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ALTERED SELECTIVITY OF REDUCTION OF STEROIDAL CARBONYLS

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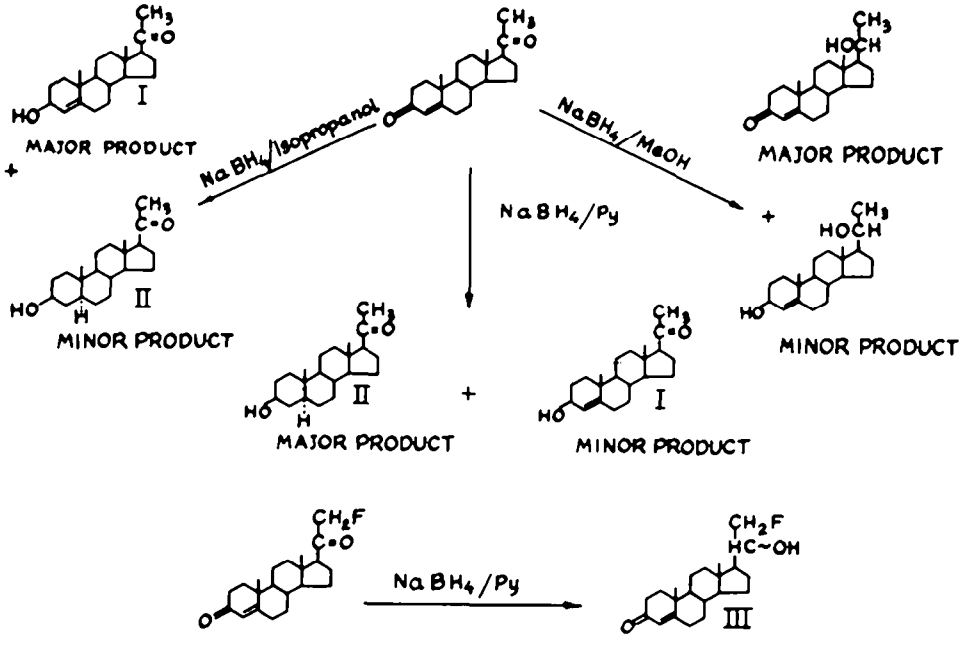
Abstract— The reduction of steroidal ketones in different solvents yielded different products. These conditions which altered the *normal* path, yielded a selective reduction of the Δ^4-3 carbonyl without the concomitant reduction of the C-17 or C 20 ketones; this permitted a one step partial synthesis of 3β-hydroxy-Δ^4-pregnen-20-one (I), 3β-hydroxy-5α-pregnan-20-one (II), and of 3β,11β-dihydroxy-androstan-17-one (IV).

CONSIDERABLE interest has been centered on 3β-hydroxy-Δ^4-pregnen-20-one (I) and related compounds as potential progestational substances. I has been previously prepared by classical procedures which involved lengthy multistep synthesis often with poor yields.[3,4] It was hoped that with the establishment of proper conditions such



compounds might be prepared by a specific one step reduction of the C-3 group of the appropriate derivative using one of the metal hydrides. Such an approach was not previously attempted because preparative studies have demonstrated that the reactivity of steroid ketones with $NaBH_4$ does not follow a steric course: 20 ketone being reduced

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[2] This investigation was aided by a grant from the Julius Schmid Company.
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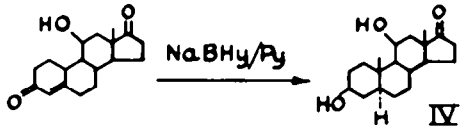
preferentially to Δ^4-3 as demonstrated by the following order: 3 > 17 or 20 > Δ^4-3 > 11 ketone.[5,7] Selectivity of reduction was increased in the presence of pyridine.[6,10] While preparative studies which were conducted in MeOH with steroids containing multiple ketonic functions showed that 17 and 20 ketones were reduced preferentially to the Δ^4-3 ketone,[5] kinetic data with monoketonic steroids in anhydrous isopropanol indicated a reversed order,[11,12] i.e. Δ^4-3 > 17 > 20.

