[CONTRIBUTION FROM THE LABORATORIES OF SCHERING CORPORATION AND EMORY UNIVERSITY]

Wagner–Meerwein Rearrangements. II. Acid-catalyzed Opening of Steroidal 16,17-Epoxides

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Reaction of 16α,17α-oxido-5-pregnen-3β-ol-20-one (I) with ethylene glycol and *p*-toluenesulfonic acid in benzene affords two rearranged products, tentatively described as 18-nor-17β-methyl-17-iso-5,12-pregnadiene-3β,16ξ-diol-20-one 20-cycloethylene ketal (II) and 18-nor-17β-methyl-17-iso-5,13-pregnadiene-3β,16ξ-diol-20-one 20-cycloethylene ketal (III). The 3-acetate of I (X) is converted mainly to the normal product, 16α,17α-oxido-5-pregnen-3β-ol-20-one 3-acetate 20-cycloethylene ketal (XI), under the same conditions, as reported by Julian.[2] However significant amounts of the rearrangement product corresponding to III are also formed in the latter reaction. Evidence for the structural assignments is presented.

The considerable therapeutic merit of 16β-methyl corticoids[3] in the treatment of diseases characterized by inflammation resulted in our attention being directed toward improved, non-hazardous procedures[4a] for introduction of the methyl group 16β-in an appropriate steroid; a well-known alkylation procedure[4b] involves the attack of methyl Grignard reagent on a 5α,6α-epoxide, affording thereby the corresponding 5α-hydroxy-6β-methylsteroid. In order that we might apply this reaction we studied first the protection of the 20-carbonyl group in 16α,17α-oxido-5-pregnen-3β-ol-20-one (I) through ketal formation.

Julian, Meyer and Ryden[2] had reported that the 3-acetate of I (X) is converted to the corresponding 20-cycloethylene ketal (XI) in 45% yield by the action of ethylene glycol and *p*-toluenesulfonic acid in refluxing benzene. As part of a yield improvement study we treated I in the same way and there was isolated by crystallization, in 45% yield, a ketal (II), which was clearly not the normal product since mild hydrolysis of the ketal group with aqueous acetic acid did not regenerate I, but rather afforded a new ketosteroid (V). Acetylation of V with acetic anhydride in pyridine solution yielded a diacetate (VIII) (no hydroxyl band in the infrared) indicating that two hydroxyl groups were present in V. Similar treatment of II also gave a diacetate (VII), which confirmed that the new hydroxyl group appeared during the ketal introduction. The ketal diacetate VII was hydrolyzed readily with aqueous acetic acid to the same diacetate (VIII) which had been prepared from V. Oxidation of V with chromic acid in acetone containing sulfuric acid[5] afforded a trione IV, which displayed a band at 5.75 μ in its infrared spectrum, characteristic of the 5-membered ring carbonyl group. The trione IV was very unstable, decomposing rapidly in acidic or alkaline solution to oily products, and even experienced slow decomposition in the solid state. A sample preserved at room temperature gradually darkened and developed an odor reminiscent of pyruvic acid. These properties are consistent with the formulation of IV as a β-diketone, bearing an oxygen function at 16.

The nuclear magnetic resonance spectrum of VIII exhibited resonance frequencies, relative to chloroform, at 72 c.p.s. (a broad multiplet of *two vinyl protons*), 205 c.p.s. (*three* methyl ketone protons), 210 c.p.s. (*six* acetate methyl protons), 248 c.p.s. (*three* quaternary methyl protons) and 251 c.p.s. (*three* quaternary methyl protons). The 251 c.p.s. resonance is assigned to the 19-methyl from a comparison with the spectrum of the related compound VI[6] (*vide infra*) and thus the 248 c.p.s. resonance must be assigned to the 18-methyl group. This is too low for a 18-methyl located at 13[6] and gives strong indication that the 18-methyl is no longer at 13, beta to the 20-carbonyl group, but has migrated to 17, which position being alpha to the 20-carbonyl group would cause the 18-methyl to undergo its resonance at lowered frequency. From these data we conclude that a Wagner–Meerwein rearrangement similar to that described by us previously for certain 17α-hydroxysteroids,[7] occurs at a stage of the transformation of I into II. The epoxide ring is opened by the acid catalyst with resultant formation of a 16-hydroxysteroid. The attendant phenomena of methyl migration from 13- to 17- and proton elimination then follow the pattern suggested previously.[7] The location of the double bond at 12 rather than 13, the departure of the methyl group from 13 and the location of an oxygen function at 16 are directly supported by the evidence. The mechanism would seem to require that the methyl group move to 17β, and that the oxygen function at 16- be 16α-hydroxyl, but no direct support for these assignments is adduced here.

