NOTES

DECONJUGATION OF $\Delta^{1,4}$-3-KETOSTEROIDS

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We wish to report on the use of basic agents with aprotic solvents to effect deconjugation of $\Delta^{1,4}$-3-keto-steroids to their $\Delta^{1,5}$-3-keto analogues.

Recently, potassium tert.-butoxide in tert.-butanol was utilized in the deconjugation of steroidal Δ^{4}-3-keto mono-enone systems, but was not effective in the deconjugation of the steroidal crossconjugated $\Delta^{1,4}$-3-one system[1]. Although the preparation of $\Delta^{1,5}$-3-ketosteroids has already been reported[2], the process described first requires the preparation of a 6-bromo or 6-acetoxy-$\Delta^{1,4}$-3-one.

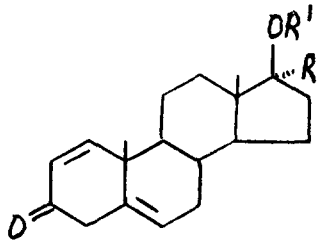
In connection with another problem[3] we chose to ethinylate the 17-ketone of 11β-hydroxy-1,4-androstadiene-3,17-dione with commercial sodium acetylide (as a suspension in xylene) in dimethylsulfoxide[4]. The desired 17α-ethinyl-11β, 17β-dihydroxy-1,4-androstadien-3-one was obtained, but another substance had apparently also formed since the mother liquor

exhibited a spectroscopic absorption at approximately 225 mμ. In order to gain insight into the reason for this absorption, the reaction was repeated on 17α-methyl-17β-hydroxy-1,4-androstadien-3-one (I). The transformation product obtained after pouring the reaction mixture into ice-water and extracting with methylene chloride was assigned the structure of 17α-methyl-17β-hydroxy-1,5-androstadien-3-one (II) [m.p. 194-198° ; $[\alpha]_D$ + 43.9° ; λ_{max} 226 mμ (ε 11,250); λ_{max} 2.91, 6.01, 6.25 μ][5] both on the basis of the similarity with the ultraviolet absorption of known $\Delta^{1,5}$-3-ketones[2] and because acid or base equilibration of II regenerated I. The deconjugation of I to II was subsequently also effected using commercial potassium tert.-butoxide in dimethylsulfoxide. Other basic media we have used successfully in deconjugation of the dienone system include sodium acetylide in dimethylformamide, and sodium hydride or sodium amide in tetrahydrofuran. With the latter two basic media, our work-up procedure utilizes a boric acid solution to effect neutralization. With the other media (as described for sodium acetylide) simply quenching the reaction mixture with water affords the desired deconjugated steroids.

Some of the $\Delta^{1,5}$-3-ketosteroids we have prepared (with the basic agent and aprotic solvent used) are: 17β-hydroxy-1,5-androstadien-3-one (III) (NaC≡CH/DMS) [m.p. 147-149°; $[\alpha]_D$ + 60.2°; λ_{max} 226 mμ (ε 10,500); λ_{max} 2.87, 5.98, 6.03, 6.23 μ]; 17α-ethyl-17β-hydroxy-1,5-andorstadien-3-one[6] (IV) (NaC≡CH/DMS) [m.p. 189-191°; $[\alpha]_D$ + 51.4°; λ_{max}

225 mμ (ε 10,600); λ_{max} 2.88, 5.95, 6.22, 11.50 μ]; 17,20;-20,21-bismethylenedioxy-11β-hydroxy-1,5-pregnadien-3-one (V) (NaC≡CH/DMS, potassium tert.-butoxide/DMS) [m.p. 244-246°; $[\alpha]_D$ -71°; λ_{max} 226 mμ (ε 11,250); λ_{max} 2.83, 2.92, 5.96, 6.03, 6.18 μ]; 17,20; 20,21-bismethylenedioxy-1,5-pregnadiene-3,11-dione (VI) (NaH or $NaNH_2$/tetrahydrofuran) [m.p. 204-206°; $[\alpha]_D$ -5° ($CHCl_3$); λ_{max} 225 mμ (ε 11,000)].

The sodium acetylide/DMS process has been used to convert 1,4-androstadiene-3,17-dione (VII) directly to 17α-ethinyl-17β-hydroxy-1,5-androstadien-3-one (VIII)[m.p. 266-268°; $[\alpha]_D$ -65.9°; λ_{max} 226 mμ (ε 10,220); λ_{max} 2.97, 3.07, 4.75, 5.70, 5.93, 6.01, 6.17 μ]. Using sodium acetylide with dimethylformamide, 17α-methyl-17β-hydroxy-1,5-androstadien-3-one 17-acetate (IX) [m.p. 163-166°; $[\alpha]_D$ + 50.9°; λ_{max} 226 mμ (ε 11,080); λ_{max} 5.74, 5.93, 6.00, 6.22, 7.97, 8.04, 8.15 μ] was obtained from the 17-acetate of I [m.p. 134-137°; $[\alpha]_D$+14.9°; λ_{max} 244 mμ (ε 16,200); λ_{max} 5.76, 6.01, 6.13, 6.23, 7.95, 8.06, 8.14, 11.23 μ].



