Beckmann Rearrangement of 3-Aza-A-homo-4α-androsten-4,17-dione Oxime and 3-Oxo-13α-amino-13,17-seco-4-androsten-17-oic 13,17-Lactam Oxime

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Rearrangements of 3-aza-A-homo-4α-androsten-4,17-dione oxime produced a mixture of the normal lactam product and the product of a "second order" cleavage, an unsaturated nitrile. The lactam 3,17α-diaza-A,D-bishomoandrost-4α-ene-4,17-dione was also obtained from the rearrangement of the *syn*-3-oxo-13α-amino-13,17-seco-4-androsten-17-oic-13,17-lactam oxime. The resolution of *syn*- and *anti*-isomers of VIII was effected by column chromatography and their structure was determined by spectral data.

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Our recent studies of modified steroids esterified with carboxylic derivatives of *N,N*-bis(2-chloroethyl)aniline, produced good activity in the transplantable animal tumors [1-4].

Thus it was found of interest to effect the synthesis of 3,17α-diaza-A,D-bishomoandrost-4α-ene-4,17-dione (VII) and to test it for antitumor activity.

3-Aza-17β-hydroxy-A-homo-4α-androsten-4-one (III) [5,6], gives by oxidation the 3-aza-A-homo-4α-androsten-4,17-dione (IV). Treatment of IV with hydroxylamine hydrochloride in a mixture of pyridine-ethanol produced the corresponding ketoxime V. Beckmann rearrangement of 3-aza-A-homo-4α-androsten-4,17-dione oxime in purified dioxane with thionyl chloride formed the diaza compound VII and the "second order" Beckmann cleavage product, 3-aza-A-homo-13,17-seco-4α-androsten-4-ene-13(18)-en-17-onitrile (VI).

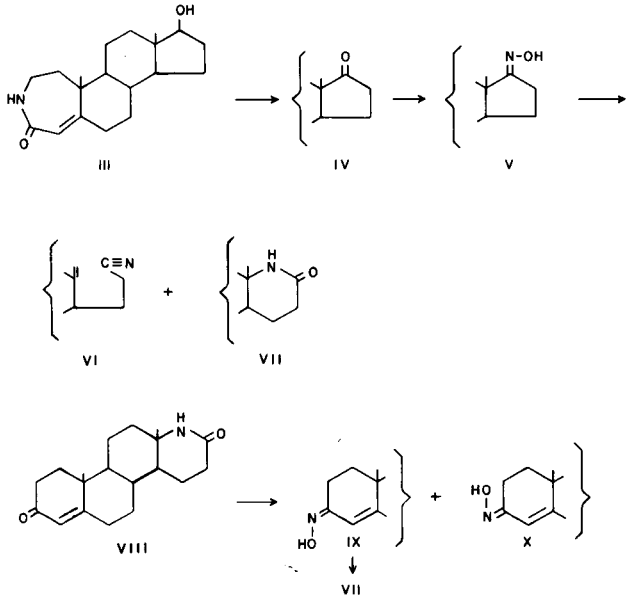
In the formation of ψ-cyano-olefin the hydroxy group of the ketoxime should be *trans*-coplanar and have antiparallel arrangement to one of the 18-CH_3 protons [7].

Singh and Parashar [8] reported Beckmann rearrangement of unresolved androst-4-ene-3,17-dione dioxime and they obtained lactam VII without isolation of the unsaturated nitrile VI.

These authors have reported that Beckmann rearrangement of unresolved 17α-aza-D-homo-androst-4-ene-3,17-dione oximes produces 54% of the lactam VII.

We examined further the reaction of 3-oxo-13α-amino-13,17-seco-4-androsten-17-oic 13,17-lactam (VIII) [9] with hydroxylamine. From this experiment two ketoximes IX and X were obtained. The resolution of *syn*- and *anti*-isomers was effected by column chromatography on silica gel, eluting with a mixture of chloroform:methanol (98:2). The assignment of *syn*- and *anti*-configurations was made from chemical shifts of the olefinic proton. The nmr spectrum of *syn*- showed a downfield shift, relative to the *anti*- of 71 Hz for the vinyl proton.

When thionyl chloride was used as catalyst for the rearrangement of ketoxime IX, lactam VII was obtained.



EXPERIMENTAL

Melting points were determined on a Fisher Johns melting point apparatus and are uncorrected. The ir spectra were recorded with a Perkin-Elmer 521 in solid phase potassium bromide. The nmr spectra were determined with a Varian Associates A-60 and XL-100 instrument using deuteriochloroform as a solvent and tetramethylsilane as the internal standard. Ultraviolet spectra were measured in ethanol solution on a Cary Model 11 instrument. Elemental analyses were performed by the Analytical Laboratory of the National Research Foundation.

