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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. XVI. Beckmann Rearrangement of 17-Ketosteroid Oximes[1]

BY ST. KAUFMANN

The 17-oximes of dehydroisoandrosterone acetate, Δ^4-androstene-3,17-dione and estrone benzoate have been submitted to the Beckmann rearrangement. The resulting lactams (dehydroisoandrololactam acetate, testololactam and estrololactam benzoate) with a six-membered D-ring can be considered as nitrogen analogs of the D-homosteroids. The position of the NH-group has been established by selenium dehydrogenation of one of these lactams. The identification of the dehydrogenation product as 1-azachrysene proves that the NH-group is in the 17a-position.

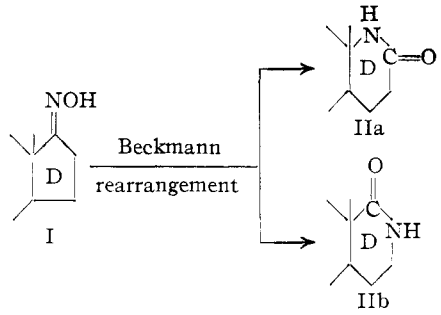
Since Westerfeld[2] described a lactone by oxidation of estrone with alkaline hydrogen peroxide, several other D-ring lactones of steroids have been reported.[3,4,5,6] Interesting physiological properties have been attributed to some of the lactones, so it seemed interesting to prepare the analogous lactams. Bachmann[7] has described a five-membered D-ring lactam of desoxyequilenin, but so far no six-membered D-ring lactams of steroids seem to have been described.

The best way for preparing this group of compounds is probably the Beckmann rearrangement of the oximes of the 17-ketosteroids (I). In fact, this rearrangement could be accomplished smoothly with the oximes of several steroids: dehydroisoandrosterone acetate, Δ^4-androsten-3,17-dione and estrone benzoate. These oximes were prepared by known methods; in the case of Δ^4-androsten-3,17-dione, however, it was necessary to protect the 3-keto group temporarily preparing its enol ether, so that only the 17-keto group was converted into the oxime group.

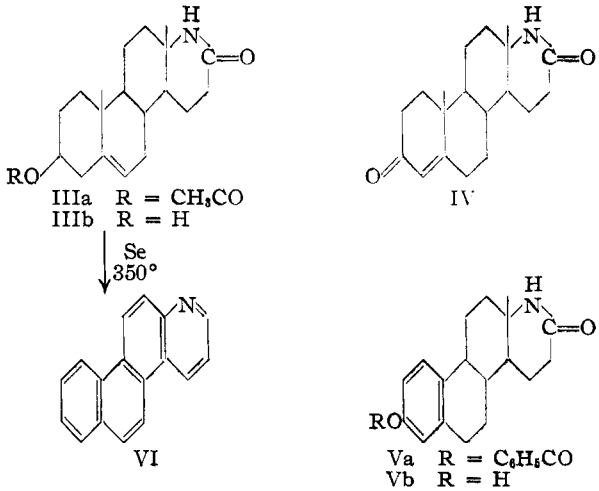
The rearrangement was carried out with *p*-acetylaminobenzenesulfonyl chloride in pyridine solution. In order to have the reaction proceed normally it was necessary to esterify the 3-hydroxy groups; no lactams could be isolated from the reaction mixture when working with the free compounds. The lactams with a free hydroxy group can be easily obtained by alkaline hydrolysis of the corresponding esters.

The lactams are very stable and high melting substances. Attempts to open the lactam ring with alkali or acids were unsuccessful. The NH-group of the lactam cannot be acetylated under ordinary conditions, but only with boiling acetic anhydride in presence of small amounts of *p*-toluenesulfonic acid.

Theoretically, the Beckmann rearrangement can proceed in two different directions to yield lactams



of the general type IIa or IIb. IIa can be considered as 17a-aza D-homosteroid and IIb as 17-aza D-homosteroid. Actually, in all cases only *one* lactam was isolated from the reaction mixture and no indications of the presence of an isomer were noted. In order to establish the position of the NH-group, the lactam obtained from dehydroisoandrosterone (IIIb) was dehydrogenated with selenium at 350°. From the acid-soluble fraction of the dehydrogenation mixture, a small amount of crystalline material was isolated, which proved to be identical with 1-azachrysene (naphtho[2,1-f]-quinoline (VI)), synthesized by Mosettig, *et al.*[8] The identity of the two substances has been established by mixed melting point,[9] ultraviolet spectrum (Fig. 1) and infrared spectrum.[10] Hence,



(1) For the preceding paper in this series see C. Djerassi and G. Rosenkranz, *Experientia*, **VI**, Feb. (1951).

