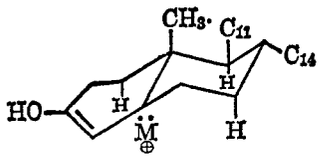

Figure 2.

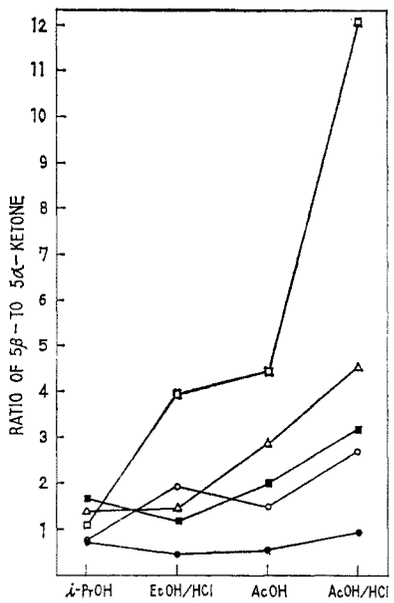

Figure 3.—Effect of acidic solvents on the $5\beta/5\alpha$ ratio of ketones formed in hydrogenation of 3-oxo-4-ene steroids with palladium catalyst: △, cholest-en-3-one; ●, testerone; ○, testerone acetate; ■, 19-nortesterone; □, 19-nortesterone acetate.

group, there exist two 1,3 interactions between two hydrogen atoms, one axial and one methyl hydrogen, and the catalyst surface at the position of the methyl group giving the greatest interaction in the intermediate leading to the 5β isomer as shown in Figure 1. On the other hand, there are three such interactions in the structure leading to the 5α isomer (Figure 2). Thus, the formation of 5β ketone will be more favored sterically even in the ketones having the angular methyl group.[8] The hydrogenation in the absence of alkali or acid will proceed with a less stereospecificity because the species hydrogenated may be a less polarized ketone in which the $5\beta/5\alpha$ ratio of the product will be controlled by an interaction of the π electrons of the unsaturated ketone and the catalyst surface. The fact that I gives much greater yields of 5β ketone than II and even than III in acidic media suggests that the 17-hydroxyl group may have some effect to decrease the formation of 5β ketone probably in combination with acids. This may be presumed further by the finding that in acidic media the acetates of II and III give much greater yields of 5β ketone than II and III, respectively (see Figure 3).

Experimental Section

Materials.—The substances hydrogenated are all known compounds of the following melting points:[9] cholest-4-en-3-one, 80.0–80.5° (lit.[10] 82°); testosterone, 155–156° (lit.[10] 155°); testosterone acetate, 140–140.5° (lit.[11] 140–141°); 19-nortestosterone, 124–125° (lit.[10] 124°); 19-nortestosterone acetate, 62–67° (lit.[12] 91–93°). Purity of these compounds was further ascertained by gas–liquid partition chromatography.

Catalysts.—Palladium oxide was prepared by the method of Shriner and Adams.[13] Palladium hydroxide was prepared by adding a slight excess of lithium hydroxide solution to a hot aqueous solution of palladium chloride, the precipitate being washed with hot distilled water thoroughly until the filtrate became neutral to thymol blue.

Hydrogenation.—The substrate (30–100 mg) dissolved in 10–15 ml of a solvent was shaken in a glass bottle with 10–30 mg of prereduced palladium oxide or palladium hydroxide at 25° and atmospheric pressure of hydrogen until hydrogen uptake ceased. In the hydrogenation using ethanol as the solvent, the absorption of hydrogen did not cease with the uptake of 1 mole, and so when 1 mole of hydrogen was absorbed, the reaction was stopped to examine the products at that stage.

Analysis of Products.—The products were analyzed by means of gas–liquid partition chromatography using a column of 1% SE-52 silicone on Chromosorb W (30–60 mesh). The following conditions were used for the analyses: for the products from cholestenone, column length 1.5 m, column temperature 238°; for the products from testosterone, 19-nortestosterone and its acetate, column length 2.25 m, column temperature 218°; for the products from testosterone acetate, column length 2.25 m, column temperature 228°. Small amounts of hydrogenolyzed products (1–5%) were formed in all the hydrogenations, but the products contained saturated alcohols in only slight amounts. This, if necessary, was confirmed by the analysis of the products treated with acetic anhydride and pyridine, since the retention times of the saturated 5α alcohols obtained from I and II were nearly the same with those of the corresponding saturated 5β ketones.