A second component was shown to be produced, together with II, during the ketal-formation step. Hydrolysis of the total steroidal product from the ethylene glycol reaction in aqueous acetic acid, chromatography and subsequent acetylation of diol fractions poorest in V with acetic anhydride in pyridine afforded a *new diacetate* (VI), of the

(1) (a) Schering Corporation; (b) Emory University.

(2) P. L. Julian, E. W. Meyer and I. Ryden, THIS JOURNAL, **72**, 367 (1950).

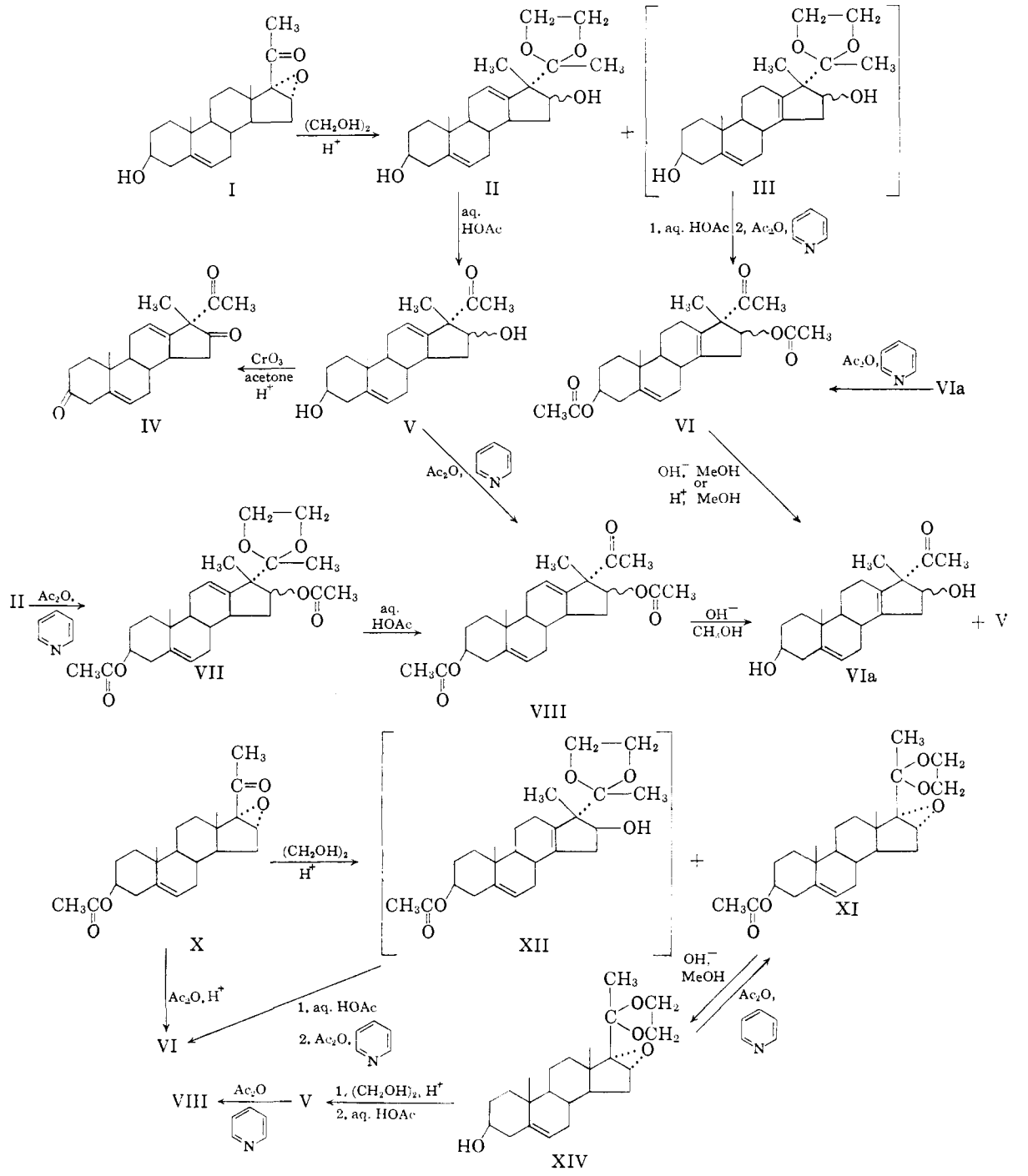
(3) E. Oliveto, *et al.*, *ibid.*, **80**, 6687 (1958), and references cited therein.

