Tetrahedron Letters,Vol.25,No.11,pp 1123-1126,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

REMOTE FUNCTIONALIZATION ON THE STEROID β-FACE: ATTACK ON AN ANGULAR METHYL GROUP, AND INTO THE SIDECHAIN

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Benzophenonealkanoate esters of 6-β-cholestanes insert photolytically into C-15, C-16, and the C-18 methyl, or into C-23 and C-25 of the sidechain, depending on the length of the attaching chain.

We have described steroid functionalizations resulting from attack by rigid reagents on positions remote from functional groups.[1] The first work involved directed photolytic insertion reactions of benzophenone derivatives;[2] subsequently we have described epoxidations,[3] nitrosations,[4] and chlorinations.[5] In all these studies attack occurred on various positions of the unhindered α face of the steroids. The steroid β face is guarded by the C-18 and C-19 axial methyl groups; however, these methyls and the steroid sidechain are attractive targets for geometrically controlled functionalization procedures. We now wish to report that functionalization of groups attached to the steroid β face is indeed possible with benzophenone photochemistry. We further find striking alternating effects on the conformations of acyclic hydrocarbon segments in these reactions.

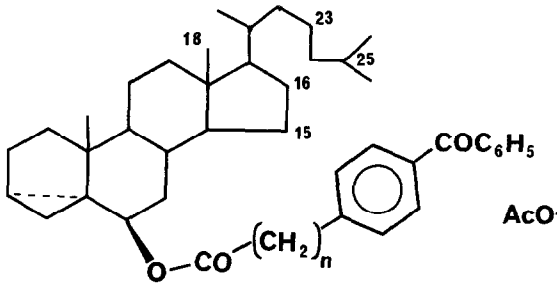
Two steroid series were examined. In the most easily available, i-cholesterol was converted to esters (1, 2, 3) with various benzophenone acids.[6] In the second series, 3-β-acetoxy-cholestan-6-β-ol was converted to an ester (4) of benzophenone-4-propionic acid.[6] The two systems behaved similarly. Thus irradiation of 1 at 0.9 mM in dry benzene led to insertion into C-15, C-16, and C-19 C-H bonds in ca. 10% yield each. Reduction of the resulting lactones with $LiAlH_4$, acetylation, and dehydration with $SOCl_2$ in pyridine afforded olefins which were oxidized with RuO_4[7] to afford 15-keto-i-cholesteryl acetate (5a), 16-keto-i-cholesteryl acetate (6a), and i-cholesteryl acetate 18-carboxylic acid (7a), respectively. The two ketones were identified by their NMR and mass spectra. The carboxylic acid was identified by rearrangement (H^+, CH_3OH) to the 3-β-cholesteryl methyl ether and reduction of the carboxylic acid (chloride) with $LiAlD_4$ to the CD_2OH derivative. This was deoxygenated by the Barton procedure[8] to afford cholesteryl methyl ether identical with authentic material except that the $-CD_2H$ group of C-18 showed a broad low intensity NMR signal and a 0.035 ppm upfield isotope shift relative

to the normal CH_3 compound. When the cholestanyl derivative 4 was photolyzed in CCl_4 the same three positions were attacked, with ca. 20% each of products from insertions at C-15, C-16, and C-18. Again the proucts were identified by $LiAlH_4$ cleavage of the lactone ring and degradation to ketone 5b and 6b, and carboxylic acid 7b.

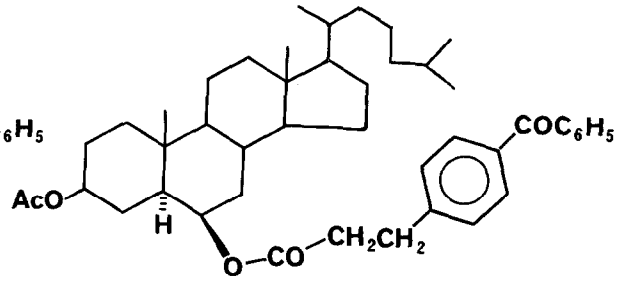
No product of attack on the steroid could be detected from photolysis of the benzophenonebutyrate ester 2. The product was apparently the pinacol from reductive dimerization of 2 after attack on solvent. However, with the benzophenonevalerate 3 a photolysis in CH_3CN led to steroid functionalization in ca. 12% total isolated yield, (45% NMR yield), divided among four products. Two were derived from insertions at C-16 (7%) and at C-18 (1%), showing that the longer chain in 3 can kink so as to give it the same effective length as in 1. The other two products resulted from attack on the steroid sidechain.