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(6) E. B. Hershberg, E. Schwenk and E. Stahl, *Arch. Biochem.*, **19**, 300 (1948).

(7) W. E. Bachmann and F. Ramirez, THIS JOURNAL, **72**, 2525 (1950).

(8) E. Mosettig and J. Krueger, *J. Org. Chem.*, **3**, 325 (1938).

(9) I thank Dr. Mosettig for having kindly sent me a specimen of 1-azachrysene for comparison purposes.

(10) The infrared spectrum has been determined in the Sloan-Kettering Institute through the courtesy of Dr. K. Dobriner.

the lactams obtained from the three above listed compounds have to be considered as Δ^5-17a-aza-D-homoandrosten-3β-ol-17-one (III) (dehydroisoandrololactam), Δ^4-17a-aza-D-homoandrosten-3,17-dione (testololactam, (IV)) and 17a-aza-D-homoestrone (estrololactam, (V)), respectively.

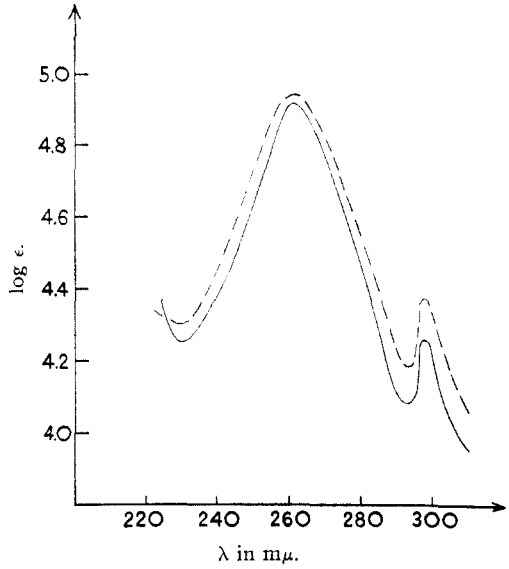

Fig. 1.—Ultraviolet absorption spectrum of synthetic 1-azachrysene (Mosettig) (— — — —) and of the dehydrogenation product of dehydroisoandrololactam (——) (95% ethanol solution).

Experimental[11]

Dehydroisoandrololactam Acetate (IIIa).—To a solution of 10 g. of dehydroisoandrosterone acetate oxime (m.p. 178–180°, $[\alpha]^{20}D$ −72.4° (chloroform)) in 100 cc. of pyridine 10 g. of *p*-acetylaminobenzenesulfonyl chloride dissolved in 50 cc. of pyridine were added. The reaction mixture was left standing for three hours at room temperature, and then poured into water and ice and neutralized with dilute hydrochloric acid. The precipitate was extracted with chloroform, the solution was washed with water and dried over sodium sulfate. After evaporation of the solvent the residue was recrystallized from methanol: big plates, m.p. 295–298°, $[\alpha]^{20}D$ −58.3° (chloroform); yield 50%.

Anal. Calcd. for $C_{21}H_{31}O_3N$: C, 73.01; H, 9.04; N, 4.05. Found: C, 73.19; H, 9.07; N, 3.69.

Dehydroisoandrololactam (IIIb).—A solution of 10 g. of dehydroisoandrololactam acetate in 200 cc. of methanol was refluxed with 5 g. of potassium hydroxide for one hour. The free lactam was precipitated in water, filtered and recrystallized from methanol: big prisms, m.p. 292–295°, $[\alpha]^{20}D$ −59.7° (alcohol).

Anal. Calcd. for $C_{19}H_{29}O_2N$: C, 75.25; H, 9.63. Found: C, 75.39; H, 9.77.

Dehydroisoandrololactam Diacetate.—The diacetate of the lactam was obtained by refluxing 10 g. of the monoacetate in 50 cc. of acetic anhydride in the presence of 500 mg. of *p*-toluenesulfonic acid. The acetylation mixture was worked up as usual and after separating some less soluble unchanged monoacetate, the diacetate could be crystallized from methanol: prisms, m.p. 162–165°, $[\alpha]^{20}D$ −74.5° (alcohol).

Anal. Calcd. for $C_{23}H_{33}O_3N$: C, 71.31; H, 8.47. Found: C, 71.36; H, 8.41.

(11) All melting points were determined on the Kofler block. The ultraviolet spectra measurements, rotations and microanalyses were carried out in our Microanalytical Department under the direction of Miss Amparo Barba.