(4) (a) Thus far the 16β-methyl group has been introduced only by diazomethane addition to a Δ[16]-20-ketosteroid followed by pyrolysis and hydrogenation; *e.g.*, E. Oliveto, *et al.*, *ibid.*, **80**, 4428 (1958), and references cited therein. (b) O. Madaeva, *et al.*, *J. Gen. Chem.* (*U.S.S.R.*), **10**, 213 (1940); G. B. Spero, *et al.*, THIS JOURNAL, **78**, 6213 (1956).

(5) C. Djerassi, R. R. Engle and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(6) This assignment is also in accord with the extensive study of J. N. Shoolery and M. T. Rogers, THIS JOURNAL, **80**, 5121 (1958), as well as other observations in these laboratories.

(7) H. L. Herzog, *et al.*, *J. Org. Chem.*, **22**, 1413 (1957) (paper I of this series).



same empirical formula as VIII. It was calculated that the precursor diol of VI, namely III, was present in the ketal-formation mixture to the extent of 1–2%. The nuclear magnetic resonance spectrum of VI exhibited resonance frequencies, relative to chloroform, at 77 c.p.s. (a broad multiplet of *one* vinyl proton), 206 c.p.s. (*three* methyl ketone protons), 209 c.p.s. and 212 c.p.s. (*six* acetate methyl protons), 243 c.p.s. (*three* quaternary methyl protons) and 250 c.p.s. (*three* quaternary methyl protons). The 250 c.p.s. resonance is assigned to the 19-methyl in accord with the spectrum of VIII,[6] thus indicating that the 243 c.p.s. resonance must be due to the 18-methyl. As discussed previously, this low frequency indicates the 18-methyl has migrated to the 17-position. It is interesting tht the Δ^{13}-compound, VI shows its 17-methyl at lower frequency than the corresponding Δ^{12}-compound VIII.[8] This finding may be rationalized by considering the Δ^{13}-compound to have a more planar D-ring than the Δ^{12}-compound, thus incurring additional strain and introducing more "S" character to the D-ring carbons of the Δ^{13}-compound. This would be expected to shift

(8) This observation for Δ^{13} rearranged compounds has been confirmed in another series; see ref. 11.

the resonances of the 17-methyl attached to the Δ^{13}-D-ring to a lower frequency than that attached to a Δ^{12}-D-ring. From these properties and from the mode of formation of VI, it seemed reasonable that VI was a double bond isomer of VIII. Additional sites of isomerism are not excluded.

Heusler and Wettstein[9] have described the product from the action of refluxing acetic anhydride with *p*-toluenesulfonic acid on X as VI with configuration of the acetoxyl group at 16 as α. We suggested[7] that the double bond in the Heusler–Wettstein compound was probably at 12. It seemed especially appropriate therefore to prepare a sample of the Heusler–Wettstein compound according to their procedure and compare it with VI and VIII. This has been done and we find that the Heusler–Wettstein compound and VI are identical. Since the double bond in VI clearly cannot reside at 12, the original formulation of Heusler and Wettstein with respect to the location of the double bond is probably correct and we withdraw our earlier proposal.[7]

Hydrolysis of VIII with methanolic alkali in an attempt to regenerate V always afforded a mixture of diols, which appeared to be composed predominantly of two products of slightly different paper chromatographic mobility. Hydrolysis of VI under the same conditions gave the same two products, as did hydrolysis with bicarbonate as described by Heusler and Wettstein.[9] The slower moving component from both VI and VIII had the same mobility as V. By partition chromatography on Celite with a benzene–formamide system,[10] the mixture was resolved into V, identical with authentic material prepared directly from II, and VIa, prepared pure for the first time and identified by reacetylation with acetic anhydride in pyridine solution to VI. Hydrolysis of VI in methanolic hydrogen chloride afforded a mixture of V and VIa as well, as assessed by paper chromatography.

