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

Steroids. LXXXI.[1] Transformation of Sapogenins to Androgens and Estrogens. Beckmann Rearrangement of Δ^{16}-20-Ketosteroids

G. ROSENKRANZ, O. MANCERA, FRANZ SONDHEIMER,[2] AND CARL DJERASSI[3]

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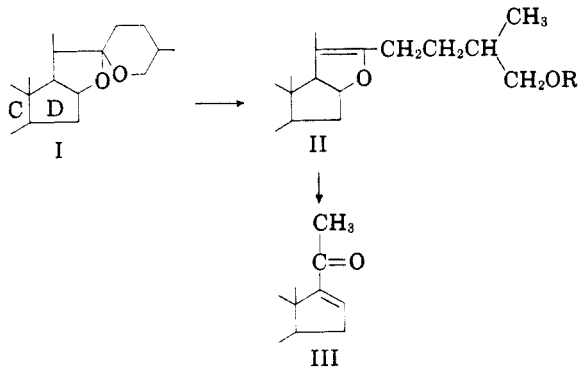
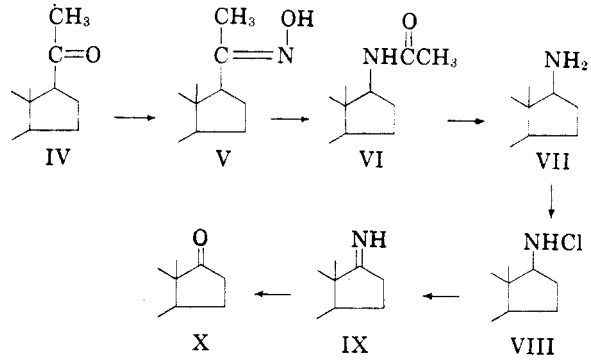
The Beckmann rearrangement of oximes of Δ^{16}-20-ketosteroids has been shown to proceed in good yield to the corresponding 17-keto steroids. This represents the method of choice for the transformation of steroidal sapogenins, such as diosgenin, to the male and female sex hormones.

The extremely facile, two-step degradation[4] of the sapogenin (spirostan) side chain (I) *via* the derived furosten (II) to the corresponding Δ^{16}-20-ketopregnene derivative (III) coupled with the ready availability of steroidal sapogenins, such as diosgenin, has made this class of steroids the preferred raw material for the synthesis[5] of hormones of the pregnane series (progesterone and cortical hormones).



I II III

The estrogenic hormones are currently prepared by partial synthesis[6,7] from the androgens and the question arises as to whether these two remaining classes of steroid hormones are also derivable from sapogenins (I) in a straight forward manner. Fieser and Fieser[8] have reviewed the methods available for the transformation of 20-ketopregnanes (IV) to 17-ketosteroids (X) of the androstane series and it is apparent that none of them are amenable to large scale operations. A very recent report by Schmidt-Thomé[9] is concerned with the same subject and a method[9a] is presented which is considered to be of economic significance. This involves transformation of a 20-keto-pregnane (IV) to the oxime (V) followed by Beckmann rearrangement to the amide VI, hydrolysis to the amine (VII) and successive conversion to the N-chloroamine (VIII), imine (IX) and finally 17-ketoandrostane derivative (X). Alternatively,[9b] the Δ^{16}-20-ketone (III) can be converted in three steps to the 17α-hydroxy-20-ketone and Beckmann rearrangement of its oxime yields directly the 17-ketone (X).



IV V VI VII X IX VIII

One procedure which has apparently been overlooked in all references on this subject[8,9] is covered in a patent[10] in which it is claimed that Beckmann rearrangement of an oxime of a Δ^{16}-20-keto-steroid (III) leads in essentially one step to the desired 17-keto steroid (X). The present paper is concerned with a detailed examination of this reaction, the isolation of the intermediate amide (XIII) and a description of the optimum reaction conditions. In the case of the commercially important $\Delta^{5,16}$-pregnadien-3β-ol-20-one acetate (XI), approximately 74% of dehydroepiandrosterone (XIVa) could be isolated thus making this clearly the method of choice insofar as the transformation of sapogenins to 17-keto steroids of the androstene series is concerned. In view of the earlier mentioned partial synthesis[6,7] of the estrogenic hormones from the androgens, there are now available short, direct

(1) Paper LXXX, H. J. Ringold, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **78**, in press (1956).