3-Aza-17β-hydroxy-A-homo-4α-androsten-4-one (III).

Testosterone-17β-acetate (6.3 g) was dissolved in a mixture of 25 ml of ethanol and 25 ml of pyridine. Hydroxylamine hydrochloride (5.5 g) was added to this solution and the mixture was heated under reflux for 2 hours. The solution was poured into ice-water, and the resulting precipitate was collected by filtration, washed with water and dried, to yield 6.8 g of mixture of *syn*- and *anti*-oximes. The product mixture (6.5 g) was chromatographed on a column of silica gel (200 g) prepared with chloro-

form. Elution with benzene-ethyl acetate (5:1) yielded *anti*-ketoxime (3.5 g). Crystallization from methanol-chloroform gave mp 204-205°; Rf, 0.33 (benzene-ethyl acetate 17:3), $[\alpha]_D^{20}$ + 142 (c, 1.3 chloroform); ir: ν max 3275 (OH), 1750, 1240 (C=O), 1650 cm^{-1} (C=C); uv: λ max 241 mμ (ϵ 21,300); nmr: δ 0.83 (18-CH_3), 1.08 (19-CH_3), 2.03 (17β-CH_3CO), 4.6 (17α-H), 5.8 (C=CH).

Anal. Calcd. for $C_{21}H_{31}NO_3$: C, 73.04; H, 8.98; N, 4.05. Found: C, 72.90; H, 8.70; N, 4.02.

Further elution of the column with benzene-ethyl acetate (3:1) yielded the *syn*-isomer (1 g). Crystallization from benzene-hexane gave mp 186-188°, Rf, 0.3, $[\alpha]_D^{20}$ + 220 (c, 1.1 chloroform); ir: ν max 3500 (OH), 1725, 1260 (C=O), 1650 cm^{-1} (C=C); nmr: δ 0.83 (18-CH_3), 1.1 (19-CH_3), 2.03 (17β-CH_3CO), 4.6 (17α-H), 6.44 (C=CH).

Anal. Calcd. for $C_{21}H_{31}NO_3$: C, 73.04; H, 8.98; N, 4.05. Found: C, 72.84; H, 8.69; N, 4.14.

A mixture of (7.5 g) of *syn*- and *anti*-testosterone-17-acetate oximes was dissolved in 180 ml of purified dioxane. The mixture was cooled to about 10°, and while the mixture was continuously stirred, 7.5 ml of purified thionyl chloride was added dropwise. The mixture was kept at room temperature, stirred for one hour poured into a solution of 2*N* potassium bicarbonate and extracted with chloroform. The organic layer was washed with water, dried over sodium sulfate and the solvent was removed under reduced pressure yielding solid material which on tlc gave three spots. This residue was chromatographed on a column of silica gel (250 g) prepared with chloroform. Elution with benzene-ethyl acetate (7:3) gave a mixture of *syn*- and *anti*-oximes. Further elution of the column with chloroform-methanol (9:1) gave the 3-aza-17β-acetoxy-A-homo-4α-androsten-4-one in 55% yield. Crystallization from acetone-*n*-hexane gave mp 239-241°; ir: ν max 3300, 3200 (NH), 1750, 1250 (CH_3CO), 1680, 1615 cm^{-1} (NHCO); nmr: δ 0.72 (18-CH_3), 1.13 (19-CH_3), 4.6 (17α-H), 5.7 (C=CH).

This compound was hydrolysed with 4*N* lithium hydroxide to 3-aza-17β-hydroxy-A-homo-4α-androsten-4-one (III) using the Mazur [5] method, mp 283-285° (ethanol) (lit [5] mp 288-291°); ν max 3300-3200 (OH, NH), 1670, 1625 cm^{-1} (NHCO); uv: λ max 221 mμ (ϵ, 17,200).

3-Aza-A-homo-4α-androsten-4,17-dione (IV).

Jones reagent (26 ml) was added dropwise with stirring to a cool suspension of 3-aza-17β-hydroxy-A-homo-4α-androsten-4-one (9.09 g) in two liters of acetone. After 24 hours the reaction mixture was diluted with water and extracted with chloroform. The chloroform extract was washed with water, dried and the solvent was removed under reduced pressure. The residue was taken up in chloroform and passed through a column of silica gel. The product so obtained was crystallized from ethyl acetate to give 6.5 g, mp 219-221°; ir: ν max 1740 cm^{-1} (C=O).

Anal. Calcd. for $C_{19}H_{27}NO_2$: C, 75.74; H, 8.97; N, 4.65. Found: C, 75.48; H, 9.00; N, 4.48.

3-Aza-A-homo-4α-androsten-4,17-dione Oxime (V).