From these observations, we conclude that the diols V and VIa are in equilibrium in alkaline and acid solution. The respective diacetates VIII and VI are *not* in equilibrium in *acid* solution since refluxing either of them in acetic acid containing dry hydrogen chloride effected no change, the starting acetates being recovered unaltered. A reasonable explanation for the alkali-catalyzed equilibration is represented schematically here. Reverse Aldol condensation permits the double bond at 12 in V to shift to 13 *via* a conjugated intermediate. Recyclization is then effected in alkaline medium to afford VIa.[10a]

As a result of these observations we decided that I was not the preferred starting material for conversion to the corresponding unrearranged 20-ketal and we turned to a re-examination of the ketal formation with X described by Julian, Meyer and Ryden.[2] From a reaction carried out according to their method we isolated the desired ketal XI in 45% yield. Hydrolysis of the mother liquor, from the crystallization of XI, with aqueous acetic acid, and careful chromatography of the resulting mixture afforded a substantial recovery of X and a series of diol-rich fractions. The latter were pooled and acetylated with acetic anhydride in pyridine and there was isolated 3% of VI. Hence it is clear that rearrangement also occurs when X is employed as the starting material, although to a lesser degree.

We next studied the stability of XIV under the conditions of transformation of I into II. Hydrolysis of XI in aqueous methanolic alkali gave XIV, which was in turn subjected to reflux in ethylene glycol–benzene–*p*-toluenesulfonic acid. The total mixture was hydrolyzed with aqueous acetic acid and acetylated with acetic anhydride in pyridine. Thereby a modest yield of VIII was isolated. This observation supports the view that XIV is an intermediate in the conversion of I into II. A more tentative conclusion is that III and XII are formed when rearrangement precedes ketal formation. This implies control of the location of the double bond in the rearranged product by the nature of the functional group at 20. A more detailed treatment of this thesis is given in the article which follows.[11]

A question which still remains is why the group at 3-(alcohol *vs.* acetate) should have an effect on the extent of rearrangement. One explanation which we have considered is that rearrangement probably occurs in the ethylene glycol phase in which the bulk of the *p*-toluenesulfonic acid is concentrated. If one assumed that XIV is more soluble in ethylene glycol and less soluble in benzene than XI, then the former should be rearranged more rapidly than the latter in the two-phase system employed for this transformation.

We thank Drs. D. H. R. Barton and J. Meinwald for helpful discussions.

Experimental[12]

18-Nor-17β-methyl-17-iso-5,12-pregnadiene-3β,16ξ-diol-20-one 20-Cycloethylene Ketal (II).—A suspension of 36 g.

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

(10) Mr. Alvin Basch, to whom we are indebted, suggested and carried out this separation.

(10a) This formulation may also be used to explain epimerization at 16; *cf.* ref. 11.

(11) E. L. Shapiro, *et al.*, THIS JOURNAL, **81**, 6483 (1959).

(12) All m.p.'s are corrected. Analyses and optical data were obtained by the Microanalytical Department and Physical Chemistry Department of these laboratories. We are indebted to Mr. R. Wayne for the interpretation of the infrared spectra.

of 16α,17α-oxido-5-pregnen-3β-ol-20-one (I) in 1.0 l. of benzene, 36 ml. of ethylene glycol and 0.75 g. of *p*-toluenesulfonic acid was heated to boiling, and water was removed from the refluxing benzene with a Dean-Stark tube. A green to purple color invariably formed during the heating. After five hours at reflux, the reaction mixture was cooled to room temperature and made alkaline with methanolic potassium hydroxide. The benzene layer was washed to neutrality with water, dried and concentrated to incipient crystallization. A total of 18.11 g. of II, m.p. 224–226°, was collected in three crops. Recrystallization from benzene raised the m.p. to 231–234°, $[\alpha]^{25}D$ −152.8° (dioxane); λ_{Nujol}^{max} 2.90 (OH), 7.98 μ (COC).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.70; H, 9.08.