Δ^4-Androsten-3,17-dione-17-oxime.—A solution of 20 g. of Δ^4-androsten-3,17-dione ethyl enol ether in 500 cc. of alcohol was refluxed with an excess of hydroxylamine acetate (prepared from 20 g. of hydroxylamine hydrochloride and 40 g. of sodium acetate) for ten minutes. After diluting with water the oxime of the enol ether crystallized in needles: m.p. 170–172°, $[\alpha]^{20}D$ −149° (alcohol). The latter compound (16 g.) was hydrolyzed by leaving it standing overnight at room temperature, dissolved in 150 cc. of alcohol with 10 cc. of concd. hydrochloric acid. By precipitation in water the 17-oxime of androstenedione was obtained. It was first crystallized from ether and then from ethyl acetate: m.p. 202–206°, $[\alpha]^{20}D$ +123.5° (alcohol).

Anal. Calcd. for $C_{19}H_{27}O_2N$: C, 75.74; H, 9.02. Found: C, 75.67; H, 9.28.

Testololactam (IV).—To a solution of 10 g. of Δ^4-androsten-3,17-dione 17-oxime in 100 cc. of pyridine, 10 g. of *p*-acetylaminobenzenesulfonyl chloride dissolved in 50 cc. of pyridine was added. After standing for three hours at room temperature the reaction mixture was worked up as in the case of the dehydroisoandrololactam acetate. The crude testololactam was purified by filtering its benzene solution through aluminum oxide. Evaporation of the solvent and recrystallization from ethyl acetate yielded prisms, m.p. 261–263°, $[\alpha]^{20}D$ +91.5° (alcohol), ultraviolet maximum 240 mμ (log ε 4.36); yield 50%.

Anal. Calcd. for $C_{19}H_{27}O_2N$: C, 75.74; H, 9.02; N, 4.65. Found: C, 75.48; H, 9.19; N, 4.58.

Estrololactam Benzoate (Va).—To a solution of 2 g. of estrone benzoate oxime (m.p. 207–210°, $[\alpha]^{20}D$ +68.5° (dioxane)) in 20 cc. of pyridine, 2 g. of *p*-acetylaminobenzenesulfonyl chloride dissolved in 10 cc. of pyridine was added. After standing for three hours at room temperature the reaction mixture was worked up as above. The estrololactam benzoate was crystallized from methanol: small needles, m.p. 300–313°, $[\alpha]^{20}D$ +90.4° (chloroform); yield 50%.

Anal. Calcd. for $C_{25}H_{27}O_3N$: C, 77.12; H, 6.94. Found: C, 76.96; H, 6.68.

Estrololactam (Vb).—A solution of 1 g. of estrololactam benzoate in 50 cc. of methanol was refluxed with 1 g. of potassium bicarbonate for two hours. On cooling, the free estrololactam crystallized in small needles. For analysis the extremely insoluble substance was sublimed at 200° and 0.005 mm. The lactam does not melt below 360°; at higher temperatures it decomposes slowly. No optical rotation could be determined because of the very low solubility in organic solvents.

Anal. Calcd. for $C_{18}H_{23}O_2N$: C, 75.78; H, 8.07; N, 4.91. Found: C, 75.68; H, 8.12; N, 5.18.

Selenium Dehydrogenation of Dehydroisoandrololactam.—A mixture of 5 g. of dehydroisoandrololactam with 10 g. of selenium was heated to 350° in a small round-bottom flask with an attached air-cooled glass tube. After ten hours the reaction mixture was exhaustively extracted with benzene. The basic fractions were extracted from the benzene solution with dilute hydrochloric acid and precipitated from the acid solution by neutralizing with sodium hydroxide The so-obtained precipitate was extracted with ether. The ether solution was evaporated and the residue (100 mg.) was dissolved in benzene and passed through 10 g. of aluminum oxide. The eluate could be crystallized from ether and the crystalline fraction (20 mg.) sublimed for further purification. Two sublimations at 150° and 0.002 mm. yielded a white crystalline substance, with m.p. to 221–223°; mixed m.p. with analytically pure synthetic 1-azachrysene (m.p. 226–227°)[9] 223–226°; ultraviolet maxima 262 mμ (log ε 4.92), 298 mμ (log ε 4.26); minima 230 mμ (log ε 4.25), 294 mμ (log ε 4.08).

Anal. Calcd. for $C_{17}H_{11}N$: C, 89.05; H, 4.84; N, 6.11. Found: C, 89.23; H, 5.06; N, 6.34.

Picrate m.p. 278–281°.

Anal. Calcd. for $C_{23}H_{14}O_7N_4$: C, 60.26; H, 3.05. Found: C, 60.33; H, 3.35.

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