(2) Department of Organic Chemistry, Weizmann Institute of Science, Rehovoth, Israel.

(3) Department of Chemistry, Wayne University, Detroit 1, Michigan.

(4) *Inter al.*, Marker, *J. Am. Chem. Soc.*, **62**, 3350 (1940).

(5) *Cf.* Djerassi, *Vitamins and Hormones*, **11**, 205 (1953); Rosenkranz and Sondheimer, *Progr. Chem. Org. Nat. Prod.*, **10**, 274 (1953).

(6) Inhoffen, *Angew. Chem.*, **59**, 207 (1947); Hershberg, Rubin, and Schwenk, *J. Org. Chem.*, **15**, 292 (1950).

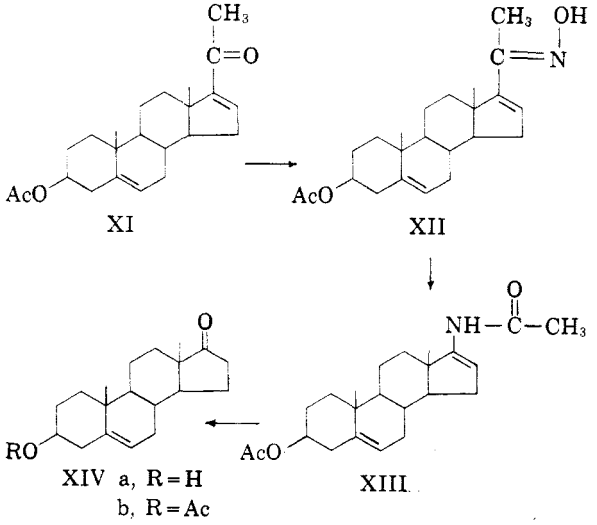
(7) Djerassi, Rosenkranz, Romo, Kaufmann, and Pataki, *J. Am. Chem. Soc.*, **72**, 4534 (1950).

(8) Fieser and Fieser, *Natural Products Related to Phenanthrene*, 3rd Edit., Reinhold Publ. Corp., New York, 1949, pp. 401–402.

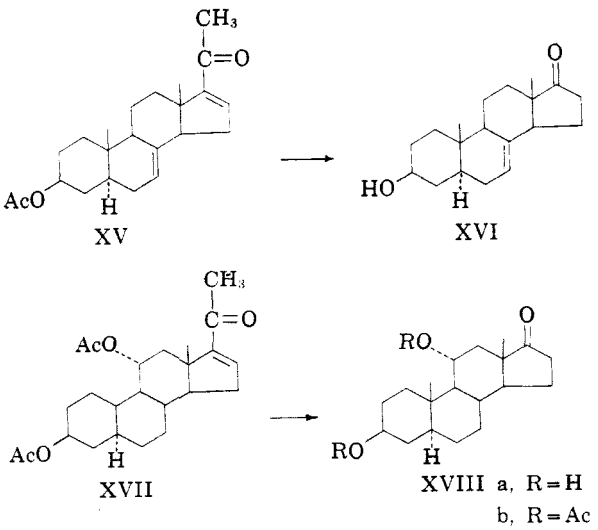
(9) (a) Schmidt-Thomé, *Ber.*, **88**, 895 (1955); (b) *Angew. Chem.*, **67**, 715 (1955) and patents cited therein.

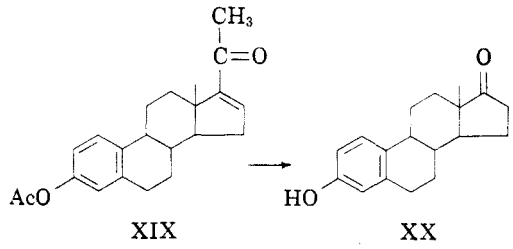
(10) Tendick and Lawson, U. S. Patent 2,335,616 (Nov. 30, 1943). A very minor modification is given in U. S. Patent 2,656,364 (Oct. 20, 1953).

routes to all of the major hormones from diosgenin and related sapogenins.