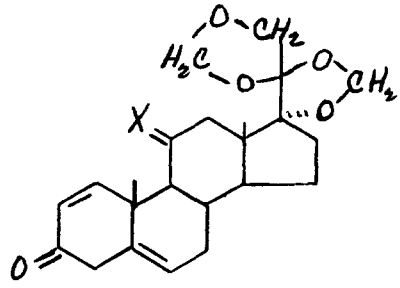
II R=CH_3, R' =H

III R=H, R' =H

IV R=Et, R' =H

VIII R' =H, R=C≡C-H

IX R=CH_3, R' =$\overset{O}{\overset{\|}{C}}$-$CH_3$



V X=$\overset{OH(\beta)}{\underset{H}{<}}$

VI X=O

Although the yields of the $\Delta^{1,5}$ -3-ketosteroids are frequently good to excellent, variations from compound to compound are observed. For example, the yield in the total crude reaction mixture appears to be higher for compounds II, III, IV (C-11 desoxy) than for V (C-11β-hydroxy). The reasons for variations in yields often times are not obvious and may be complex. On the one hand, the reactive $\Delta^{1,5}$ -3-ketosteroid may be transformed back to the $\Delta^{1,4}$ -3-ketosteroid during work-up, either because of the degree of instability of the particular steroid (depending on which substituents are present) to the pH of the medium or because substituents on the steroid nucleus may change its solubility in the complex work-up medium and thus change the exposure time to reagents capable of transforming it to its $\Delta^{1,4}$ analogue. On the other hand, these yield differences may be due primarily to a) variations in the percentage of the requisite anion formed by base deprotonation in the aprotic medium, or to b) conformational requirements of the molecule which may affect the distribution of the charge density[7] of the generated anion, A in Fig. 1.

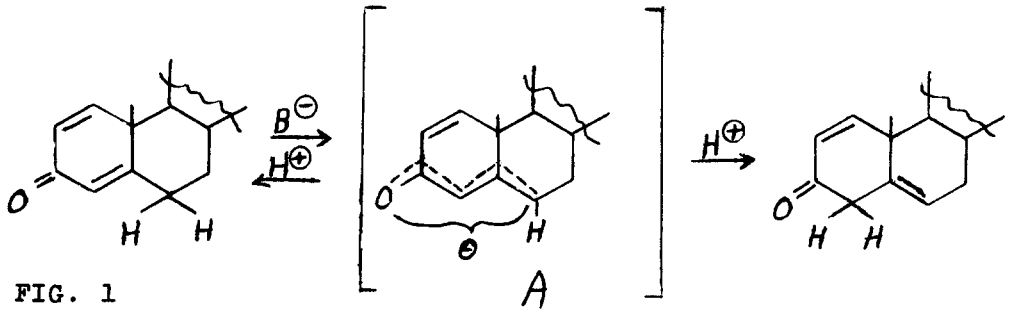


FIG. 1

In the case where the electron distribution is concentrated in the region of the electronegative oxygen, kinetic control will result in the formation of the $\Delta^{1,5}$ -3-keto system. Where the substituent of the steroid nucleus exerts a conformational effect so that the electron charge is less localized in the oxygen region, some $\Delta^{1,4}$ -3-ketone will be directly formed by protonation at C-6. In the extreme situation, the kinetic and thermodynamic control becomes indistinguishable in the exclusive formation of the $\Delta^{1,4}$ -3-ketone.

The utilization of these $\Delta^{1,5}$ -3-ketosteroids as intermediates in the preparation of biologically interesting steroids is currently under investigation.

REFERENCES

1. Ringold, H.J. and Malhotra, S.K., TETRAHEDRON LETTERS 15, 669 (1962).

2. Nussbaum, A.L., Topliss, G. Brabazon, Popper, T.L. and Oliveto, E.P., J.AM.CHEM.SOC. 81, 4572 (1959).

3. "Further Application of the Nitrite Photolysis Reaction", Shapiro, E.L., Legatt, T. and Oliveto, E.P., paper presented at New York-New Jersey Regional Meeting, January 22, 1962.

4. The process was essentially that described by Campbell, J.A., Babcock, J.C. and Hogg, J.A., J.AM.CHEM.SOC. 80, 4717 (1958) except that xylene was not removed from the sodium acetylide suspension.

5. The carbon and hydrogen microanalytical values are acceptable for all new compounds. Unless otherwise noted rotations are in dioxane, at approximately 1% conc.; ultraviolet absorptions in methanol; and infrared absorptions in Nujol.

6. Prepared from 17α-ethyl-17β-hydroxy-1,4-androstadien-3-one [m.p. 144-146°; $[\alpha]_D$+2°; λ max 244 mμ (ε 16,200); λ max 2.90, 6.04, 6.18, 6.25, 11.25 μ] , which in turn was prepared from 17α-ethyl-17β-hydroxy-4-androsten-3-one using the dichlorodicyanobenzoquinone dehydrogenation process of Burn, D., Kirk, D.N. and Petrow, V., PROC. CHEM. SOC., 14 (1960).

7. See Birch, A.J., J.CHEM.SOC. 2325 (1950) and also 1551 (1950), especially p. 1552 for a relevant discussion on monoenone anion systems.