Acknowledgment.—The authors are grateful to Teikoku Hormone Manufacturing Company, Ltd., for providing testosterone, 19-nortestosterone, and some of their derivatives.

(8) The same conclusion may also be deduced in hydrogenation of 4,5-unsaturated steroids in neutral media [H. I. Hadler, *Experientia*, **11**, 175 (1955)]. However, it may be suggested that the steric control will be more pronounced in the formation of the intermediates as shown in Figures 1 and 2, since the adsorption between a carbonium ion and the catalyst surface is involved.

(9) All melting points were measured on a hot-stage apparatus and were not corrected.

(10) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959.

(11) L. Ruzicka and A. Wettstein, *Helv. Chim. Acta*, **18**, 1275 (1935).

(12) J. A. Hartman, *J. Am. Chem. Soc.*, **77**, 5151 (1955). The acetate was prepared from the 19-nortestosterone of mp 124–125°. Although the melting point of the resulting acetate was considerably lower than that reported in the literature, it was confirmed by gas chromatography that the acetate contained only a trace of impurities.

(13) R. L. Shriner and R. Adams, *ibid.*, **46**, 1683 (1924).

Steroids. CCXCV. A Novel Ring A Aromatization Reaction[1]

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The aromatization of ring A in steroids containing a CH_3 group at C-10 has been mainly accomplished starting either from $\Delta^{1,4}$-3 ketones[2] or more recently through microbiological transformation of 19-oxygenated steroids.[3] The reactions involved in these trans-

(1) Steroids. CCXCIV: C. Beard, I. Harrison, L. Kivkham, and J. Fried, *J. Am. Chem. Soc.*, in press.

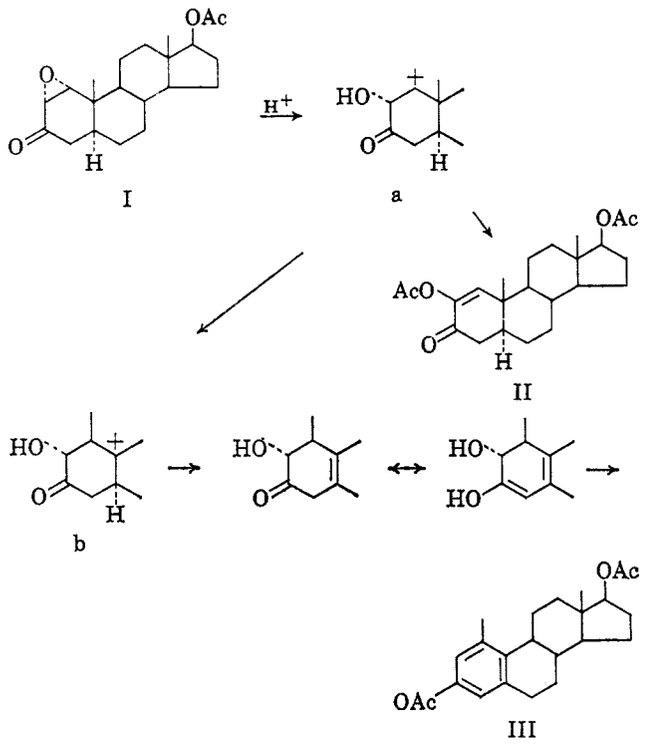
(2) L. F. Fieser and M. Fieser, "Steroids," Rheinhold Publishing Corp., New York, N. Y., 1959, p 479.

(3) R. M. Dodson and R. D. Muir, *J. Am. Chem. Soc.*, **83**, 4627, 4631 (1961). C. J. Sih, S. S. Lee, Y. Y. Tsong, K. C. Wang, and F. N. Chang, *ibid.*, **87**, 2765 (1965), and earlier papers.

formations have been thoroughly studied and rationalized. We wish to report the aromatization of ring A achieved by the action of acid on 1α,2α-epoxy-3-keto steroid.

When we subjected 17β-acetoxy-1α,2α-epoxy-5α-androstan-3-one (I,[4] Scheme I) to rearrangement

SCHEME I



with *p*-toluenesulfonic acid in acetic anhydride, the expected 2,17β-diacetoxy-5α-androst-1-en-3-one (II) could be isolated from the reaction mixture by chromatographic separation. Surprisingly, II was accompanied by another substance which was identified as the diacetate of 1-methylestradiol (III) by its physical characteristics and mixture melting point comparison with an authentic sample.[5] The compound III was obtained in a higher yield than II and consequently should be considered as the main reaction product.

