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Conversion of the Cholesterol Sidechain to a 17-Acetyl Group by Remote Chlorination Reactions

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Abstract: Two methods to convert cholesterol to pregnane derivatives are described. In one, template directed chlorination of C-20 with an iodoaryl ester attached at the 6 β position was used to convert i-cholesterol to pregnenolone.

We have described the use of templates esterified to sterols to direct chlorination reactions.[2] By the radical relay mechanism[3] a template iodine or sulfur captures a chlorine atom and passes it to an accessible hydrogen. With this process, appropriate templates attached to the hydroxyl group of 3-α-cholestanol have been used to achieve selective chlorination at C-9, C-14, and C-17, all tertiary hydrogens on the α face.

We also described a sequence that permitted us to use 17-chlorination to remove the cholesterol or sitosterol sidechains, affording androsterone acetate, a 17-keto steroid.[4] Later work by Welzel[5] and by us[6] improved the procedure, converting the 17-chlorosteroid to a 17(20) olefin under carefully defined conditions; oxidation then removed the entire sidechain. We now wish to describe a method to convert this 17(20) olefin to a 17-acetyl group, removing all but two of the sidechain atoms. Furthermore, we have learned how to direct halogenation to C-20, the first example of this reaction on the β face of the steroid nucleus. This furnishes an alternative synthesis of 17-acetyl steroids, key intermediates in the synthesis of corticosteroids and other pregnane derivatives.

The E 17(20) olefin 1, prepared as described earlier,[6] was converted to the 16,20(22) diene 2 by treatment of a 54 m**M** solution in CCl_4 with 1.3 equiv N-bromosuccinimide and 6 mol% benzoyl peroxide for 3 hr at room temp, then 6 hr reflux of the filtrate. Compound 2 was obtained by chromatography in 53% yield (with a little of the 20(21) isomer), and showed the expected[7] U.V. with λ_{max} = 243 nm (ε = 15,600) in isooctane, the correct M + 1 by CI/MS, and an NMR spectrum (300 MHz) with 18-H at δ 0.928, 19-H at δ 0.826, 21-H at δ 1.759, and

16-H and 22-H at δ 5.6. With Ag(fod), the vinyl protons were resolved as a broad singlet (16-H) and a resolved triplet (22-H) which showed some coupling to the 21 hydrogens. Treatment of the diene 2 with OsO_4[8] chiefly hydroxylated the 16(17) double bond. The product was converted to the acetonide, and cleaved with $RuCl_3/NaIO_4$[9] to afford the 17-acetyl steroid 3 in 43% overall yield.[10]

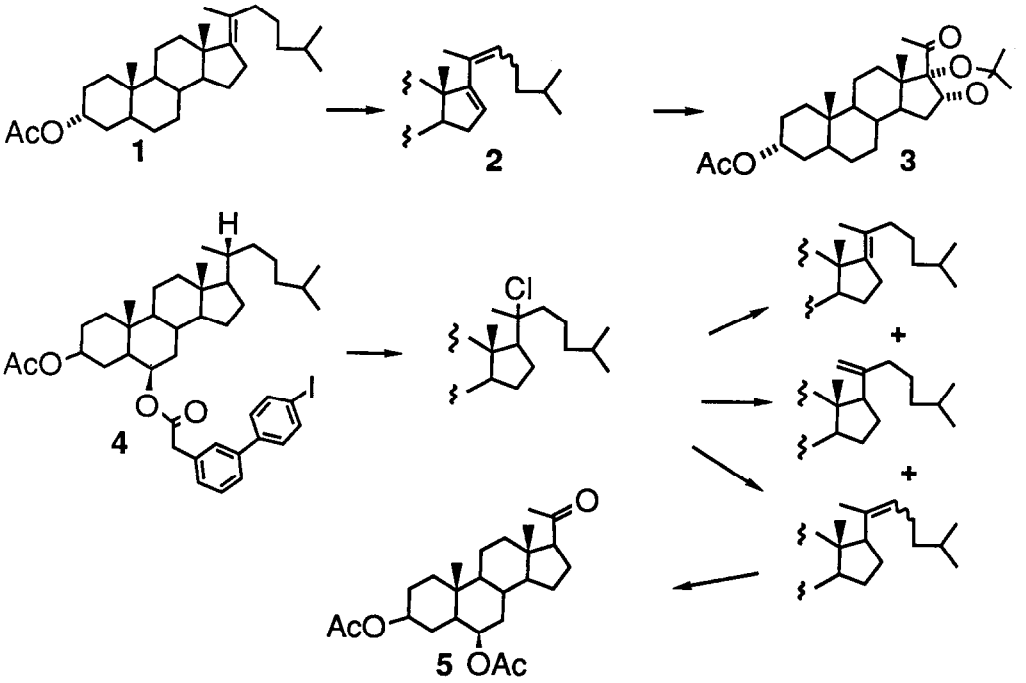
No example of template-directed chlorination on the β face of a steroid has been reported, although we have recently described[11] benzophenone photochemical insertion at carbons 15, 16, 18, 23, and 25 by a reagent esterified at the 6β position of i-cholesterol derivatives. It would be attractive to direct halogenation to C-20, to permit formation of a 20(22) olefin and easy conversion of the cholesterol or sitosterol sidechains to a 17-acetyl group. However, molecular models show that a direct line from C-6 to H-20 must pass over the methyl group C-18; this presumably explains why no attack at C-20 was seen in our photochemical reaction.[11]

