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DECONJUGATION OF α,β-UNSATURATED KETONES

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BIRCH[1] demonstrated in 1950 that a steroidal α,β-unsaturated ketone (I) may be deconjugated to its β,γ-unsaturated ketone isomer (III) by irreversible protonation of the conjugate anion (II), however, the requisite anion has been prepared only by indirect means (e.g. through the enol acetate,[1,2] from a 6-bromo-Δ^4-3-ketone,[3] or by lithium-ammonia reduction of a $\Delta^{4,6}$-diene-3-one[4]). An attempt[1] to convert Δ^4-cholestenone to the Δ^5-3-one (III) by treatment with potassium amide in liquid ammonia followed by protonation gave only the Δ^4-3-one presumably because of preferential formation of the C-2 anion.[1] We have found that deconjugation may be readily effected by acetic acid protonation of the anion derived from treatment of Δ^4-3-keto steroids with potassium t-butoxide in t-butanol. Alhtough this base and solvent system have been extensively utilized for C-4 alkylation[5] of steroids and more recently for air oxidation[6] it had not been obvious that a high concentration of steroid anion would be present at any given time.

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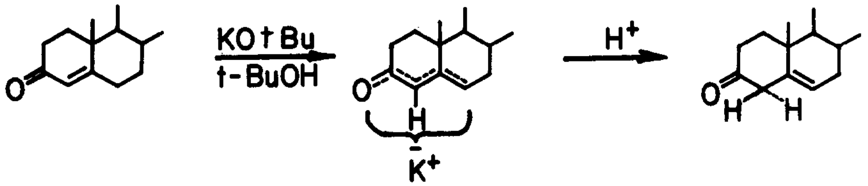

I II III

The deconjugation of 17α-methyltestosterone is representative of our procedure. A mixture of steroid (200 mg) and potassium t-butoxide (750 mg) in t-butanol (5 ml) was stirred under nitrogen for 1.5 hr at room temperature and then quenched by the rapid addition of 25 ml of 10 per cent acetic to the resulting slurry.[7] Excess aqueous bicarbonate was added and the product, which was isolated by ether extraction, showed λ_{max}^{EtOH} 242 mμ (ε 750); $\lambda_{max}^{EtOH \atop NaOH}$ 242 mμ (ε 14,500); λ_{max}^{KBr} 5.80 μ (strong), 6.00 μ (inflection). Crystallization from acetone-water gave 65 per cent of 17α-methyl-Δ^5-androstene-17β-ol-3-one (III), (m.p. 159-163°); λ_{max}^{EtOH} 242 mμ (ε 200); $\lambda_{max}^{EtOH \atop NaOH}$ 242 mμ (ε 15,400). (Found: C, 79.32; H, 9.87; Calc. C, 79.42; H, 10.00), which was converted to 17α-methyltestosterone by either dilute acid or base.

The results of similar deconjugation of Δ^4-cholestenone, progesterone and testosterone are summarized in Table 1. In each case the extent of deconjugation was determined by infrared and ultraviolet spectroscopy and, after dinitrophenylhydrazine development, by visual inspection of thin layer silica chromatograms where the unconjugated ketones were invariably less polar than the Δ^4-3-ketones. More polar oxidation[6] byproducts, which were detected in varying amounts, are presumably due to the failure to rigorously exclude oxygen during the reaction although even the purified Δ^5-3-ones were found to undergo auto-oxidation as well as partial conjugation on standing at room temperature. While no attempt was made to determine the isolable yield of β,γ-unsaturated ketone in each case, it was possible to obtain by

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[7] This procedure gave better results than inverse quenching.

TABLE 1

Compounds	Equivalents potassium t-butoxide	Solvent	Reaction time (hr)	Deconjugation (%)
Δ^4-Cholestenone	10	t-butanol	1.5	95
Testosterone	10	t-butanol	1.5	75
Progesterone	10	t-butanol	1.5	90
10-Methyl-Δ^4-octalin-3-one	10	t-butanol	1.5	80
17α-Methyl-testosterone	0.15	t-butanol	60	10
17α-Methyl-testosterone	1	t-butanol	1	40
17α-Methyl-testosterone	1	t-butanol	16	75
17α-Methyl-testosterone	10	t-butanol	0.5	87
17α-Methyl-testosterone	10	t-butanol	1.5	95
17α-Methyl-testosterone	2	diglyme	1	80
17α-Methyl-testosterone	10	benzene	1.5	13
17α-Methyl-testosterone	10	benzene	40	50
17α-Methyl-Δ^5-androstene-17β-ol-3-one	0.15	t-butanol	12	17

several crystallizations "pure" (containing about 2 per cent of Δ^4-3-ketone as the only contaminant) samples of Δ^5-cholestene-3-one[8] and Δ^5-pregnene-3,20-dione[9] whose properties agreed well with materials prepared by a different route.[9] It was necessary to resort to silica gel chromatography to obtain a pure sample of Δ^5-androstene-17β-ol-3-one, m.p. 160-164° (reported[4] 160-168°).

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[8] L.F. Fieser, Org. Synth. 35, 43 (1955) and references cited therein.

[9] C. Djerassi, R.R. Engle and A. Bowers, J. Org. Chem. 21, 1547 (1956).

Conjugate anion formation was found to be a relatively slow reaction since, with one equivalent of base, 17α-methyltestosterone was only 40 per cent, deconjugated after 1 hr but 75 per cent deconjugated after 16 hr. The unlikely possibility that a significant concentration of β,γ-unsaturated ketone (i.e. not in the form of its anion) would be present in solution was eliminated by treatment of 17α-methyltestosterone for 60 hr with 0.15 equivalents of base whence only 10 per cent deconjugation occurred. Treatment of the corresponding β,γ-unsaturated ketone (III) with the same concentration of base for 12 hr resulted mainly in conjugation, the crude product showing only 17 per cent of Δ^5-3-one.

We were unable to effect deconjugation of a cross-conjugated ($\Delta^{1,4}$-androstadiene-3,17-dione) or long-conjugated ($\Delta^{4,6}$-androstadiene-3,17-dione) dienone by the 17α-methyltestosterone conditions. A model bicyclic compound, 10-methyl-Δ^4-octalin-3-one, underwent 80 per cent deconjugation with 10 equivalents of base after 1.5 hr.

Diethyleneglycol dimethyl ether (diglyme), which is known to solvate metal cations,[10] could be substituted for t-butanol, 80 per cent deconjugation resulting after 1 hr treatment with 2 equivalents of potassium t-butoxide. Conjugate anion formation in benzene, a solvent in which the steroid potassium salt should exist as a polymeric ion pair aggregate,[11] was extremely slow. With 10 equivalents of base only 13 per cent of deconjugated ketone was formed after 1.5 hr and 50 per cent in 20 hr.

The deuteration of the conjugate anion with deuteroacetic acid is under investigation in an attempt to establish the stereochemistry of protonation.

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[10] H.D. Zook and T.J. Russo, J. Amer. Chem. Soc. **82**, 1258 (1960).

[11] See H.E. Zaugg, B.H. Horrom and S. Borgwardt, J. Amer. Chem. Soc. **82**, 2895 (1960) for a general discussion of ion aggregation and solvation.