A sample of II recrystallized from ether melted at 240–243°, $[\alpha]^{25}D$ −152.9° (dioxane).

Evidence for the Formation of 18-Nor-17β-methyl-17-iso-5,13-pregnadiene-3β,16ξ-diol-20-one 20-Cycloethylene Ketal (III).—A mixture of 1.0 g. of I, 20 ml. of benzene and 1 ml. of ethylene glycol was refluxed with 100 mg. of *p*-toluenesulfonic acid for four hours. Benzene was continuously removed by distillation during this time and continuously replaced by an equal amount of dry benzene. The reaction mixture was then cooled to room temperature and neutralized with alcoholic potassium hydroxide. The benzene layer was washed to neutrality with water, dried and concentrated. The residue was taken up in 20 ml. of 85% acetic acid–15% water mixture and heated to reflux for 10 minutes. The resulting solution was cooled, concentrated to a small volume *in vacuo* and diluted with water. Chromatography of the resulting precipitate on 20 g. of Florisil and elution (60-ml. fractions) with the indicated solvents gave the following results: 9 fractions from 10% ether-in-hexane which contained mixtures of unidentified, ultraviolet-absorbing products by paper chromatography in toluene–propylene glycol; 15 fractions from 25% ether-in-hexane, the first 6 of which melted about 178–181°. These six were pooled and crystallized from acetone–hexane affording 17 mg., m.p. 176–181°. Paper chromatography of the recrystallized product showed two spots which were visualized by staining with phosphomolybdic acid reagent spray.[13] One, present in trace amounts, moved on paper at the same rate as V. The major product moved at the same rate as VIa; 12 fractions from 50% ether-in-hexane and 100% ether (The last eight fractions from 25% ether group were pooled with the 50% and 100% ether groups, affording 305 mg. of crystalline solid, m.p. 155–161°, which was essentially pure V by paper chromatography. A recrystallized sample melted 160–169°, did not depress the melting point of V and displayed the same infrared spectrum.)

A 5-mg. sample from the pooled fractions melting 176–181° was acetylated in 0.1 ml. of acetic anhydride and 0.1 ml. of pyridine at room temperature overnight. The water-precipitated product (4.7 mg.) melted at 190–200°, and displayed the same infrared spectrum as VI.

18-Nor-17β-methyl-17-iso-5,12-pregnadiene-3β,16ξ-diol-20-one (V) from II.—A solution of 1.0 g. of II in 20 ml. of 85% aqueous acetic acid was heated at reflux for 10 minutes. The reaction mixture was cooled to room temperature and concentrated. Water was then added and the resulting precipitate (0.75 g.) was removed by filtration. Chromatography of the solid on Florisil (15 g.) afforded, by elution with ether, the crystalline diol V which was recrystallized from acetone–hexane as long needles (0.46 g.), m.p. 168–169°, $[\alpha]^{25}D$ −83.2° (chloroform), $[\alpha]^{25}D$ −60° (dioxane); λ_{Nujol}^{max} 3.02 (OH), 5.96 (20-carbonyl); $\lambda_{CS_2}^{max}$ 2.92 (OH), 5.92 μ (20-carbonyl). A second crop (0.12 g.), m.p. 160–168°, $[\alpha]^{25}D$ −84.8 (chloroform), was also obtained.

Anal. Calcd. for $(C_{21}H_{30}O_3)_2 \cdot C_6H_{14}$: C, 77.17; H, 9.98. Found: C, 77.22, 77.12; H, 9.75, 9.89.

Integration of the hydroxyl band of a pyridine solution of V showed two hydroxyl groups.