One product (2%) could be dehydrated to an E and Z mixture of olefins whose oxidation afforded the 23-keto-i-cholesteryl derivative 8. The ketone was identified by conversion to its thioketal with ethanedithiol; the mass spectrum showed the expected fragment[9] with m/e = 161. The other product (2%) could not be dehydrated, indicating insertion at a tertiary center. The C-26 and C-27 methyl groups of most cholestanyl compounds are seen in the PMR near 0.86 ppm, sometimes slightly split by diasterotopicity, but in any case as doublets because of ca. 6.5 Hz coupling to the C-25 hydrogen. In our insertion product 9, the C-26 and C-27 methyls are shifted to 1.115 ppm and no longer split by the C-25 proton (although ca 2.1 Hz split at 300 MHz because of diastereotopicity). The increased solvent shifts of C-26,27 ($CDCl_3$ vs. C_6D_6) are supportive of the attachment of a flat benzene ring nearby, and the T_1 of C-26,27 decreases as expected because a bulky group is attached.

The benzophenone ester of 3 should be able to reach at most 8.6 A from the steroid oxygen. From the crystal structure data on i-cholesteryl chloroacetate[10] the O(6) to C(18) distance is 5.77 Å, so the chain of the probe must kink a bit to allow attack. However, in the crystal the sidechain is fully extended, and the O(6) to C(23) distance is 10.35 Å, while the O(6) to C(25) distance is 12.74 Å. Thus the observed attack on these positions in 3 requires that the sidechain curl back in solution. We find no evidence for attack on C-22 or C-24, however. $LiAlH_4$ reduction, acetylation, dehydration, RuO_4 cleavage, and thioketalization gave a crude product whose mass spectrum showed m/e 161 for the C-23 product, but no significant peaks[9] for the expected products at C-22 or C-24. Thus in the folding back of the sidechain the alternating geometry characteristic of an extended chain is to some exent preserved, so that the hydrogens on odd carbons face the ketone probe while the hydrogens on even carbons face away. The finding that attack is seen



1: n= 2
2: n= 3
3: n= 4



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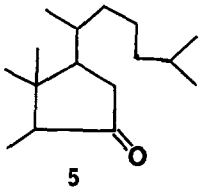

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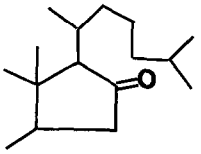

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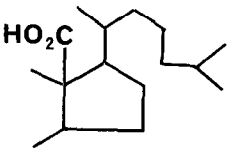

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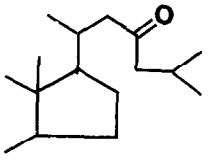
a: i-cholesteryl b: 3-acetoxycholestanyl



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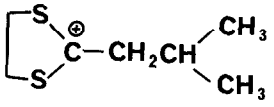
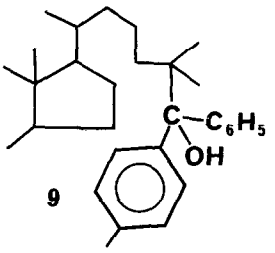


m/e =161



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with compounds 1 and 3, but not with 2, must also reflect such conformational alternating effects.

Attack on the methyl group C-18 in these reactions is striking, considering the normal 50/1 preference of benzophenone triplet for attack on CH_2 vs. CH_3 and a 300/1 preference for tertiary C-H over CH_3.[11] Thus the methyl attack must be strongly favored geometrically, and could become the dominant process in a chemical reaction with less bias against reaction at CH_3. Furthermore, our studies with these ketone insertions show that remote functionalization reactions can be performed on the steroid β face, even into the sidechain. It remains to be seen whether this will permit the development of high yield, practical new procedures for sidechain removal or for the C-25 functionalization which is of interest in vitamin D chemistry.

Acknowledgement. This work was supported by the National Science Foundation.

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(Received in USA 19 December 1983)