Homoallylic Rearrangement of 19-Iodocholesterol

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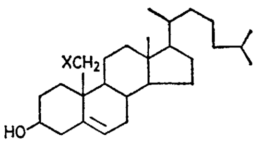
Summary Homoallylic rearrangement of 19-iodocholest-5-en-3β-ol (II) afforded 6β-iodomethyl-19-norcholest-5(10)-en-3β-ol (III).

Counsell *et al.*[1] reported the synthesis of the iodide (II) by the reaction of the toluene-*p*-sulphonate (I) with NaI, and its radioactive iodine labelled analogue is widely used clinically as a tracer in adrenal gland tester[2] It is well known[3] that solvolytic displacement of 19-tosyloxy(or mesyloxy)-5-en-steroids with π-electron participation give three types of rearrangement products: 5β,19-cyclo-6-substituted steroids, B-homo-5(10)-en-steroids, or 6β-substituted 19-nor-5(10)-en-steroids.

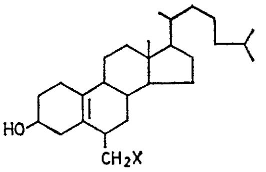
We have reinvestigated the reaction of (I) with NaI and found that (II) rearranges to 6β-iodomethyl-19-norcholest-5(10)-en-3β-ol (III). T.l.c. analysis† of the mixture from the reaction of (I) with NaI in boiling propan-2-ol showed that (III) was formed along with (II). Longer reaction times increased the yield of (III). Heating of (II) alone in boiling propan-2-ol for 7 h also gave (III), and chromatography gave pure (III)‡ in 65% yield [glass, $[\alpha]^{23}_{D}$ +39° (c 1, cyclohexane); λ_{max} (cyclohexane) 228 (ϵ 7290) and 259sh nm (ϵ 3020); δ ($CDCl_3$; 100 MHz) 0·68 (3H, s, 18-Me), 2·07 (OH, D_2O exchangeable), 3·08 (1H, t, J 10 Hz, 6-CH_2I), 3·50 (1H, dd, J 10, 2Hz, 6-CH_2I), and 3·97 (1H, m, 3-H)]. The pattern for the 6β-iodomethyl resonances is, as expected, the AB part of an ABX system comprising the methylene and the 6α-protons.[4] Compound (II) also rearranged to (III) in refluxing Me_2CO or in glacial AcOH at 80°.

Reduction of (III) in ether with $LiAlH_4$ gave 6β-methyl-19-norcholest-5(10)-en-3β-ol (IV)‡ in 70% yield [glass,$[\alpha]^{25}_{D}$ +73° (c 0·95, cyclohexane)]. Structure (IV) was confirmed by the doublet signals at δ1·16 (J 7 Hz) for 6β-Me, split by coupling to 6α-H. The 3-acetyl derivative of (II) was not converted into the corresponding rearrangement product under the conditions used for (II).

Under solvolytic conditions, compound (II) behaves differently from other 19-tosyloxy (or mesyloxy) 5-en-steroids, and the conversion of (II) into (III) is the first example of the rearrangement of 19-halogenated 5-en-steroid systems. The rearrangement of (II) to (III) might involve the formation of a homoallylic cation§ and an ion-pair[5] intermediate.



(I) X = OTs
(II) X = I



(III) X = I
(IV) X = H

The product (III) is important physiologically, and we have recently confirmed that radioiodinated (III) is a far more effective adrenal scanning agent than radioiodinated (II).

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† 0·25 mm silica gel plates with $CHCl_3$ as eluent. The R_f value for (III) (0·27) was slightly higher than that (0·20) for (II).

‡ All new compounds reported here gave satisfactory elemental analyses.

§ Separate experiments have ruled out a free-radical mechanism. The β-configuration to the C(6)-substituent in (III) is assigned from the assumed mode of formation of the rearrangement product *via* the homoallylic cation.

[1] R. E. Counsell, V. V. Ranade, R. J. Blair, W. H. Beierwaltes, and P. A. Winhold, *Steroids*, 1970, **16**, 317.

[2] D. E. Schteingart, J. W. Conn, L. M. Lieberman, and W. H. Beierwaltes, *Arch. Intern. Medicin.*, 1972, **130**, 384; W. H. Beierwaltes, L. M. Lieberman, A. N. Ansari, and H. Nishiyama, *J. Amer. Medicin. Ass.*, 1971, **216**, 275.

[3] J. J. Bonet, H. Wehrli, and K. Schaffner, *Helv. Chim. Acta*, 1962, **45**, 2615; J. Tadanier, *J. Org. Chem.*, 1966, **31**, 2124, 3204; K. Syhora, J. A. Edwards, and A. D. Cross, *ibid.*, p. 3411; M. Musseron-Canet and J.-C. Lanet, *Bull. Soc. chim. France*, 1969, 1745.

[4] J.-L. Borgna and M. Mousseron-Canet, *Bull. Soc. chim. France*, 1970, 2210.

[5] E. M. Kosower and S. Winstein, *J. Amer. Chem. Soc.*, 1956, **78**, 4347, 4354.