_{28}O_3$: C, 74.95; H, 9.27. Found: C, 74.88; H, 9.21.

Rearrangement Experiments. Acid Catalysis.—Ten-milligram samples of the four isomeric estrogen ketols Ia, IIa, IIIa and IVa were each dissolved in 2 ml. of methyl alcohol to which was added 1 ml. of 6 *N* sulfuric acid. After standing at room temperature for 72 hours the solutions were diluted with water and extracted with chloroform which was dried and evaporated. A portion of each residue was chromatographed for 3 hours on Whatman No. 1 paper in the system chloroform–formamide. Standards were run simultaneously and the papers were stained with potassium ferricyanide–ferric chloride reagent. The mobility of the pure compounds in this system was in ascending order—16-ketoestradiol-17β (IVa), 16-ketoestradiol-17α (IIIa), 16β-hydroxyestrone (Ia) and 16α-hydroxyestrone (IIa). Both of the 16-keto isomers IIIa and IVa, as well as 16α-hydroxyestrone (IIa) showed only single spots corresponding to the respective unchanged starting materials. 16β-Hydroxyestrone (Ia) showed two spots, one of low intensity corresponding to unchanged starting material and an intense spot coincident with that of 16-ketoestradiol-17β (IVa).

The remainder of the residues from Ia, IIIa and IVa were suspended in ether and each was stirred with excess lithium aluminum hydride for 2 hours at 0°. Addition of excess 5% sulfuric acid was followed by thorough extraction with chloroform, which was dried and evaporated. The residues were chromatographed on Whatman No. 1 paper in the system chloroform–formamide for 16 hours, and were also stained with the potassium ferricyanide–ferric chloride reagent. Standards which were run simultaneously showed the following mobilities for the four estriols in ascending order: 3,16α,17β, 3,16β,17α, 3,16β,17β and 3,16α,17α. The reduction products from the acid-treated Ia and IVa both showed spots corresponding with 3,16α,17β- and 3,16β,17β-triols, and no others. That obtained from IIIa showed only two spots corresponding to 3,16β,17α- and 3,16α,17α-triols.

Base Catalysis.—Five milligram samples of Ia, IIa, IIIa and IVa were allowed to stand overnight in 3 cc. of 0.05 *N* sodium hydroxide in 60% aqueous methanol. Acidification with excess 0.1 *N* sulfuric acid was followed by extraction with chloroform and the usual work-up. Portions of the residues were chromatographed on paper exactly as described above with the following results: IIIa and IVa both exhibited single spots corresponding to their respective starting materials. The product from IIa exhibited two spots, the major one representing about 90% of the material, corresponding to 16-ketoestradiol-17β (IVa), and a far less intense spot coincident with unchanged IIa. The material from Ia resulted in only one spot identical with IVa.

Rearrangement of 16-Ketoestradiol-17α (IIIa).—A 20-mg. sample of IIIa was refluxed in 10 cc. of 4% potassium hydroxide for 2 hours in an atmosphere of nitrogen. Acidification with dilute sulfuric acid was followed by extraction with chloroform which was dried and evaporated. The residue was acetylated overnight with pyridine and acetic anhydride at room temperature. On work-up, the diacetate was crystallized from petroleum ether, m.p. 135–138°, undepressed on admixture with authentic 16-ketoestradiol-17β diacetate (IVb). The infrared spectrum of the rearrangement product was also identical with authentic IVb.

Rearrangement Experiments with 3β,17α-Dihydroxyandrostan-16-one (Xa).—A 2-mg. sample of Xa was allowed to stand overnight at room temperature in 2 cc. of 0.05 *N*

(26) W. Charney, L. Weber and E. Oliveto, *Arch. Biochem. and Biophys.*, **79**, 402 (1959).

(27) Carried out at Schering Inc., Bloomfield, N. J., through the courtesy of Dr. Hershel Herzog for which the author is very grateful.

sodium hydroxide in 60% aqueous methanol. The product was obtained after the usual work-up and the infrared spectrum showed it to be unchanged starting material.

Another 2-mg. sample of Xa was similarly allowed to stand overnight in 4% ethanolic potassium hydroxide. The infrared spectrum of the oily product was not comparable to either Xa or XIa and showed infrared absorption at 1709 cm.$^{-1}$. A sample of 3β,17β-dihydroxyandrostane-16-one (XIa) similarly treated resulted in a product with an identical infrared spectrum.

Rearrangement of 3β,16β-Dihydroxyandrostan-17-one Diacetate (VIIIb) with Acetic Acid–Hydrochloric Acid.—A solution of 20 mg. of VIIIb in 4 cc. of glacial acetic acid containing 0.2 cc. of concentrated hydrochloric acid was allowed to stand for 48 hours. Dilution with ice-cold water was followed by immediate extraction with chloroform which was washed with water, dried and evaporated. The residue was crystallized from petroleum ether to give crystals with a m.p. 176–179° undepressed on admixture with authentic 3β,17β-diacetoxyandrostan-16-one (XIb). The mother liquors were evaporated and an infrared spectrum of the residue showed it also to be 90% XIb.

