Tetrahedron Letters,Vol.25,No.18,pp 1947-1948,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

SELECTIVE FLUORINATION OF BILE ACIDS USING ELEMENTAL FLUORINE

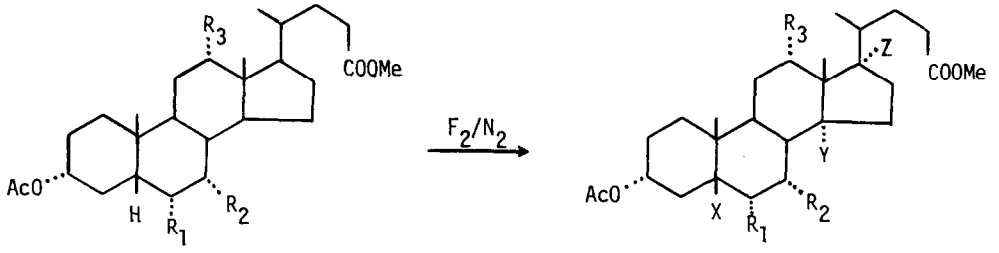
Shlomo Rozen* and Giora Ben-Shushan

Department of Chemistry, Tel-Aviv University, Tel-Aviv 69978, Israel

Abstract: Specific direct mono fluorinations on various sites of the steroidal skeleton of bile acids were achieved by introduction of electronegative groups at selected points.

Reactions around unactivated sites in organic molecules are very rare. In steroids this problem is particularly difficult because of the complexity of the molecule and the number of the unactivated sites involved which do not encourage selectivity. We have shown that elemental fluorine can react in electrophilic mode with organic substances without destroying them and even perform surprisingly selected and unusual reactions[1-4]. We report here for the first time on the regio and stereospecific reaction of F_2 with tertiary hydrogens of some representative bile acids. It is of interest fo find out if one can direct the fluorination to a specific site using the deactivation effect introduced by electronegative groups attached at various sites.

In 5β-cholanic acid-3α-ol acetate methyl ester (1) the two electronegative groups at 3 and 24 deactivate the C-H bond at 5 and to some extent also at 17. Two compounds were thus isolated and purified by HPLC. The more polar one proved to be 5β-cholanic acid-14α-fluoro-3α-ol acetate methyl ester (2), 40% yield, m.p. = 133° (from MeOH), $[\alpha]_D$ = +39.5°, ^{19}F NMR: -164 ppm (m)[5]. The less polar compound was identified as 5β-cholanic acid-17α-fluoro-3α-ol acetate methyl ester (3) 15% yield, m.p. = 158° (from MeOH), $[\alpha]_D$ = +34.2°, ^{19}F NMR: -171 ppm (q, J = 31 Hz). Unlike all the trans steroids no fluorination takes place at the 9α position in the 5β series. We believe that this is caused by the difficult approach to this site imposed by ring A which is practically perpendicular to the steroid plane in the A/B cis steroids.



1 $R_1 = R_2 = R_3 = H$

4 $R_1 = OAc$; $R_2 = R_3 = H$

7 $R_1 = R_2 = H$; $R_3 = OAc$

2 X = Z = H; Y = F
3 X = Y = H; Z = F
5 X = Z = H; Y = F
6 X = Y = H; Z = F
8 X = Y = H; Z = F
9 X = Z = H; Y = F
10 X = F; Y = Z = H

