AN α-AMINO KETONE TO α-KETOL TRANSFORMATION IN THE REDUCTION OF 16-OXIMINO-17-KETOSTEROIDS[1]

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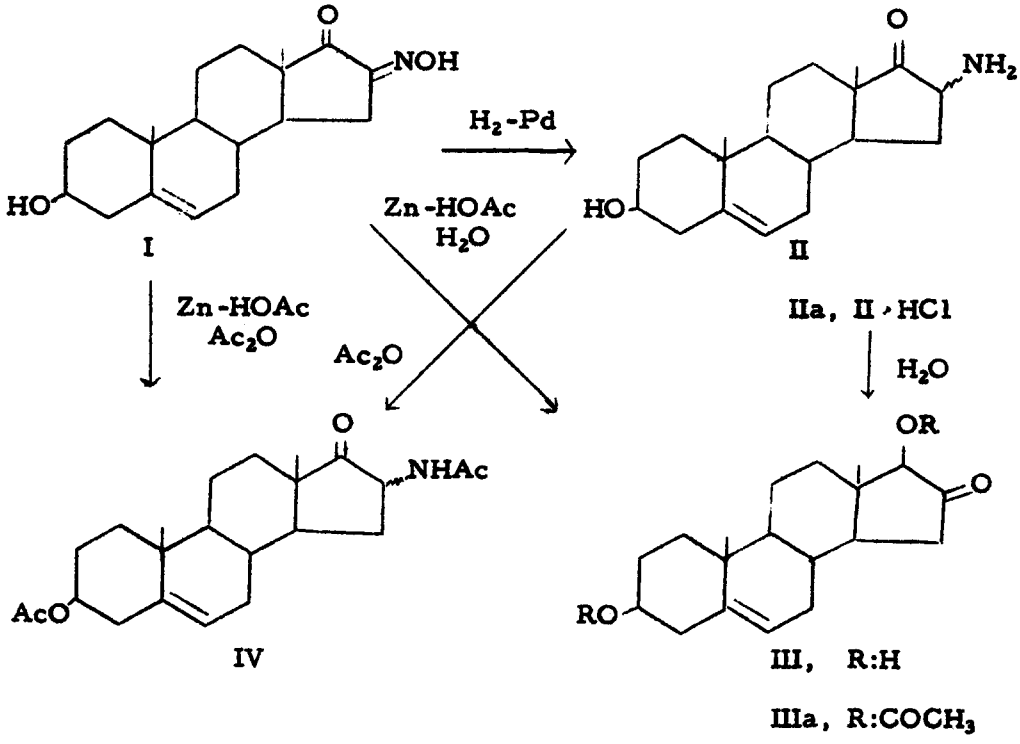
The unusual conversion of 16-oximino-5-androsten-3β-ol-17-one (I) to 5-androsten-3β,17β-diol-16-one (III) with zinc in acetic acid is shown to proceed via the 16-amino-17-ketosteroid intermediate II. Deuterium labelling experiments were used to elucidate the reaction path.

The zinc-acetic acid reduction of 16-oximino-17-ketosteroids was shown by Stodola, Kendall and McKenzie[2] to yield 16-keto-17-hydroxysteroids instead of the expected amino ketones. It was later proved[3] that the 16-keto-17-hydroxysteroids resulting from this reduction possess the C-17 hydroxyl group in the β-configuration.

Normally α-oximino ketones can readily be reduced to α-amino ketones and no ketol formation seems to be observed.[4] This fact and our interest in the chemistry of 16-oximino-17-ketosteroids[5] made it desirable to clarify the unusual reduction path in this system and to establish whether an α-amino ketone is an intermediate in this reaction.

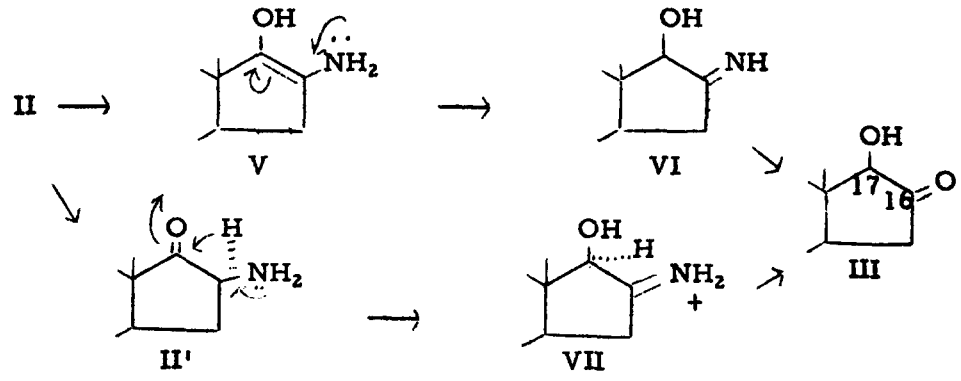
We have now been able to isolate 16ξ-amino-5-androsten-3β-ol-17-one (II), as its hydrochloride IIa, from catalytic reduction of 16-oximino-5-androsten-3β-ol-17-one (I), and to demonstrate its conversion to 3β,17β-dihydroxy-5-androsten-16-one (III) in 67% yield under the conditions of the zinc reduction of α-oximino ketone I to α-ketol III.

