Chemical Studies with 11-Oxygenated Steroids. VII. The Oxidation of 3-Hydroxysteroids with *t*-Butyl Hypochlorite

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t-Butyl hypochlorite (TBH), a readily prepared[1] reagent of considerable stability, has been used to oxidize β-phenylethyl and benzyl alcohols to the corresponding aldehydes,[2] but the reaction with secondary alcohols has been reported only recently.[3] We have found that TBH in *t*-butyl alcohol without added pyridine[3a] oxidizes the 3-hydroxysteroids smoothly and in excellent yields to the corresponding 3-ketosteroids, which may be isolated in a high state of purity simply by evaporation of the solvent and excess TBH. Thus 3α-hydroxypregnane-11,20-dione,[4] 3α,17α-dihydroxypregnane-11,20-dione,[5] cholestan-3β-ol,[6] 3α,17α,21-trihydroxypregnane-11,20-dione 21-acetate[7] and 3β-hydroxyallopregnane-11,20-dione[8] were oxidized quantitatively with TBH in anhydrous *t*-butyl alcohol to pregnane-3,11,20-trione,[9] 17α-hydroxypregnane-3,11,20-trione,[5] cholestan-3-one,[6] 17α,21-dihydroxypregnane-3,11,20-trione 21-acetate[5] and allopregnane-3,11,20-trione,[10] respectively. The 11α-hydroxy group does not appear to be susceptible to oxidation under these conditions, 11α-hydroxypregnane-3,20-dione[11] being recovered unchanged after treatment with TBH.

TABLE I

3-HYDROXYSTEROIDS OXIDIZED TO 3-KETOSTEROIDS

Steroid oxidized	Reacn. time, hours	Crude 3-ketone Yield, %	Crude 3-ketone M.p.,[a] °C.	Solvent[b]	Recryst. 3-ketone Yield, %	Recryst. 3-ketone M.p., °C.	Reptd. m.p., °C.
3α-Hydroxypregnane-11,20-dione	4	100	146–150	EA–SB	80	153–156	154–156[9]
3α,17α,21-Trihydroxypregnane-11,20-dione 21-acetate	22[c]	100	217–222	A	67	225–228	228–230[5]
3β-Hydroxyallopregnane-11,20-dione	16	100	208–210	EA	90	210–212	212–216[10]
Cholestan-3β-ol	5	100	126.5–128	.....	..	.....	128–129[6]

[a] The infrared spectra of these products were identical with those of the authentic materials. [b] Solvent for recrystallization: A, acetone; EA, ethyl acetate; SB, Skellysolve B. [c] Iodometric titration showed no TBH consumption after 6 hours.

Although the crude products isolated from these reactions by removal of the volatile constituents were of a high degree of purity, a small amount of halogenated impurity was present in most cases. This is probably attributable to the presence of traces of water in the solvent, since it has been found in these laboratories that by the incorporation of additional water the α-chloroketones are obtained in good yields.[12] That light in some cases may contribute also to the formation of halogenated impurities was shown by the fact that cholestan-3β-ol forms a chlorocholestanone when treated with TBH in anhydrous *t*-butyl alcohol in the presence of ordinary daylight.

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Experimental[13]

Reagents.—*t*-Butyl hypochlorite was prepared by the procedure of Teeter and Bell.[1] The product was assayed by iodometric titration and was invariably of 97% purity or better. *t*-Butyl alcohol was dried by refluxing with and distillation from calcium hydride.

Oxidation of Steroid Alcohols.—The following description of the oxidation of 3α,17α-dihydroxypregnane-11,20-dione to 17α-hydroxypregnane-3,11,20-trione serves as an example of the general method. The other oxidations, summarized in Table I, were carried out similarly except that in some cases a longer reaction time (as determined by iodometric titration data) was required.

A solution of 0.86 g. of 3α,17α-dihydroxypregnane-11,20-dione in 50 ml. of *t*-butyl alcohol containing 0.875 ml. of TBH was allowed to stand in the dark at room temperature for two hours. During this time the course of the reaction was followed by withdrawing aliquot samples and determining the active halogen content by iodometric titration. After one hour no further reagent was consumed. Removal of the volatile constituents of the reaction mixture (*i.e.*, solvent, excess reagent and chlorine) by distillation at reduced pressure gave a quantitative yield (after correction for the aliquots withdrawn) of 17α-hydroxypregnane-3,11,20-trione, m.p. 193–198° (reported[5] m.p. 205–206°) whose infrared spectrum was identical with that of an authentic specimen and which gave a negative Beilstein test for halogen. One recrystallization from aqueous acetone afforded an 80% yield of product, m.p. 200–203°.

When the oxidation of cholestane-3β-ol was carried out as described but without rigorous exclusion of light, the sole isolated product (89% weight yield) was a crude crystalline material, m.p. 115–130° with partial subsequent resolidification and complete liquefaction by 150°, believed to be a mixture of 2-chlorocholestan-3-one and 2,2-dichlorocholestan-3-one on the basis of the halogen analysis and infrared spectrum: $\lambda_{\max}^{\text{Nujol}}$ 1732 cm.$^{-1}$, no absorption in the 1715 cm.$^{-1}$ region. Beereboom, *et al.*,[14] have reported recently the preparation of pure 2-chlorocholestan-3-one, m.p. 178–179°, $\lambda_{\max}^{\text{CHCl}_3}$ 1736 cm.$^{-1}$ (5.76 μ), and pure 2,2-dichlorocholestan-3-one, m.p. 145–146°, $\lambda_{\max}^{\text{CHCl}_3}$ 1730 cm.$^{-1}$ (5.78 μ).

Anal. Calcd. for $C_{27}H_{45}ClO$: Cl, 8.43. Calcd. for $C_{27}H_{44}Cl_2O$: Cl, 15.93. Found: Cl, 9.67.

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[13] Melting points were determined on a Fisher–Johns block and are uncorrected.

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