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PINACOL TYPE REARRANGEMENTS IN THE D RING OF STEROIDS

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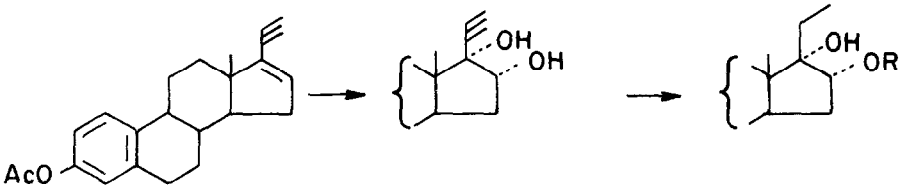
The ring contracting pinacol type rearrangement, as well as other four center ionic rearrangements in conformationally rigid cyclohexane rings, generally follow the course imposed by the geometry of the molecule (1), even when the electronic factor could have exercized an unfavorable influence upon this course (2). The five membered D ring in steroids, bearing a C-20 ethylene ketal substituent, is converted exclusively to a cyclobutane ring as a result of a pinacol type rearrangement (3). Since the four center anti coplanarity is attained in five membered systems with more difficulty than in cyclohexanes and angle strain is involved in this ring contraction, it was considered of interest to establish if the electronic factor can exercise an influence upon the course of this rearrangement.

We now report the synthesis and the results of base-catalysed rearrangement of two steroid systems, IV and XIII, in which the +I effect of a 17 β -alkyl side chain provides a reason for a competing course of rearrangement. The 16-methanesulphonate of 3-acetoxy-16α ,17α -dihydroxy-17β -ethyl-estra-1,3,5(10)triene(IV) has been prepared by a sequence starting from 17-ethinyl estradiol 3-acetate, which on dehydration

with phosphorous oxychloride in pyridine yielded the enyne I, m.p. 115-116°, $[\alpha]_D$ + 48° (4). Stereoselective hydroxylation with osmium tetroxide in pyridine yielded the triol acetate II, m.p. 186-188°, $[\alpha]_D$ + 45°, which, on hydrogenation over palladium on calcium carbonate in ethanol, furnished the corresponding, homogenous, 17β -ethyl derivative III m.p. 109-110°, $[\alpha]_D$ + 26°. Treatment with methanesulphonyl chloride in pyridine afforded the methanesulphonate IV, m.p. 177-179°, $[\alpha]_D$ + 9° which was completely converted by potassium t-butoxide in t-butyl alcohol (70°, 14 hrs.) into a mixture of isomeric ketones homogenous on t.l.c. Two epimeric D-nor-derivatives (total yield 69%) have been separated from this mixture and isolated as their acetates, VI and VII. The major product, VI (16β -isomer), had m.p. 114-115°, $[\alpha]_D$ + 145°, $\lambda_{max}^{CHCl_3}$ 5.73, 5.88μ , H-18 resonance at δ ($CDCl_3$) 0.88 and positive Cotton effect in o.r.d. The 16α epimer VII, $[\alpha]_D$ + 46° could not be obtained crystalline but readily formed a semi-carbazone (m.p. 205-206°); compound VII exhibited a negative Cotton effect and the H-18 signal was shifted to δ 1.27. Each of the epimers could be converted to the equilibrium mixture by base. Final proof of structure was provided by a Baeyer-Villiger oxidation of VI followed by hydrolysis of the resulting ester and oxidation with chromic acid in acetone to the D-norestrone VIII, m.p. 254-256°, λ_{max}^{KBr} 5.64μ .

The remaining ketonic product (total yield 31%) was identified as 3-hydroxy-17β -ethyl, 1,3,5 (10) estratrien-16-one (IX), m.p. 282-284°, $[\alpha]_D$ - 76° (pyr), λ_{max}^{KBr} 5.79μ . This formulation was confirmed by labeling with deuterium (3 H exchanged in ring D) and by an independent synthesis starting from the diacetate V (m.p. 140-141°) by way of a Serini reaction (5) followed by epimerization with base. The product obtained was identical in all respects with compound IX.