Furthermore, an aqueous solution of II or IIa, when heated on the steam bath, was converted in 96% and 81% yield respectively to (III), which upon acetylation afforded the diacetate IIIa identical in every respect with an authentic sample.



The α-amino ketone intermediate II could also be trapped as its amide IV by carrying out the zinc-acetic acid reduction of oxime I in the absence of water and in the presence of acetic anhydride. The amide thus obtained was identical to 3β-acetoxy-16ξ-acetamido-5-androsten-17-one (IV) resulting from acetylation of II or IIa.

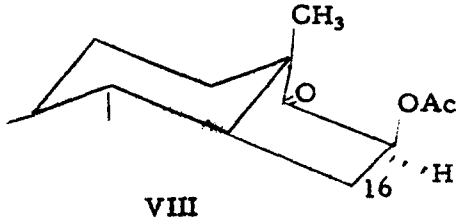
In view of these findings, we suggest that the first step in the zinc-acetic acid reduction of 16-oximino-17-ketosteroids is the reduction of the oximino group to the amine, followed by tautomerization and subsequent hydrolysis of the 16-imino compound VI to the 16-ketone III in the presence of water.



Unlike the amino ketone II, its amide IV was recovered unchanged upon heating in aqueous solution, indicating the unavailability of the electron pair on nitrogen in IV to assist step V → VI. Accordingly, the amide IV was found not to exchange its 16-H for deuterium upon warming with deuterium oxide, as indicated by the lack of diminution of the resonance signal at 5.85 τ in the n.m.r. spectrum. The readiness with which the 16-amino-17-ketosteroid II isomerizes to a 16-imino-17-hydroxysteroid VI probably reflects relief of non-bonded interactions in the D-ring during the process and is reminiscent of the conversion of 3β,16β-diacetoxyandrostan-17-one (but not of the 16α-isomer) to III in the presence of acid or base.[6] The latter data suggest that the amino group in II also might be in the β-configuration.

The fact that 16α-acetoxy-17-ketosteroids are not converted to III on hydrolysis, like 16β-acetoxy-17-ketones, has led Johnson et al.[6] to discount enolization as the reaction path and to postulate a reversible stereospecific hydride shift analogous to that pictured in II' → VII. Yet, an explanation involving a preferential hydride shift of 16α-H, but not of 16β-H, suffers from the same shortcomings as an explanation of preferential enolization. The stereospecific hydride shift reasoning requires that 17α-hydroxy-16-ketosteroids should isomerize

to 16α-hydroxy-17-ketosteroids in acid solution. Fishman,[7] however, has shown that 17α-hydroxy-estrone-16 was stable in acid, i.e., was not converted to 16α-hydroxy-estrone, and in base was epimerized to the more stable 17β-hydroxy-estrone-16. Conformational analysis of the system, on the other hand, does indicate that enolization of the 17-keto function would lead to greater reduction of non-bonded interactions (cf. CH_3 and OAc in VIII) in 16β than in 16α-substituted compounds.



VIII

To differentiate, at least in the case of our amino ketone II, between an enolization, cf. V, and a hydride transfer mechanism, cf. II', we carried out the conversion of II to III in deuterium oxide. Incorporation of deuterium at C-17 would favor an enolization path, whereas a 17α-H in the product would indicate hydride transfer from the 16-position.

An n.m.r. spectrum as well as infrared studies of the product III, obtained from a reaction of amino ketone II in deuterium oxide, indicate incorporation of deuterium at C-17; under similar conditions (even in the presence of two equivalents of ammonia) ketol III exchanges only its hydroxyl hydrogens. The slow enolization in the 16-ketosteroid III can be explained by its ability to assume the energetically more favored half chair conformation.[8] The fact that enolization is faster in 17-keto than in 16-ketosteroids is amply substantiated by the relative ease of bromination and enol acetate formation in these systems.[7]

However, deuterium incorporation at C-17 in III could also result if there were a rapid enolization leading to exchange of the C-16 hydrogen for deuterium in the amino ketone II, followed by deuteride

transfer. To exclude this possibility the amino ketone II was treated with deuterium oxide under reaction conditions for a short period of time (15 min.). The recovered II did not contain deuterium at C-16. The results of these experiments are incompatible with a hydride shift mechanism and suggest the alternate enolization path, cf. V.