The present study demonstrates a method for the selective reduction of the Δ^4-3 carbonyl with $NaBH_4$ in anhydrous isopropanol to the 3β-hydroxy-Δ^4 compound without concomitant reduction of the C-20 carbonyl. Similarly with $NaBH_4$ in pyridine, reduction of the Δ^4 carbonyl was preferential to that of 17 and 20 ketones; but under these latter conditions saturation of the double bond also took place. On the other hand reduction of 21 fluoroprogesterone in pyridine followed the "normal" route and resulted with the exclusive reduction of the 20-carbonyl. These



IV

findings allowed the preparation of I and of 3β-hydroxy-5α-pregnan-20-one (II) from progesterone and the preparation of 3β,11β-dihydroxy androstan-17-one (IV) from 11β-hydroxy-Δ^4-androstene-3,17 dione by a one step reduction.

EXPERIMENTAL

3β-hydroxy-Δ^4-pregnen-20-one (I). Progesterone (200 mg) was dissolved in anhydrous isopropanol (32 ml) and sodium borohydride (25 mg) added. The resulting solution was mixed at room temp for 15 hr. Water (100 ml) was added and the resulting suspension extracted several times with ether. The ether phase was dried (Na_2SO_4) and evaporated to dryness under reduced press. Infra-red spectra of the resulting oil (ca. 200 mg) indicated an appearance of a band at 2·8 μ (OH) and a considerably larger decrease of the band at 6·0 and 6·15 μ (conj C O) than at 5·9 μ (saturated C O). The β-hydroxy derivatives were separated from the rest of the mixture by the conventional digitonide separation. The decomposition of the insoluble digitonide complex was achieved by dissolving in pyridine at room temp letting stand for 5 min followed by the addition of ether. The ether phase was washed with cold 0·2N HCl,[13] cold 5% aqueous $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to dryness under vacuum. Colorless oil (ca. 100 mg) resulted. λ_{max}^{FILM} 2·90 (OH), 5·9 (C O) and only minor band at 6·0 (Conj C O) μ. Chromatography on 3 g of neutral alumina and elution with benzene–petroleum ether mixtures resulted in the isolation of 50 mg (25% yield) of crystalline substance; m.p. 156 159·5°; reported[5] m.p. 155 161°. λ_{max}^{KBR} 2·80 (OH), 5·92 (C O) and 6·1 (c c) μ; the infra-red spectrum was identical to an authentic sample prepared by a different route.[5]

3β-hydroxy-5α-pregnan-20-one (II). Progesterone (200 mg, 0·64 mmole) was dissolved in anhydrous pyridine (2 ml) containing $NaBH_4$ (50 mg, 1·2 mmoles). The resulting solution was mixed at room temp for 4½ hr. Water (100 ml) was added and the resulting suspension immediately extracted with

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[12] J. L. Mateos, *J. Org. Chem.* **24**, 2034 (1959).
[13] Care should be taken to avoid prolonged contact with acid to avoid elimination of the allylic alcohol.

ether. The ether phase was washed with cold 0·2N HCl, 5% cold $NaHCO_3$ and water (till neutral); dried over Na_2SO_4 and evaporated under reduced pressure to dryness. The resulting oil (214 mg) showed in the infra-red, an insignificant reduction of the 20 ketone but a considerable reduction of the Δ^4-3 ketone and an appearance of a band at 2·75 μ (OH) λ_{max}^{EtOH} indicated 20% of residual conjugated ketone. Chromatography on silica gel and elution with benzene ethylacetate mixtures yielded 122 mg of crystalline material. Crystallization from ether and from acetone resulted in colorless plates; m.p. 189–192°; reported[14] m.p. 194°. The substance showed no absorption in the ultra-violet between 220–290 mμ and no U.V. absorption after prolonged acid treatment, which was indicative of no traces of allylic alcohol. Infra-red spectrum was identical to that of an authentic sample of 3β-hydroxy-5α-pregnan-20-one.

21-fluoro-Δ^4-pregnen-20-ol-3-one (III). 21-Fluoroprogesterone (m.p. 140–145°; 50 mg) was dissolved in pyridine (0·5 ml) to which was added $NaBH_4$ (12 mg). The solution was mixed at room temp for 4 hr. The reaction mixture was worked up similarly to that described for II resulting in 44 mg of oil. The infra-red spectrum indicated a total reduction of 20-ketone and practically no reduction of Δ^4-3 ketone. Chromatography on silica gel and elution with benzene ethylacetate mixtures yielded a colorless oil. A fraction of this oil was chromatographed on paper in the ligroin-propylene glycol, located on paper by its U.V. absorption. Elution with methanol and methylene chloride resulted in a crystalline solid; m.p. 142–152°, λ_{max}^{KBr} 2·90 (OH), 6·0, 6·2 (conj C–O) and no band at 5·79 (α-fluoro C O) λ_{max}^{MeOH} 241, ε – 13,100 (calculated for III). Oxidation of III without further purification by Py–CrO_3 complex yielded an oil λ_{max}^{Film} 5·80 (α-fluoro C O) 6·05 (conj C O) and no band at 2·90 μ (OH). The infra-red spectrum was identical to that of 21-fluoroprogesterone.