Diacetate of V (VIII) from V.—A solution of 0.20 g. of V in 3.0 ml. of pyridine and 2.0 ml. of acetic anhydride was allowed to stand at room temperature overnight. Water precipitation afforded 0.210 g. of VIII, m.p. 100–103°. Recrystallization from ether–hexane or aqueous methanol, did not change the melting point, $[\alpha]^{25}D$ −13.8° (dioxane), $[\alpha]^{25}D$ −28.3° (chloroform); $\lambda_{CS_2}^{max}$ 5.78 μ (acetate carbonyl) 5.88 (20-carbonyl), 8.14 μ (COC).

Anal. Calcd. for $C_{25}H_{34}O_5$: C, 72.43; H, 8.27. Found: C, 72.61; H, 8.02.

Diacetate of II (VII) from II.—A solution of 5 g. of II in 17 ml. of pyridine and 10 ml. of acetic anhydride was allowed to stand at room temperature for 72 hours. From water precipitation of the product there was isolated 6.12 g., m.p. 124–130°. Recrystallization of 5.12 g. of this solid afforded 4.0 g. of VII as needles, m.p. 134–137°. Repeated methanol crystallization raised the m.p. to 137–139°, $[\alpha]^{25}D$ −98° (dioxane), $[\alpha]^{25}D$ −101° (chloroform).

Anal. Calcd. for $C_{27}H_{38}O_6$: C, 70.71; H, 8.36. Found: C, 70.91; H, 8.32.

VIII from VII.—A solution of 0.300 g. of VII in 3 ml. of acetic acid and 0.3 ml. of water was refluxed for one minute, cooled and excess water was added. The resulting precipitate (0.23 g., m.p. 97–100°) was recrystallized from aqueous methanol affording 0.19 g. of needles, m.p. 100–102°. The infrared spectrum of VIII thus obtained was identical with that of VIII from V, and there was no depression of the mixed melting point.

18-Nor-17β-methyl-17-iso-5,12-pregnadiene-3,16,20-trione (IV) from V.—A solution of 1.0 g. of V in 100 ml. of acetone which had been distilled from potassium permanganate was treated with 1.67 ml. of CrO_3 reagent[6] under nitrogen at 8–10° for 8 minutes. A few drops of methanol was added to scavenge the remaining CrO_3 and excess water to precipitate the product. The resulting slurry was kept at 0° overnight and filtered. There was isolated 0.5 g. of IV, m.p. 129–131°. Recrystallization from acetone–water gave needles, m.p. 134–135.5°. The analytical sample was dried one hour *in vacuo* at 56°; λ_{Nujol}^{max} 5.72 (16-carbonyl) 5.84, 5.89 μ (3- and 20-carbonyl).

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 76.92; H, 8.00.

The solid sample of IV was unstable. It developed an orange color and a pyruvic acid-like odor on storage for several months. In this condition it could no longer be recrystallized to afford pure IV.

A solution of 5.5 mg. of IV in 100 ml. of methanol displayed no ultraviolet absorption. If to this was then added 6.0 ml. of 1 *N* aqueous potassium hydroxide, a peak developed at 241 mμ (ε 19,800) in two hours at 60°.

18-Nor-17β-methyl-17-iso-5,13-pregnadiene-3β,16ξ-diol-20-one 3,16-Diacetate (VI) from X.—The procedure of Heusler and Wettstein[9] using hot acetic anhydride with *p*-toluenesulfonic acid was employed to prepare VI. From 4.0 g. of X there was isolated 2.30 g. of VI, m.p. 212–217°. Recrystallization from ether at −78° gave VI, m.p. 214–217°, $[\alpha]^{25}D$ −9.3° (dioxane), $[\alpha]^{25}D$ −18.1° (chloroform), λ_{Nujol}^{max} 5.72, 5.76 (acetate carbonyl), 5.88 (20-carbonyl), 8.20 μ (COC).