The applicability of the reaction to the conversion of other α-amino ketones to ketols is under investigation.

Experimental

Melting points were taken on a Fisher melting block and are uncorrected. Analyses were performed by A. Bernhardt Laboratories, Muelheim, Germany. Infrared spectra were deteremined in potassium bromide pellets with a Beckman IR-5 infrared spectrophotometer. The n.m.r. spectra were run on a Varian Model A-60 instrument.

16ξ-Amino-5-androsten-3β-ol-17-one hydrochloride (IIa). Hydrogenation of 952 mg. of 16-oximino-5-androsten-3β-ol-17-one (I)[5] m.p. 253-256°, in 35 ml. of anhydrous methanol saturated with dry hydrogen chloride was carried out in the presence of 300 mg. of 10% palladium-on-charcoal at room temperature and atmospheric pressure. The hydrogenation was interrupted after 1 hr. during which period 6 mmoles (135 ml.) of hydrogen had been absorbed. The reaction mixture was filtered to remove the catalyst and the filtrate was evaporated under reduced pressure to yield a crystalline residue. The solid was crystallized three times from absolute methanol-ether to give 615 mg. (60% yield) of white chalky rods decomposing above 235°.

Anal. Calcd. for $C_{19}H_{30}O_2NCl$: C, 67.14; H, 8.90; N, 4.12. Found: C, 67.37; H, 8.81; N, 4.02.

Conversion of the Amino Ketone II or its Hydrochloride (IIa) to 3β,17β-Dihydroxy-5-androsten-16-one (III). --To a solution of 150 mg. of 16ξ-amino-5-androsten-3β-ol-17-one hydrochloride (IIa) in 5 ml. of glacial acetic acid and 0.3 ml. of water at 40-45° was added with stirring 400 mg. of zinc dust. After the addition of zinc, 0.2 ml. of water was added and the light yellow mixture was refluxed 1 hr., cooled and filtered to remove the zinc. The clear solution was poured into ice water and the product, 90 mg. (67% yield), melting at 130-150° was collected. The diol III melted at 198-201° (lit.,[3] m.p. 197-199°) after two recrystallizations from aqueous methanol and had an infrared spectrum identical to that of the authentic sample prepared according to Stodola.[2]

In another experiment a solution of 650 mg. of IIa in 25 ml. of distilled water was heated on the steam bath for 20 hr., cooled, and filtered to yield 362 mg. of product melting at 190-210°. The light yellow aqueous filtrate was further heated on the steam bath for 24 hr. to yield 78 mg. of product melting at 185-195°. An additional 33 mg., m.p. 123-133°, was obtained by heating the filtrate an additional 36 hr. The infrared spectrum of each fraction was identical to that of authentic sample. The three fractions (473 mg., 81% yield) were combined and recrystallized from ethanol-water to yield 208 mg., m.p. 198-200°. No mixed melting point depression with authentic sample was observed. Acetylation of this material with acetic anhydride-pyridine yielded 194 mg., m.p. 126-126.5° after crystallization from ethanol-water. The melting point was not depressed when admixed with authentic diacetate (lit.,[3] m.p. 124.5-125°), and the infrared spectrum was identical to that of the authentic diacetate III.

In a similar manner, the free amino ketone II (200 mg., m.p. 185-195° dec.), obtained by neutralization of IIa, in 40 ml of reagent grade acetone (distilled from $KMnO_4$) and 20 ml. of distilled water was refluxed (58°) for 24 hr. The acetone was removed by distillation and the precipitated product (197 mg., m.p. 125-133°) collected. Thin-layer chromatography indicated one major component and one minor impurity. Recrystallization from acetic acid-water and ethanol-water gave 68 mg., m.p. 194-197°. The melting point was not depressed upon admixture with authentic sample; in addition, the infrared spectra of both samples were identical. The diacetate of this material was identical to authentic diacetate in every respect.

On the other hand, 16-acetamido-5-androstene-3β-ol-17-one acetate (IV) was recovered unchanged upon refluxing for 24 hr. in acetone-water.