11 $R_1 = H$; $R_2 = R_3 = OAc$
13 $R_1 = R_2 = H$; $R_3 = O$=

12 X = Y = H; Z = F
14 X = F; Y = Z = H

The addition of another electronegative group at C-6, as in 5β-cholanic acid-3α,6α-diol diacetate methyl ester (4), does not much affect the 17 position, but the 14 one becomes more deactivated. This fact was reflected in the yields of the respective fluorinated derivatives. The more polar compound in this case proved to be 5β-cholanic acid-14α-fluoro-3α,6α-diol diacetate methyl ester (5), 25% yield, m.p. = 108° (from MeOH), $[\alpha]_D$ = +22.3°, ^{19}F NMR: -164 ppm (m), while the less polar one was the corresponding 17α-fluoro derivative - 6, 15% yield, m.p. = 124° (from MeOH), $[\alpha]_D$ = +14.6°, ^{19}F NMR: -171 ppm (q, J = 31 Hz). Moving the acetoxy group from C-6 to C-12 (7), causes stronger deactivation toward electrophilic substitution at 14 and 17. This occurs to the point of the C-H bond at the 5β position being then practically equal in activity to those at positions 14 and 17. Obviously, such deactivation will also be responsible for lowering the overall yield of any electrophilic fluorination. Here, then, the expected three fluorinated products at 17, 14 and 5 were obtained in equal yields. It was possible to isolate and purify 5β-cholanic acid-17α-fluoro-3α,12α-diol diacetate methyl ester (8), 10% yield, m.p. = 140° (from MeOH), $[\alpha]_D$ = +101.3°, ^{19}F NMR; -168 ppm (q, J = 31 Hz), but we were unable to separate completely the 14α-fluoro (9) from the 5β-fluoro (10) derivative and their structures were deduced mainly from the spectral data of the mixture[6].

Addition of a third electronegative group in a form of an acetoxy moiety at 7α, (11), deactivated the molecule even further, especially at the 5α- and 14α-positions. Consequently, the disappearance of the starting material was much slower than usual and no signs of any appreciable amount of mono-fluoro derivatives at C-5 or C-14 could be found. The only site which was relatively unaffected by the additional substitution, was the C-H bond at C-17 and indeed 5β-cholanic acid-17α-fluoro-3α,7α,12α-triol-tiracetate methyl ester (12) was obtained in 25% yield, m.p. = 103° (from MeOH), ^{19}F NMR: -168 ppm (q, J = 31 Hz). When the acetoxy group at C=12 in 7 was replaced by a ketone, the 14 and the 17 positions became more deactivated relative to the 5 one. This was reflected in the reaction of 13 with F_2, which resulted in cholanic acid-5β-fluoro-3α-ol-12-one acetate methyl ester (14), 25% yield, m.p. = 152° (from MeOH), $[\alpha]_D$ = +88°, ^{19}F NMR: -151 ppm (m) (see also ref. 6).

In conclusion we can see that this quite unusual reaction is very sensitive to small differences in the electron density of carbon hydrogen bonds induced by electronegative groups. One should remember that the radical pathway, although depressed, always coexists to some extent, resulting in indiscriminate fluorination. When a molecule becomes less and less suitable for electrophilic reaction the starting material deteriorates because of these fluorine radicals and no reaction at a desired specific site takes place.

References and Notes

1. Alker, D.; Barton, D.H.R.; Hesse, R.H.; James, J.L.; Markwell, R.E.; Pechet, M.M.; Rozen, S.; Takeshita, T.; Toh, H.T. Nouv. J. DeChimie 1980, 4, 239.
2. Rozen, S.; Gal, C.; Faust, Y. J. Am. Chem. Soc. 1980, 102, 6861.
3. Gal, C.; Ben-Shushan, G.; Rozen, S. Tet. Lett. 1980, 21, 5067.
4. Gal, C.; Rozen, S. Tet. Lett. 1984, 25, 449.
5. The analytical data for the new fluorinated compounds described here are in excellent agreement with the assigned structures and stereochemistry. The ^{19}F NMR spectra were recorded with Bruker WH-90 at 84.67 MHz, $CFCl_3$ serving as internal standard.
6. The ^{19}F NMR of the mixture shows two signals at -164 ppm (m, F at 14α) and at -151 ppm (m, F at 5β). The latter signal is very characteristic of fluorine at the 5β position as we have noticed also in several other cases which will be published shortly.

(Received in UK 7 March 1984)