The reaction also proceeded under much milder conditions in considerably poorer yield. A suspension of 1.15 g. of X in 12 ml. of acetic acid and 12 ml. of acetic anhydride containing 0.18 g. of *p*-toluenesulfonic acid was stirred at room temperature for 18 hours. The steroid dissolved slowly and a blue color developed in the solution. At the end of the reaction period water and sodium acetate were added and the solvents were removed by evaporation. The residue was triturated with water and recrystallized twice from ether at −78° affording thereby 0.180 g. of VI, m.p. 211–214°. The infrared spectrum of this material was identical with that prepared by the literature method.[9]

Acetylation of V with Acid Catalysis.—A solution of 0.100 g. of V in 4 ml. of acetic anhydride containing 0.010 g. of *p*-toluenesulfonic acid was heated at reflux for 3 hours. The reaction mixture was then cooled to room temperature, 0.01 g. of sodium acetate was added and solvents were removed by evaporation. The residue was chromatographed over 15 g. of Florisil and the product was eluted with ether. Recrystallization of the resulting solid from aqueous methanol afforded 70 mg. of VIII as needles, m.p. 99–102°. The infrared spectrum was identical with that of VIII prepared by pyridine-catalyzed acetylation.

Both VIII and VI were recovered unchanged after 100 mg. of each (separately) was refluxed in 3 ml. of acetic acid saturated with hydrogen chloride for one hour.

(13) The reagent was a 10% solution of phosphomolybdic acid in methanol. The papergram was developed by heating at 60° until the spots showed (usually 10–15 minutes).

Alkaline Hydrolysis of VIII.—A solution of 412 mg. of VIII in 15 ml. of methanol and 2 ml. of water containing 500 mg. of potassium hydroxide was stirred at room temperature for 65 minutes. An aliquot which had been withdrawn after 15 minutes of reaction was diluted with water and the resulting precipitate examined by paper chromatography in the toluene–propylene glycol system. No starting material remained (phosphomolybdic acid stain) and two new, more polar products appeared, the most prominent and most polar moving like V. The entire reaction mixture was water precipitated (combined recovery of aliquot and bulk of reaction, 328 mg.) and the resulting crude solid, m.p. 167–169°, was recrystallized from acetone–hexane, affording 123 mg., m.p. 164–170°, still containing the two new products. Chromatography of 95 mg. of recrystallized product in a benzene–formamide–Celite partition column (stationary phase, formamide on Celite; moving phase, benzene saturated with formamide) and collection of fifteen 20-ml. fractions afforded a clean separation of the components of the mixture.

From beakers 6–9 there was isolated 35 mg. of homogeneous (only the faster moving component) crystalline solid, which, after recrystallization from acetone–hexane, gave 25 mg. of VIa as needles, m.p. 198–199°, $[\alpha]^{25}D$ −132.8° (chloroform), $[\alpha]^{25}D$ −15.4° (dioxane); λ_{Nujol}^{max} 2.94, 3.04 (OH), 5.92 μ (20-carbonyl). This appears to be a pure sample of the diol described by Heusler and Wettstein (m.p. 189–191°, $[\alpha]^{25}D$ −131° ($CHCl_3$)[9]). Attempts to repeat the Heusler and Wettstein procedure ($NaHCO_3$–methanol–water) gave VIa contaminated with V, as indicated by paper chromatography. Acetylation of VIa with acetic anhydride in pyridine regenerated VI.

From beakers 11–15 (one component moving like V in toluene–propylene glycol) there was obtained 39.6 mg. of V, m.p. 158°, resolidify and remelt 171–172°. Recrystallization from acetone–hexane afforded 30 mg. of V as needles, m.p. 169–170°. The infrared spectrum of V, prepared in this way, was identical with that prepared directly from II.

Alkaline Hydrolysis of VI.—A suspension of 0.100 g. of VI in 3.5 ml. of methanol and 0.5 ml. of water containing 50 mg. of potassium hydroxide was warmed until the suspended solids dissolved and then cooled to room temperature. After one hundred minutes at room temperature the reaction mixture was acidified with acetic acid, diluted with water, extracted with methylene chloride and the extracts were washed with water, dried and concentrated to a residue. Crystallization from acetone–hexane afforded 0.0488 g., m.p. 167–169°, and a second crop of 0.0049 g., m.p. 164–166°. Each fraction displayed two components in toluene–propylene glycol paper chromatograms (phosphomolybdic acid spray) which moved like V and VIa, respectively.