Labelling Experiments. --Heating of 16-amino-5-androsten-3β-ol-17-one II (100 mg., m.p. 185-195° dec.) in acetone (4 ml.) and 99% deuterium oxide (2 ml.) for 7 hr. gave ketol III, the spectrum of which showed O-D (2488 cm^{-1}) and C-D (2096 cm^{-1}) absorption in the infrared. An n.m.r. spectrum of IIIa, obtained by acetylation of III, indicated replacement of the 17-H in IIIa by deuterium to the extent of ca. 70%, as measured by the intensity of the singlet at 5.11τ.

In a comparison experiment ketol III was heated with acetone-deuterium oxide for 24 hr. The infrared spectrum of recovered III, m.p. 193-196°, indicated O-D absorption which disappeared on acetylation. There was no decrease in the intensity of the singlet responsible for the 17-H absorption in III (6.00τ) or IIIa (5.11τ). When the ketol III (200 mg.) was heated one hour at 55° in dioxane-

deuterium oxide containing one drop of concentrated ammonia and the solution was reduced to dryness, the n.m.r. spectrum of recovered III showed no decrease in the intensity of the singlet responsible for the 17-H absorption. However, the infrared spectrum of this material indicated absorption at 1745 as well as 1710 cm^{-1}. Fishman also observed absorption at 1710 cm^{-1} in the infrared when 3β,17β-dihydroxy-androstane-16-one was treated with dilute base at room temperature. This reaction is being further investigated.

A solution of 150 mg. of II in 1.4 ml. of dioxane and 1 ml. of 99% deuterium oxide was heated at 50-55° for 15 min. and the material was precipitated (112 mg., m.p. 185-195° dec.) by the addition of 4 ml. of deuterium oxide with cooling. The n.m.r. spectrum of recovered II indicated no replacement of the 16-H by deuterium as measured by the intensity of the signal at 6.7τ.

When the amide IV (200 mg. in 5 ml. of dioxane and 4 ml. of 99% D_2O) was heated to reflux for 6 hr. and the solution was evaporated to dryness, the residue (m.p. 112-115°) showed strong absorption at 2387 cm^{-1} (N-D) and the band at 1470 cm^{-1} was intensified. The amide II band, present in the starting material at 1567 cm^{-1}, disappeared upon deuteration. The n.m.r. spectrum indicated no replacement of the 16-H by deuterium, as measured by the intensity of the peak at 5.85τ.

16β-Acetamido-5-androsten-3β-ol-17-one acetate (IV). a. Acetylation of 16-Amino-5-androsten-3β-ol-17-one Hydrochloride (IIa). --A solution of 34 mg. of IIa in 1.0 ml. of dry pyridine and 1.0 ml. of acetic anhydride was allowed to stand for 24 hr., then poured into ice water. The product (34 mg.) melted at 105-110°

and was crystallized from methanol-ether Skellysolve F (b.p. 40-60°) to give 15 mg., m.p. 113-116°. ν_{max} 3378 cm^{-1} (NH), 1739 cm^{-1} (17 C=O), 1721 cm^{-1} (acetate C=O).

Anal. Calcd. for $C_{23}H_{33}O_4N$: C, 71.29; H, 8.58; N, 3.61

Found: C, 71.11; H, 8.68; N, 3.63.

b. Reductive Acetylation of Oxime I. --To a solution of 317 mg. of I in 11 ml. of glacial acetic acid and 2 ml. of acetic anhydride was added with stirring 0.8 g. of zinc dust. The mixture was stirred at 55° and an additional 2 ml. of acetic anhydride was added. Stirring was continued at 55-60° for 9 hr. The mixture was filtered to remove excess zinc and the filtrate was poured into 300 ml. of ice water. The product (211 mg.) melted at 112-117° and was crystallized from methanol to yield 146 mg. melting at 112-114°. This amide is identical by infrared spectrum and mixed melting point experiments with IV obtained from the acetylation of II (see above).

References

1. (a) This investigation was supported by Public Health Service Grant CY-4474 from the National Cancer Institute.
   (b) Presented in part before the Division of Organic Chemistry at the 146th National Meeting of the American Chemical Society, Denver, Colo., Jan., 1964.
   (c) Paper V on The Chemistry of Oximes. For paper IV see A. Hassner and W. A. Wentworth, Tetrahedron Letters in press.

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3. M. N. Huffman and M. H. Lott, J. Am. Chem. Soc., 69, 1835 (1947); ibid., 71, 719 (1949); ibid., 73, 878 (1951). For the corrected assignment see ref. 6(b).

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(b) N. S. Leeds, D. K. Fukushima and T. F. Gallagher, ibid., 76, 2943 (1954).

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