Consistent with this, we find no chlorination at C-20 when p-iodophenylacetic acid or p-iodophenylpropionic acid is esterified at a 6β hydroxyl, and template-directed chlorination is attempted. Models show that the chief problem is shielding of C-20 by the C-18 methyl group. Accordingly, we have constructed a curved template that can go around the methyl group to reach C-20. With this we are indeed able to perform C-20 halogenation.

A 52 mL solution (8mM) of ester 4, m.p. 121.5 - 123° C, in CH_2Cl_2 with 0.3 M t-BuOH[12] and 3 equiv. $PhICl_2$ with 12 mL 4% aqueous $NaHCO_3$[12] was deoxygenated and irradiated for 60 min with a 275 W sunlamp. After workup, base hydrolysis/dehydrochlorination, and acetylation, there was 40% conversion to the three olefins [17(20), 20, and 20(22)] derived from the 20-chloro compound, with 25% recovered unfunctionalized steroid. The principal olefin isomer was Δ20(22), with 80% as much Δ20. Ozonolysis of the mixture afforded a 20% isolated yield[10] of 5, and traces of ketones derived from the other isomers. The ester 6 related to 4 was prepared from i-cholesterol. It led to a 15% yield[10] of 7, which was isomerized with TsOH to pregnenolone (8) identical with an authentic sample.

A crystal structure of 4 showed (Fig. 1) that the template lies in an extended geometry, with its benzene ring in contact with the C-18 methyl group. The solution conformation that permits iodine-directed halogenation at C-20 can be obtained by single bond rotations.

This work demonstrates two chemical procedures to degrade cholesterol sidechains to 17-acetyl groups. With appropriate development work to optimize yields these procedures might compete with microbiological procedures currently used to convert sitosterol to useful steroid products. They would be especially attractive if adapted to the catalytic methods described elsewhere.[13,14]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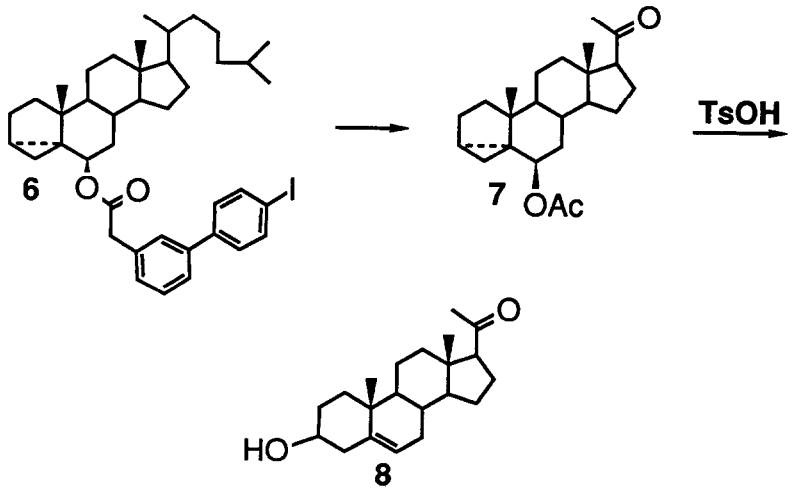
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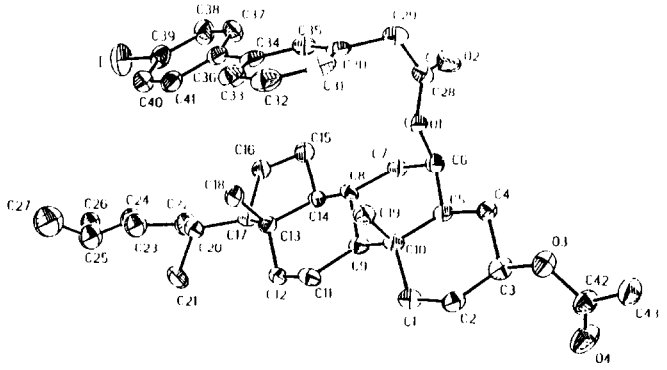

Fig. 1. Structure of 4, from X-ray

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12. We find that t-BuOH improves the yields in many of these halogenations, for reasons that are still unclear. C-20 chlorination did not occur in the absence of t-BuOH. Scavenging of the product HCl is often helpful, and is critical with sensitive compounds such as 6.

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