The formation of these two widely different compounds can be explained by the following mechanism. Acid-catalyzed opening of the epoxy ring at C-1 generates the intermediate carbonium ion a which passes over to II by proton loss from C-2 and acetylation. Alternatively, migration of the C-19 angular methyl group in the ion a to C-1 leads to the carbonium ion b which then undergoes aromatization by enolization and proton loss at C-5 followed by elimination of the C-2 oxygen function as water or acetic acid. The formation of 1-methylestradiol diacetate (III) is reminiscent of the acid-catalyzed rearrangement of 3α-acetoxy-16α,17α-epoxy-pregn-5-en-20-one to 3α,16α-diacetoxy-17β-methyl-17α-pregna-5,13-dien-20-one.[6] In the latter case, however, Wagner–Meerwein rearrangement is initiated by cleavage of the epoxide ring at C-17.

(4) W. M. Hoehn, *J. Org. Chem.*, **23**, 929 (1958).

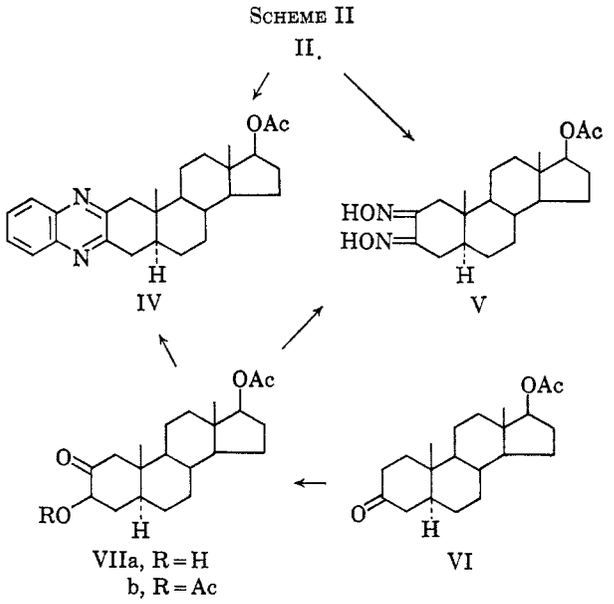
(5) C. Djerassi, J. Romo, J. Pataki, and S. Kaufmann, *J. Am. Chem. Soc.*, **72**, 4540 (1950).

(6) K. Heusler and A. Wettstein, *Ber.*, **87**, 1301 (1954).

The structure of compound II was established by its ultraviolet spectrum [λ_{max} 237 mμ (log ε 4.00)][7] and by the formation of the crystalline quinoxaline and dioxime derivatives IV and V.

For comparison purposes we have prepared the free diosphenol (VIIa) *via* selenium dioxide oxidation of 17β-acetoxy-5α-androstan-3-one (VI) in accordance with a method originally described by Stiller and Rosenheim.[8] VIIa forms the same quinoxaline derivative (IV, Scheme II) and dioxime (V) as those prepared from II. Mild acetylation of VIIa with acetic anhydride in pyridine leads to the isomeric diacetate 3,17β-diacetoxy-5α-androst-3-en-2-one (VIIb) which is not identical with II as expected.

SCHEME II



Experimental Section[9]

2,17β-Diacetoxy-5α-androst-1-en-3-one (II) and 1-Methylestradiol Diacetate (III).—A solution of 5.0 g of 17β-acetoxy-1α,2α-epoxy-5α-androstan-3-one (I) in 50 ml of acetic anhydride was treated with 5.0 g of *p*-toluenesulfonic acid and the mixture was heated for 2 hr on the steam bath. After cooling, the reaction mixture was poured into water and extracted with ether. The organic layer was washed with water and a solution of sodium bicarbonate until neutral. The solvent was evaporated to dryness and the oily residue was crystallized by addition of methanol. The crude crystalline product (1.5 g) was separated into two fractions by chromatography on 50 g of silica gel.

Elution with benzene containing 2% ether yielded 1-methylestradiol diacetate (III, 0.7 g), which recrystallized from methanol as plates: mp 177–78°, $[\alpha]_D$ +108.2°, λ_{max} 269 mμ (log ε 2.529) [lit.[5] mp 178–180°, $[\alpha]_D$ +111°, λ_{max} 268 mμ (log ε 2.53)] identical by mixture melting point and infrared comparison with an authentic sample.[5] Continued elution with the same solvent mixture afforded compound II (0.4 g). Several recrystallizations from methanol yielded a pure specimen as prisms: mp 189–190°; $[\alpha]_D$ +40.5°; λ_{max} 237 mμ (log ε 4.00); ν_{max} 2900, 1770, 1730, 1640, 1375, 1250, and 1095 cm^{-1}.