Acknowledgment.—The author wishes to express his thanks to Dr. T. F. Gallagher for his advice and interest in this work, and Dr. David K. Fukushima for his helpful discussion. He also wishes to thank Beatrice S. Gallagher and staff for the infrared spectra. The technical assistance of Rosemarie Lehman and Maria Tomasz is also gratefully acknowledged.

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C(16)–C(18) Rearrangements of Steroid Alkaloids

BY JOHN C. SHEEHAN, RICHARD L. YOUNG AND PHILIP A. CRUICKSHANK

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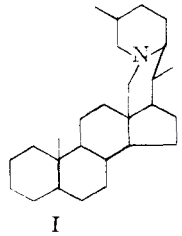
Skeletal rearrangements of certain 18-substituted solanidane alkaloids are described in which the nitrogen migrates between C(16) and C(18). Upon heating solanidane-18-oic acids with acetic anhydride a lactam was formed between C(18) and the nitrogen, while an acetoxy group was introduced at C(16). Acid hydrolysis of these 16α-acetoxy lactam derivatives regenerated the starting solanidane-18-oic acid. Lithium aluminum hydride reduction of 16α-chloro or 16α-tosyloxy lactam derivatives also led to regeneration of the solanidane skeleton. Similar reduction of 16α-acetoxy or 16-desoxy lactam derivatives afforded products free of oxygen at C(18) in which the new ring system had been retained. Hofmann or Emde degradations of isorubijervine monotosylate also were shown to afford compounds with this new skeleton.

The presence of substituents on C(16) and C(18) of steroids has been shown to have a profound effect on physiological activity.[1] As a result there has been considerable interest recently in the preparation of steroids substituted at these positions.[2] Among the naturally occurring steroid derivatives only the alkaloid isorubijervine (VI) is known to have substituents at both of these carbon atoms.[3] The β-nitrogen at C(16) and the hydroxyl at C(18) offer a unique relationship, and their proximity permits an opportunity to study interactions of substituents at these positions.

When solutions of solanidane-18-oic acids are heated under reflux in acetic anhydride solution, a skeletal rearrangement occurs to give the new ring system I for which we propose the name "cevanidane."[4] In the products of this acetolysis reaction the new E ring is in the form of a lactam, and an acetoxy group is introduced at C(16),



I

the site of the C–N bond cleavage.[5] This reaction is illustrated by the conversion of 3β-acetoxy-5-solanidene-18-oic acid (IX) to 3β,16α-diacetoxy-18-oxo-5-cevanidene (X). Regeneration of the solanidane skeleton from certain 16-substituted-18-oxocevanidane derivatives also takes place readily. Hydrolysis of the lactam ring in the presence of the 16α-acetoxy group led to formation of solanidane-18-oic acid. Reduction of the lactam ring with lithium aluminum hydride in the presence of more easily displaceable 16-substituents (tosyloxy or chloro) gave isorubijervine derivatives. These reactions illustrate the facile interconversion of the solanidane (II) and cevanidane (I) ring systems.

No naturally occurring alkaloid has yet been found to have the cevanidane skeleton. The ring system is of considerable interest in that it can be looked upon as the normal steroid analog of cevane (III). The alkaloids of the veratrum group,[6] of which isorubijervine (VI) is a member, can be assigned to one of three skeletal classifications: the solanidane (II) skeleton of isorubijervine (VI), the cevane (III) skeleton of germine, and the skeleton IV found in jervine and veratramine. Only solanidane has the normal steroid skeleton; the other two have a C-nor-D-homo steroid ring system. The cevanidane ring system (I) thus exemplifies a "missing link" between the solanidane and cevane types of alkaloids.

Interaction between C(18) and the nitrogen

(1) J. Fried and A. Borman, *Vitamins and Hormones*, **16**, 303 (1958).

(2) See L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 689–696, 863–867, for summary of recent literature.

(3) (a) F. L. Weisenborn and D. Burn, THIS JOURNAL, **75**, 259 (1953); (b) S. W. Pelletier and W. A. Jacobs, *ibid.*, **75**, 4442 (1953).

(4) This name was chosen to indicate the relationship of the ring system to that of *ce*vane (III) and sol*anidane* (II).

(5) Intramolecular reactions of carboxyl derivatives with γ- or δ-dialkylamino groups have been reported by R. L. Clarke, A. Mooradian, P. Lucas and T. J. Slauson, THIS JOURNAL, **71**, 2821 (1949). Upon heating γ- or δ-dialkylamino acid chlorides, lactams and alkyl chlorides are formed. This reaction is analogous to that obtained with solanidane-18-oic acids in acetic anhydride, and suggests that the acetolysis proceeds *via* activation of the carboxyl as a mixed anhydride.

(6) For a review see K. J. Morgan and J. A. Barltrop, *Quart. Revs.*, **12**, 34 (1958).