3β, 11β-dihydroxy-androstan-17-one (IV). 11β-Hydroxy-Δ^4-androstene-3, 17-dione (75 mg) was dissolved in cold pyridine (1 ml) containing $NaBH_4$ (19 mg) and mixed at room temp for 4½ hr. The reaction mixture was worked up similarly to that described for II (numerous extractions were required because of water solubility of the products).

Chromatography on neutral alumina, yielded colorless amorphous substance. Two crystallizations from ether yielded crystals melting at 228–231°; reported[15] 234–235°. The crystals showed no U.V. absorption in the ultra-violet between 220–290 mμ; λ_{max}^{KBr} 2·85 (OH), 5·80 (cyclopentyl C O) and no absorption at 6–6·2 μ.

Results and Discussion

The method described permits a simple one step preparation of 3β-hydroxy-Δ^4-pregnen-20-one (I), 3β-hydroxy-5α-pregnan-20-one (II) and of 3β, 11β-dihydroxy-androstan-17-one (IV).

It is interesting to note that a mere change in the solvent employed had modified the site of $NaBH_4$ attack, i,e., the reduction of progesterone in MeOH resulted mainly in 20β-hydroxy-Δ^4-pregnen-3-one with an occasional formation of Δ^4-pregnen-3β, 20β-diol,[5] in isopropanol yielded mainly I with only small quantities of II and in pyridine yielded mainly II and occasionally significant quantities of I. But in no case could we demonstrate significant formation of 20β-hydroxy-Δ^4-pregnen-3-one in either isopropanol or pyridine.

Similarly the reduction of Δ^4-androstene-3,17-dione and Δ^4-androstene-3,11,17-trione in methanol yielded testosterone and 11-ketotestosterone respectively.[5] On the other hand, the reduction of 11β-hydroxy-Δ^4-androstene-3,17-dione in pyridine yielded IV; here again no 11β-hydroxy-testosterone could be demonstrated.

While the Δ^4-3 ketone is least hindered sterically and therefore should be most reactive, its slow reactivity has been attributed to resonance interactions which tend to reduce the charge on the ketone group.[11] Thus, conditions which will tend to decrease the importance of this interaction will tend to increase the reactivity of the Δ^4-3 ketone. This may well be the case when isopropanol and pyridine instead of methanol are employed.

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Our results indicate that a delicate balance of steric and polar factors is at play and a slight shift in the magnitude of each will tend to effect the course of the reaction. This could be demonstrated in the reduction of 21-fluoroprogesterone in pyridine. The inductive effect of a vicinal fluorine has increased the reactivity of the C-20 carbonyl and allowed a selective reduction of the 20 carbonyl. Kinetic studies have demonstrated that the rate of reduction of 2-bromo-3-keto is ten fold that of the corresponding unsubstituted 3 keto.[12]

In addition, it is interesting to note that the reduction of Δ^4-3 keto groups with a large excess of $NaBH_4$ yielded saturated products, i.e. 3β-hydroxy-5α derivatives. While the reduction in isopropanol when the molar ratio of $NaBH_4$:steroid was 1:1, yielded primarily the allylic alcohol, a mere increase in this ratio to 2:1 yielded as much as 60 per cent of the saturated product. Similarly, progesterone-20-ethylene ketal in 90 per cent ethanol yielded the saturated derivative 5α-pregnan-3β-ol-20 ethylene ketal; the molar ratio of $NaBH_4$ to steroid was 10:1 and the reaction time was 16 hours.[4] On the other hand, a similar reaction in methanol with a lower molar ratio of $NaBH_4$ to steroid (3·5:1) and a shorter reaction time (2 hours) yielded 3β-hydroxy-Δ^4-pregnen-20-ethylene ketal in good yields.[3]

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