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UNUSUAL STRUCTURAL EFFECTS ON THE CHEMICAL DEGRADATION OF STEROID SIDECHAINS[1]

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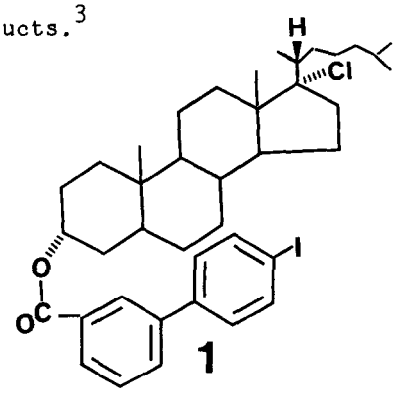
Abstract: 17-Chlorosteroids from template-directed halogenation can be converted to 17(20) olefins with DBU or DBN. The dependence of this reaction on base-structure and reaction conditions suggests geometric control by liquid packing effects related to those operating in liquid crystals.

We have described[2] methods to achieve selective chlorination of steroids using template-directed halogenation. In particular, we have shown that iodophenyl templates attached at 3α,[3] at 7α,[3] or at 5α[4] OH groups can be used to direct chlorination at C-17 of cholesterol or sitosterol derivatives. Under all conditions we examined,[3] treatment of the 17-chloro products such as 1 with various bases led predominantly to the 16(17) olefins 2, not the desired 17(20) olefins 3. The latter, whose oxidation removes the steroid sidechain, were produced only by chemical isomerization of the original 16(17) olefin products.[3]



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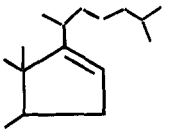

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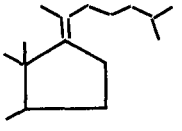

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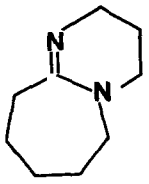
Recently Welzel et al. have reported[5] a side-chain removal sequence which utilizes template-directed halogenation at C-17 with a template attached to the OH group of 5α-hydroxy-3-β-acetoxycholestane. The 5-α-ol was prepared by an unusual sequence including photolysis. They referred to our report[4]

of such a halogenation process using the same 5-ol, which we prepared by the convenient standard epoxidation of cholesterol and reduction. They also reported that treatment of the 17-chlorosteroid products with DBU 4 afforded a mixture of 16(17) and 17(20) olefins in which the desired 17(20) isomer predominates. We have investigated this situation further, and can confirm the special character of DBU in such eliminations. However, the dependence of product distribution on reaction conditions is unusual and unprecedented. The data suggest strongly that the nature of the product is being influenced by liquid structure effects, related to the well-known[6] tendency of some steroid esters to form liquid crystals.

Welzel et al. reported[5] that their 17-chlorosteroids, carrying an iodophenyl template ester attached at C-5α, gave a 4:1 mixture of the 17(20) olefin 3 and the 16(17) olefin 2 in 64% yield, on "treatment" with DBU at 90°C. We have examined the 17-chlorocholestanol 1 which carries an iodophenyl template at 3α, whose dehydrochlorination we had studied earlier.[3] Indeed heating this ester with 50 equivalents of DBU in the absence of any solvent also afforded a 4:1 mixture of the 17(20) and 16(17) olefins, as judged by ^{1}H NMR.

There are actually three olefins formed: the endocyclic 16(17) olefin (2), the exocyclic E 17(20) olefin (3), and the Z 17(20) olefin (6). These can be distinguished by ^{1}H NMR, but the best analytical data are from HPLC on EM LiChrospher Si 60/II with 0.35% ethyl acetate in 2,2,4-trimethylpentane. The Z olefin 6 is formed in a relatively constant 3% yield under various conditions, and is probably the product of trans elimination from the 17-β chlorosteroid also present in the chlorination product. However, the ratio of exocyclic E olefin (3) to endocyclic olefin (2) is an extremely sensitive function of reaction conditions. Dilution of the DBU/steroid mixture with even small amounts of a variety of solvents (benzene, toluene, acetonitrile, isopropyl alcohol) leads to a 3/2 ratio of less than one. Remarkably, even dilution by DBU itself, by going to 390 equivalents of the base, diminishes the 3/2 ratio to a value of 3:1.