From a preparative standpoint, it was preferable to carry out the entire sequence without purification of intermediates: the oxime (XII), obtained in quantitative yield from the Δ^{16}-20-ketone (XI) by the pyridine procedure, was treated in pyridine solution with *p*-acetamidobenzenesulfonyl chloride and then poured into excess acid. After standing overnight, the crude 3-acetoxy-17-ketone (XIVb) was directly saponified and dehydroepiandrosterone (XIVa) was isolated in 74% over-all yield. The extreme ease of hydrolysis (dilute acid, 0°) raised the question whether the intermediate was the N-acylated vinylamine (XIII) or the corresponding N-acylimine. In one experiment, the Beckmann rearrangement product was isolated without treatment with acid and it thus was possible to secure an analytical sample of the intermediate amide. The infrared and especially the ultraviolet absorption spectrum (λ_{max}^{EtOH} 240 mμ, log ε 3.82) clearly demonstrated[11] that it was the vinyl amine derivative (XIII).





The generality of this reaction is supported by three additional examples given in the experimental section in which the respective Δ^{16}-20-ketosteroid (XV, XVII and XIX) is transformed without isolation of intermediates into the corresponding 17-ketone (XVI, XVIII, XX). Of particular interest is the unsaturated ketone XIX with an aromatic ring A which has been obtained from diosgenin by two routes.[12,13] Beckmann rearrangement of its oxime led to estrone (XX) thus representing the first partial synthesis of this female sex hormone in which an androstane derivative is not involved as a precursor.

EXPERIMENTAL[14]

Conversion of $\Delta^{5,16}$-pregnadien-3β-ol-20-one acetate (XI) *to dehydroepiandrosterone* (XIVa). A mixture of 25 g. of XI, 30 cc. of pyridine, 130 cc. of 95% ethanol and 8.5 g. of hydroxylamine hydrochloride was refluxed for 30 minutes and cooled in ice. The precipitate was collected, washed with hot water and dried, thus giving 24.5 g., m.p. 228–230°. The oxime (XII), was dissolved in 70 cc. of anhydrous pyridine, cooled to 0° and a solution of 30 g. of *p*-acetamidobenzenesulfonyl chloride in 70 cc. of pyridine was added with stirring, the temperature being maintained below 5°. After stirring for 2 hours at 10° and an additional 2 hours at room temperature, the mixture was poured into 500 g. of ice and 150 cc. of conc'd sulfuric acid and left in the refrigerator overnight. The product was collected, washed well with hot water and since infrared examination showed it to be a mixture of dehydroepiandrosterone (XIVa) and the corresponding 3-acetate (XIVb) it was directly saponified by refluxing with 150 cc. of 2.5% methanolic potassium hydroxide for 30 minutes. The usual work-up followed by recrystallization from methanol furnished 15.0 g. (74%) of dehydroepiandrosterone (XIVa), m.p. 151–153°, $[\alpha]_D$ +5.5°.

The transformation of $\Delta^{7,16}$-allopregnadien-3β-ol-20-one acetate (XV)[15] to Δ^{7}-androsten-3β-ol-17-one (XVI)[16] was carried out in the same manner and proceeded in essentially the same yield. In this instance the intermediate oxime of the unsaturated ketone XV was purified, m.p. 213–216°, $[\alpha]_D$ +48°.

(11) *Cf.* Leonard and Locke, *J. Am. Chem. Soc.*, **77**, 437 (1955).

(12) Djerassi, Rosenkranz, Iriarte, Berlin and Romo, *J. Am. Chem. Soc.*, **73**, 1523 (1951).

(13) Sondheimer, Neumann, Ringold, and Rosenkranz, *J. Am. Chem. Soc.*, **76**, 2230 (1954).

(14) Melting points are uncorrected. Rotations were determined in chloroform solution. We are grateful to Srta M. T. Cárdenas for these measurements.

(15) Djerassi, Romo, and Rosenkranz, *J. Org. Chem.*, **16**, 754 (1951).

(16) Neumann, Rosenkranz, Romo and Djerassi, *J. Am. Chem. Soc.*, **73**, 5478 (1951).

Anal. Calc'd for $C_{23}H_{33}NO_3$: C, 74.36; H, 8.95. Found: C, 74.50; H, 9.08.