Acid Hydrolysis of VI.—A suspension of 0.120 g. of VI in 14 ml. of methanol and 2.4 ml. of concentrated hydrochloric acid was heated at reflux for 40 minutes, during which time the suspended solid went into solution. Water precipitation afforded 0.054 g. of a mixture, m.p. 160–185°, which was composed of two components with the same migration rates as V and VIa, respectively, in a toluene–propylene glycol paper chromatogram.

Ketal Formation (XI) and Rearrangement (→ XII → VI) with X.—Crystallization of a run with 20 g. of X exactly according to Julian[3] afforded 10 g. of XI. The crystallization mother liquor was concentrated, the residue was taken up in 230 ml. of 85% acetic acid–15% water and heated at reflux for 10 minutes. The solvents were removed at room temperature, the residue was taken up in methylene chloride, washed with water, dried and taken to a volume of 600 ml. A 60-ml. aliquot was taken to a residue (1.05 g.) which was in turn redissolved in methylene chloride–hexane and chromatographed over 50 g. of Florisil prepared with hexane. A series of sixty 60-ml. fractions were collected. Numbers 2–15 were eluted with 10% ether-in-hexane. The combined group weighed 280 mg. and moved like X in a toluene-propylene glycol chromatogrm. Recrystallization from ether gave 0.194 g. of X, m.p. 150–153°, whose infrared spectrum was identical with that of an authentic sample. Fractions number 16–19 were collected with 25% ether-in-hexane and afforded 40 mg. of X.

Fractions number 20–40, eluted with 50% ether–hexane and with ether, afforded 310 mg. of a mixture which contained at least five components (paper chromatogram), among them one which moved like X and one ultraviolet-absorbing product. The entire pool was acetylated with 3 ml. of acetic anhydride in 3 ml. of pyridine, the products were water precipitated (oily), dried and chromatographed over 15 g. of Florisil. From the 25% ether eluates 98 mg. of crystalline solid, m.p. 150–215°, was obtained. Recrystallization from ether at 0° afforded 29 mg. of VI, m.p. 213–216°, whose infrared spectrum was identical with that of an authentic sample. No other crystalline products were isolated.

An additional 225 mg. of oily products with substantial ultraviolet absorption were isolated by elution of the column with methylene chloride containing 5% methanol.

Alkaline Hydrolysis of XI to XIV.—To a suspension of 0.400 g. of XI in 20 ml. of methanol and 2 ml. of water was added 0.200 g. of potassium hydroxide. The mixture was heated to reflux for 5 minutes during which time the suspended solid went into solution. The solution was then cooled and ice was added. The precipitated solid, XIV, weighed 0.370 g. and melted at 175–181°. Recrystallization from ether–hexane gave needles of XIV, m.p. 184–186°, $[\alpha]^{25}D$ −43.3° (dioxane); λ_{Nujol}^{max} 2.94, 3.00 μ (OH).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.83; H, 8.73.

Acetylation of XIV with acetic anhydride in pyridine solution regenerated XI.

Conversion of XIV into VIII.—The second experiment of this section (I → III) was repeated using 0.100 g. of XIV in place of I. From chromatography on 5 g. of Florisil of the acetic acid hydrolyzate there was isolated in the 50% ether-in-hexane and 100% ether fractions (7–15) a solid, which after recrystallization from acetone–hexane gave 0.0157 g. of V, m.p. 155–161°, identified by its paper chromatographic mobility in toluene–propylene glycol compared with authentic V. A second crop of solid (18 mg.), principally V, m.p. 140–160°, was also isolated.

The higher-melting portion of V was acetylated in 0.5 ml. of acetic anhydride and 0.5 ml. of pyridine at room temperature overnight. The water-precipitated solid was crystallized from methanol–water affording 0.013 g. of VIII, m.p. 93–97°, whose infrared spectrum matched that of VIII previously described.

Nuclear Magnetic Resonance Spectra.—The nuclear magnetic resonance spectra were determined using a Varian Associate model 4300 V high resolution spectrometer with super stabilizer and spinning sample. The resonance frequencies are reported in c.p.s. at 40 mc. relative to chloroform and were determined via the procedure given by Shoolery and Rogers.[6] Vinyl proton areas were measured relative to the area of the quaternary methyl protons. In all cases deuteriochloroform was used as solvent and the reference was chloroform added to the sample in a capillary tube.

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