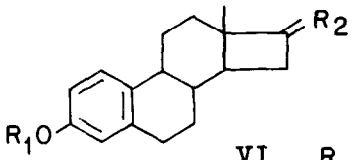
It was desirable to perform the base catalyzed rearrangement also on a system with a C-17 branched alkyl substituent which would be sterically more similar to the previously studied C-20 ketal derivatives (3) and in which the influence of a somewhat increased + I effect of the side chain

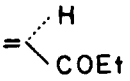


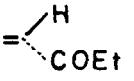
I II III , R = H

IV , R = CH_3SO_2

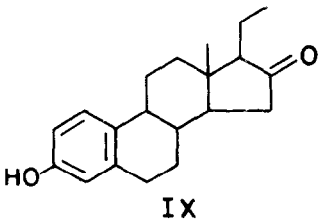
V , R = Ac



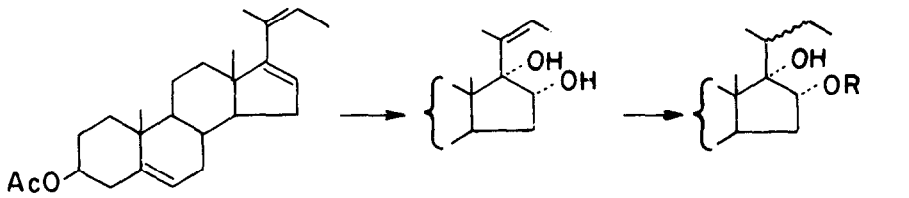
VI , R_1 = Ac, R_2 = 

VII , R_1 = Ac, R_2 = 

VIII, R = H, R_2 = O

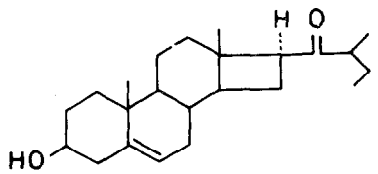


IX

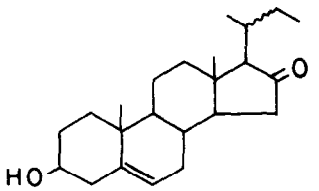


X XI XII , R = H

XIII , R = CH_3SO_2



XIV



XV

could be examined. Accordingly, the 16 mathanesulphonates XIII (mixture of two C-20 epimers) have been synthesized (6) by a four-step sequence, starting from 3β -acetoxypregna-5,16-dien-20-one. Wittig reaction of the latter with ethylidenetriphenylphosphorane yielded a single, homogenous triene, X, m.p. 129-131°, $[\alpha]_D$-66°, λ_{max}^{isooct} 242mμ (ε , 13,800), which could be selectively hydroxylated by osmium tetroxide in pyridine at low temperature to afford, in good yield, the corresponding 16α ,17α -diol XI, m.p. 182-184°, $[\alpha]_D$ - 102°. Hydrogenation of the side chain (PtO_2, dioxane) gave a mixture of C-20 epimers (XII, m.p. 146-165°) which was converted to the methanesulphonates XIII. Rearrangement of XIII (as before), gave a mixture of isomeric ketones. This mixture has been separated by repeated chromatography into a fraction containing five membered cyclic ketones (54%, $\lambda_{max}^{CHCl_3}$ 5.78μ) and another fraction containing the D-norepimers (46%, $\lambda_{max}^{CHCl_3}$ 5.88μ). The pure D-nor-16β -epimer, XIV, had m.p. 131-132°, $[\alpha]_D$ + 49°, and its spectral data (n.m.r., o.r.d.) were analogous with those found in the previous series and in agreement with the proposed structure. The mixture of five membered cyclic ketones, m.p. 75-110°, most probably contains the C-20 epimers of 17β -isobutyl pregn-5-en-3β -ol-16-one (XV), as confirmed by mass spectral fragmentation (identical with the fragmentation of analogous ketones (8)), labeling with deuterium (d_3 in ring D) and negative Cotton effect.

The formation of 16-ketones in both series can be envisaged as proceeding through solvolysis of the methanesulphonate followed by epoxide formation and subsequent cleavage and rearrangement (9); the concerted 1,2 migration of the side chain does not take place for geometrical reasons.

The present results indicate a marked difference in the course of rearrangement of five membered ring systems as a function of substituents. It does not appear that steric factors are significant enough to account for this difference, particularly since the more branched alkyl substituted system differs in a greater degree from the ketals studied previously, although sterically it is more similar to them.

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4. Satisfactory analyses were obtained for all compounds whose melting points (uncorrected) are reported. The optical rotations were determined in chloroform solution unless specified otherwise.
5. See M. B. Rubin and E. C. Blossey, Steroids, 1, 453 (1963).
6. The difficulties in preparing Δ^{16} derivatives with a branched 17-alkyl substituent will be reviewed elsewhere. The previously reported Δ^{16}-17-isopropyl analogue (7) is actually the $\Delta^{17(20)}$-isomer, as we found by n.m.r. analysis.
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