Beckmann rearrangement of $\Delta^{5,16}$-pregnadien-3β-ol-20-one 3-acetate 20-oxime (XII).[17] A solution of 5.0 g. of the oxime XII in 20 cc. of pyridine was treated with 5.0 g. of *p*-acetamidobenzenesulfonyl chloride and stirred for 2 hours at 10° and 2 hours at room temperature. The mixture was poured into ice-water, and the brown gummy precipitate was extracted with chloroform, washed with water, dried and evaporated. Crystallization of the residue from methylene chloride-hexane (decanting first from a colored oil which separated) afforded 1.75 g. of yellowish crystals, m.p. 230–236° and an additional 0.3 g. (m.p. 233–236°) by chromatography of the mother liquors. The analytical sample of the amide (XIII) was obtained from the same solvent pair as colorless crystals, m.p. 237–240°, $[\alpha]_D$ −18°, $\lambda_{max.}^{EtOH}$ 240 mμ, log ε 3.82, $\lambda_{max.}^{CHCl_3}$ 2.90, 5.76, 5.90, and 6.58 μ (N—H deformation).

Anal. Calc'd for $C_{23}H_{33}NO_3$: C, 74.36; H, 8.95. Found: C, 74.81; H, 8.83.

The unsaturated amide (XIII) could be converted to the 17-ketone by acid hydrolysis as well as by alkaline treatment: 37.5 g. of amide was refluxed for 1 hour with 700 cc. of 5% ethanolic potassium hydroxide whereupon 22.5 g. of dehydroepiandrosterone (XIVa) was obtained.

Conversion of Δ^{16}-allopregnene-3β,11α-diol-20-one diacetate (XVII) *to androstane-3β,11α-diol-17-one* (XVIIIa). A 4.0-g. sample of Δ^{16}-allopregnene-3β,11α-diol-20-one diacetate (XVII)[18] was converted to the amorphous oxime (m.p. *ca.* 115–140°) by refluxing for 30 minutes with 7 cc. of pyridine, 35 cc. of ethanol, and 2.0 g. of hydroxylamine hydrochloride. The Beckmann rearrangement was carried out as described above in 15 cc. of pyridine using 5.0 g. of *p*-acetamidobenzenesulfonyl chloride and the reaction mixture was poured into ice containing 20 cc. of conc'd sulfuric acid. The crude product was saponified with 5% methanolic potassium hydroxide and purified by chromatography on 100 g. of alumina. Elution with ether and ether-chloroform mixtures gave 2.0 g. of androstane-3β,11α-diol-17-one (XVIIIa), m.p. 100–106° which was recrystallized several times from hexane-acetone to yield the analytical sample, m.p. 103–106°, $[\alpha]_D$ +50°, $\lambda_{max.}^{CHCl_3}$ 5.76 μ.

Anal. Calc'd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87. Found: C, 74.00; H, 9.73.

Oxidation of 150 mg. of the dihydroxy-ketone with chromium trioxide in acetic acid led to 130 mg. of androstane-3,11,17-trione, m.p. 174–176°, $[\alpha]_D$ +150°, undepressed upon admixture with an authentic specimen, prepared by hydrogenation of androsterone.[19]

Acetylation of a sample of XVIIIa with acetic anhydride-pyridine on the steam-bath followed by recrystallization from hexane-acetone furnished the diacetate XVIIIb, m.p. 141–143°, $[\alpha]_D$ +10°.

Anal. Calc'd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 71.11; H, 8.86.

Conversion of 3-acetoxy-17-acetyl-1,3,5,16-estratetraene (XIX) *to estrone* (XX). The Beckmann rearrangement of 1.9 g. of the oxime (crude, m.p. 80–113°) of the unsaturated ketone XIX[12,13] was carried out as above to yield, after saponification, 0.48 g. of crude estrone, m.p. 248–256°, raised to m.p. 253–257° (0.4 g.) after one recrystallization from methanol. No attempt was made in this instance to establish the optimum reaction conditions.

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(17) This experiment was carried out by Dr. Carl T. Lenk in these laboratories.

(18) Djerassi, Batres, Romo, and Rosenkranz, *J. Am. Chem. Soc.*, **74**, 3634 (1952).

(19) Steiger and Reichstein, *Helv. Chim. Acta*, **20**, 817 (1937).