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.04; H, 8.29.

Preparation of the Quinoxaline Derivative IV.—A solution of 2 g of II in 50 ml of alcohol was treated with 2 g of *o*-phenylenedi-

(7) L. F. Fieser and M. Fieser, ref. 2, p 304.

(8) E. T. Stiller and O. Rosenheim, *J. Chem. Soc.*, 353 (1938).

(9) Melting points were recorded in a Thomas–Hoover melting point apparatus and are corrected. Except where stated otherwise rotations and infrared spectra were determined in chloroform, and ultraviolet spectra in ethanol solution. Microanalysis were performed by Midwest Micro Laboratories, Indianapolis, Ind., or by A. Bernhardt, Mühlehim (Ruhr), West Germany.

amine and a solution of 1 g of potassium bicarbonate in 5 ml of water. The mixture was heated under reflux for 2 hr. On cooling, IV crystallized from the reaction mixture in slightly yellow plates (1.8 g). Recrystallization from methylene chloride–methanol yielded a pure sample: mp 242–244°; $[\alpha]_D$ +68.3°; λ_{max} 239, 263, and 321 mμ (log ε 4.503, 3.339, and 4.074).

Anal. Calcd for $C_{27}H_{34}N_2O_2$: C, 77.55; H, 8.11; N, 6.69. Found: C, 77.53; H, 8.32; N, 6.52.

Preparation of the Dioxime Derivative V.—A solution of 1 g of II in 50 ml of methanol was treated with a solution of 2 g of hydroxylamine acetate in 10 ml of methanol. After a few minutes of heating on the steam bath the dioxime V precipitated in fine needles, mp 272.5–275° dec, $[\alpha]_D$ +57.4 (pyridine).

Anal. Calcd for $C_{21}H_{32}N_2O_4$: C, 67.00; H, 8.58; N, 7.43. Found: C, 67.54; H, 8.35; N, 8.01.

3,17β-Diacetoxy-5α-androst-3-en-2-one (VIIb).—To a solution of 15 g of 17β-acetoxy-5α-androstan-3-one in 300 ml of alcohol there was added 120 g of selenium dioxide dissolved in 70 ml of water and 300 ml of alcohol. The mixture was heated under reflux for 15 min and then cooled. The precipitated selenium was removed by filtration and the filtrate was diluted with 1 l. of ether. The organic layer was washed first with 1 l. of a concentrated salt solution and then with 500 ml of a concentrated solution of sodium bicarbonate. The potassium salt of the diosphenol (VIIa) precipitated at the interface by shaking the etheral layer with 300 ml of 20% aqueous potassium hydroxide.

The resinous, dark precipitate was separated from the liquid layers and washed thoroughly with ether. The free diosphenol was liberated from its potassium salt by treatment with dilute hydrochloric acid followed by extraction with ether. The organic layer was washed with water, dried, and decolorized with activated charcoal. Upon concentration of the ether solution the diosphenol was crystallized in small, yellow plates. Recrystallization from ether yielded 3.5 g of pure VIIa: mp 151.5–153°, $[\alpha]_D$ +80.5°, λ_{max} 272 mμ (log ε 3.753).

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.81; H, 8.73. Found: C, 72.99; H, 8.58.

Treatment of the diosphenol VIIa with *o*-phenylenediamine and hydroxylamine acetate afforded the quinoxaline (mp 242–244°) and dioxime (mp 272.5–275°), respectively, which were identical in all respects with the corresponding derivatives obtained from II.

The enol acetate VIIb was prepared from the diosphenol by dissolving the latter in acetic anhydride and pyridine at room temperature. After standing for 24 hr the reaction mixture was worked up in the usual way. Crystallization from methanal yielded well-formed prisms: mp 184–184.5°; $[\alpha]_D$ +82.4°; λ_{max} 240 mμ (log ε 3.898); ν_{max} 2900, 1770, 1730, 1640, 1375, 1250, 1155, 1135, and 1065 cm^{-1}.

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 70.78; H, 8.22.