Ketone IV (1.204 g) was dissolved in a mixture of 20 ml of ethanol and 20 ml of pyridine. Hydroxylamine hydrochloride (1.2 g) was added to this solution and the mixture was heated under reflux for 5 hours. The solution was poured into ice-water and the resulting precipitate was collected by filtration, washed with water and dried, to yield 0.9 g of oxime. Crystallization for methanol gives mp 280-281°; ir: ν max 3400-3200 cm^{-1} (CONH, OH), and absence of the keto group.

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Anal. Calcd. for $C_{19}H_{28}N_2O_2$: C, 72.15; H, 8.80; N, 8.86. Found: C, 71.80; H, 8.56; N, 8.88.

Bckmann Rearrangement of 3-Aza-A-homo-4α-androsten-4,17-dione Oxime.

Oxime V (3.9 g) was dissolved in 750 ml of purified dioxane, 10 ml of purified thionyl chloride in 20 ml of purified dioxane was added dropwise while the mixture was continuously stirred at room temperature. This mixture was stirred for an additional period of 20 hours. Then it was poured into ice-water neutralized with ammonium hydroxide and extracted with chloroform. The organic layer was washed with water, dried over sodium sulfate and after evaporation of the solvent under reduced pressure the resulting residue (1.8 g) was chromatographed on a column of silica gel (120 g). Elution with chloroform-methanol (92:2) gave the ω-cyano-olefin VI (1 g). Crystallization from chloroform-ethyl acetate gave mp 192-193°; ir: ν max 2220 cm^{-1} (C≡N); nmr: δ 1.08 (19-CH_3), 4.530 and 4.835 (C=CH_2), 6.750 (C=CH), 6.83 (NH).

Anal. Calcd. for $C_{19}H_{26}N_2O$: C, 76.51; H, 8.72; N, 9.39. Found: C, 76.70; H, 8.89; N, 9.15.

After elution of the column with chloroform-methanol (95:5) a mixture of untreated oxime and ω-cyano-olefin (100 mg) was obtained. Finally with the same mixture of solvents the 3,17α-diaza-A,D-bishomoandrost-4α-ene-4,17-dione (350 mg) was isolated. Crystallization from chloroform-methanol gave mp above 300° (lit [8] mp >300°); ir: ν max 3210 (NH), 1740, 1680, 1610 cm^{-1} (CONH).

Lactam VIII [9] (2.75 g) was dissolved in a mixture of 25 ml of ethanol and 25 ml of pyridine. Hydroxylamine hydrochloride (2.75 g) was added to the solution and the mixture was heated under reflux for 5 hours. The solution was poured into ice-water and extracted with chloroform. After evaporation of the solvent a residue of 2.8 g was obtained. This product was chromatographed on a column of silica gel (120 g). Elution with chloroform-methanol (98P2) yielded *anti*-ketoxime X (1.9 g). Crystallization from methanol gave mp 288-289°; ir (potassium bromide): ν max 3500-3200 (OH, NH), 1680, 1640 cm^{-1} (NHCO); nmr: δ 1.09 (18-CH_3), 1.18 (19-CH_3), 5.67 (C=CH).

Anal. Calcd. for $C_{19}H_{28}N_2O_2$: C, 72.15; H, 8.86; N, 8.86. Found: C, 72.45; H, 8.95; N, 8.89.

Further elution of the column yielded a mixture of *anti*- and *syn*-ketoximes (400 mg). Finally after elution of the column with the same mixture of solvents, *syn*-ketoxime XI (280 mg) was obtained. Crystallization from chloroform-methanol gave mp 279-280°; ir: ν max 3300-3200 (OH, NH), 1670, 1640 cm^{-1} (NHCO); nmr: δ 1.08 (18-CH_3), 1.19 (19-CH_3), 6.38 (C=CH).

Anal. Calcd. for $C_{19}H_{28}N_2O_2$: C, 72.15; H, 8.86; N, 8.86. Found: C, 71.85; H, 8.69; N, 8.67.

3,17α-Diaza-A,D-bishomoandrost-4α-ene-4,17-dione (VII) from Ketoxime IX.

Oxime IX (350 mg) was dissolved in 100 ml of purified dioxane. Th solution was stirred and to this 2.5 ml of purified thionyl chloride in 6 ml of dioxane was added at 0°. Then the mixture was continuously stirred for 24 hours at room temperature. After this time the mixture was worked up as usual and the residue was chromatographed on a column of silica gel (30 g). Elution with chloroform-methanol (95:5) yielded (50 mg) of lactam VII and oxime IX mixture. Further elution of the column with the same mixture of solvents produced 100 mg of lactam VII. The infrared spectrum and melting point was identical with that of authentic VII.

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