Only one other base we have examined, DBN (5), has the ability of DBU to promote as much formation of the exocyclic olefin 3. Diisopropylethylamine, tris-(2-hydroxyethyl)amine, N,N-dimethylaniline, quinoline, imidazole, piperidine, and tributylamine formed little of 3 when heated neat with the 17-chlorosteroid. 4-Pyrollidinopyridine, 4-dimethylaminopyridine and pentamethylguanidine afford essentially 1:1 mixtures of 2 and 3 when 40-50 equiv. are heated neat with the 17-chlorosteroid. The bicyclic guanidine 7 (23 equiv.) affords ca. 1.5:1 of the 3/2 mixture. However, DBN (5) behaves like DBU. With 50 equiv. neat an almost 4:1 ratio of 3/2 is formed, but the ratio decreases with only 10 equiv. or with 200 equiv.



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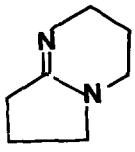

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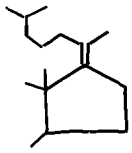

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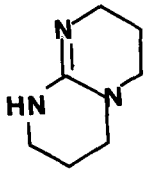

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The specificity of these requirements is remarkable. Elimination to form the desired 17(20) olefin 3 is apparently favored by the flat DBU and DBN, but not by similarly flat and basic guanidines. The decrease in the desired ratio on dilution with various solvents may reflect a decrease in the fraction of the reaction catalyzed by DBU or DBN, since simple heating of 1 in the solvents alone leads to formation of the endocyclic olefin 2. The decrease in selectivity when more DBU or DBN is added is accompanied by a decrease in conversion of 1 to products at a given time as well; this is a base-catalyzed reaction whose pseudo-first-order rate constant decreases when the concentration of base is raised above a certain point.

All of these observations are consistent with the idea that the neat steroid ester, not too diluted by solvent or base, is the ideal medium for

rapid elimination to form 3. Welzel reports[5] the selective formation of the exocyclic isomer with DBU when the sitosterol or campesterol sidechain is present, and we find increases in the ratio of exo/endo olefin formation with DBU when the steroid carries a simple isopropyl group at C-17. We suggest that the unique property of neat steroids in promoting and directing the HCl elimination in the desired direction with the flat bases 4 and 5 is related to at least short range geometrical organization of these anisotropic molecules, related to the packing which in other steroid esters leads to the formation of liquid crystalline mesophases.

Regardless of the reason, these studies confirm that within certain parameters the use of DBU (or DBN) can achieve the direct conversion of 17-chloro steroids to 17(20) olefins (3). Coupled with the chlorination of C-17 using templates attached at C-5, as described by us[3,4] and by Welzel,[5] this leads to an attractive overall chemical sequence for sidechain removal that could be competitive with microbiological methods.[7]

References

1. Support of this work by the National Science Foundation is gratefully acknowledged.

2. For a review, see R. Breslow, Accts. Chem. Res., 13, 170 (1980).

3. R. Breslow, R.J. Corcoran, B.B. Snider, R.J. Doll, P.L. Khanna and R. Kaleya, J. Amer. Chem. Soc., 99, 905 (1977).

4. Ref. 3, footnote 20.

5. P. Welzel, K. Hobert, A. Ponty, and T. Milkova, Tet. Letters, 24, 3199 (1983).

6. F.D. Saeva, ed., "Liquid Crystals. The fourth state of matter." Marcel Dekker, Inc., New York, 1979.

7. We have also examined the isomerization of some of these olefins with the lithium salt of ethylenediamine(ref. 8). Starting with either a 16,17 or 17,20 olefin (3-ol), the mixture equilibrates to 25% 16,17,50% of the two 17,20 isomers, and 15% of the 20,22 olefin. Thus this isomerization is less attractive than the direct DBU process.

8. E. Ayanoglu, A. Chan, and C. Djerassi, Tetrahedron, 35, 1591 (1979).

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