The Synthesis of Nitrogen-Containing Steroids. I. Diels–Alder Adducts of Steroids and 4-Phenyl-1,2,4-triazoline-3,5-dione[1]

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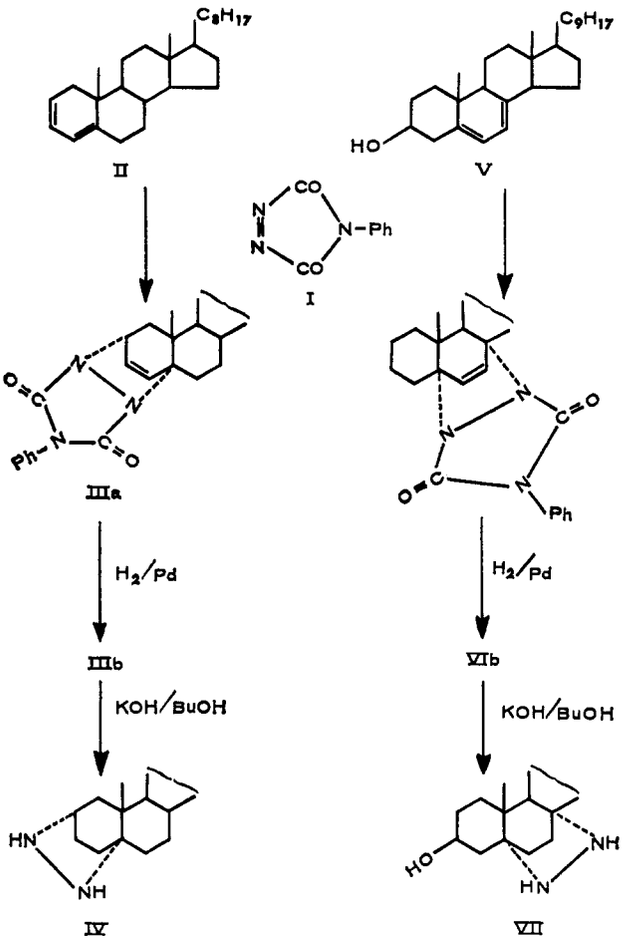
As part of a general program for the investigation of nitrogen-containing steroids, we have investigated the incorporation of azo and hydrazo bridges into rings A and B of $\Delta^{2,4}$-cholestadiene (II) and ergosterol (V). respectively, by the use of the dienophilic reagent 4-phenyl-1,2,4-triazoline-3,5-dione (I) (see Scheme I), Despite reports that the Diels–Alder reaction between

SCHEME I



ergosterol and maleic anhydride is slow[2] and that hydrogen abstraction–addition constitutes an undesirable side reaction in the ergosterol–ethyl diazocarboxylate reaction,[3] it was hoped that I would behave normally on the basis of its reactivity in various systems[4] including steroids.[5]

I reacted instantly with $\Delta^{2,4}$-cholestadiene in acetone–benzene solution at 0° as shown by disappearance of the red color of I. The adduct IIIa was isolated and characterized as such by several lines of evidence: the diene ultraviolet absorption pattern of II (λ_{max} 275 and 267 mμ) had disappeared; in the infrared spectrum, a carbonyl doublet at 1705 and 1760 cm^{-1} typical of adducts of I[4,5] had appeared; the pmr spectrum showed peaks at δ 6.25 and 6.34 (doublet integrating for two protons, J = 4 cps) assigned to ring A vinyl protons and a singlet at δ 7.4 assigned to N-phenyl; and finally, absence of NH peaks in the infrared spectrum and elemental analysis lend strong support to structure IIIa.

The adduct IIIa was hydrogenated at 3-atm pressure (5% Pd–C) to give the dihydro adduct IIIb which was isolated and characterized by analysis, absence of peaks for vinyl protons at δ 6.25 and 6.34 in the pmr spectrum, and the presence of the N-phenyl peak at δ 7.4. Hy-

(1) This work was supported by Grant GM 11603 from the National Institutes of Health, U. S. Public Health Service.

(2) H. H. Inhoffen, *Ann.*, **508**, 81 (1934).

(3) A. Van Der Gen, J. Lakeman, M. A. M. P. Gras, and H. O. Huisman, *Tetrahedron*, **20**, 2521 (1964).

(4) R. C. Cookson, S. S. H. Gilani, and I. D. R. Stevens, *Tetrahedron Letters*, 615 (1962).

(5) A. J. Solo, H. Sachdev, and S. S. H. Gilani, *J. Org. Chem.*, **30**, 769 (1965).