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A NEW METHOD FOR FLUORINATION OF STEROLS

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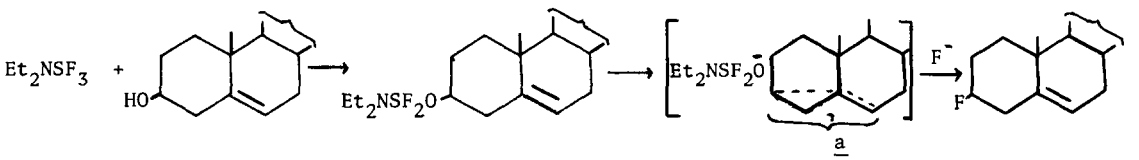
Summary: Diethylaminosulfurtrifluoride (DAST) is a good fluorinating reagent for sterols. The fluorinating reactions proceed through SN_2 mechanism, while reactions through free carbonium ion are responsible for rearrangements and eliminations.

Replacing hydroxyl by fluorine is a feat which chemists have been seeking for a long time. The main methods which have been developed for this purpose are the reaction of diethylaminotrifluorochloroethane with the free alcohol[1], the reaction of metal fluorides or tetrabutylamoniumfluoride with the corresponding tosylates[2] and the reaction of phenyltetrafluorophosphorane with silyl ethers or the corresponding alcohols[3,4]. The main interest in these methods lies however in their usefulness in the synthesis of fluorosteroids.

Sulfurtetrafluoride is mainly used in the synthesis of gemdifluorides from the corresponding carbonyls. However it was demonstrated that this reagent can also convert some hydroxyamino acids into the corresponding fluoro derivative.[5] More attractive is the reaction of diethylaminosulfurtrifluoride (DAST) with a hydroxyl group. Several aliphatic alcohols[6] as well as few sugars[7] were thus converted into the corresponding fluorides.

We have found that sterols usually react readily with DAST at low temperatures but the product is highly dependent on the structure of the steroid. When such a molecule possesses a 5-en-3-ol structure, the corresponding 5-en-3β-fluoro steroid is obtained in high yields. This result confirms the suggestion that the stable carbonium ion a is involved as intermediate, leading to the 3β-fluoro derivative.

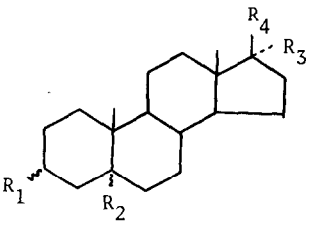


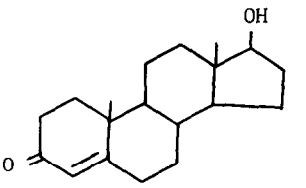
Thus cholesterol, pregnenolone and androstenolone yield 3β-fluoro-5-cholesten(1) (m.p.=96°; yield 95%)[8], 3β-fluoro-5-pregnen-20-on(2) (m.p.=161°; yield 82%) and 3β-fluoro-5-androsten-17-on(3) (m.p.=155°; yield 81%) respectively. The IR and NMR (H^1 and F^{19}) spectra of these compounds are in full agreement with their assigned structure and with literature data[3].

When the stabilizing effect of the double bond at C-5 is absent, the DAST adduct with the sterol(b) decomposes, either through SN2 mechanism with complete inversion of the configuration or through a free carbonium ion which leads mainly to elimination and/or rearrangement.

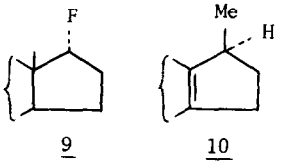
$$ROH + Et_2NSF_3 \longrightarrow HF + ROSF_2NEt_2 \longrightarrow RF$$
$$\searrow [R^{+-}OSF_2NEt_2]$$

Thus, when cholestanol was reacted with DAST, two main products were isolated chromatographically. The less polar compound which arose from the free carbonium ion was identified as 2-cholesten (m.p. 73°; yield 32%)[9] while the more polar one proved to be 3α-fluorocholestan (4) (m.p. 104°; yield 43%)[4]. No traces of 3β-fluorocholestan could be detected in the reaction mixture.



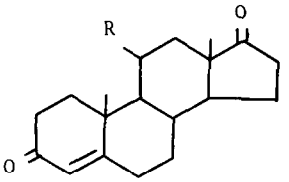


DAST



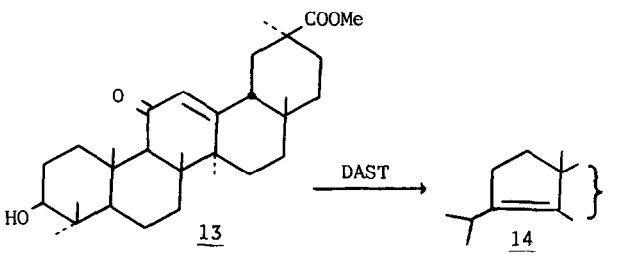
9 10

1.	R_1 = β-F	;	R_2 = Δ^5	;	R_3 = H	;	R_4 = C_8H_{17}	
2	R_1 = β-F	;	R_2 = Δ^5	;	R_3 = H	;	R_4 = Ac	
3	R_1 = β-F	;	R_2 = Δ^5	;	R_3,R_4 = O	;		
4	R_1 = α-F	;	R_2 = H(5α)	;	R_3 = H	;	R_4 = C_8H_{17}	
5	R_1 = α-OH	;	R_2 = H(5α)	;	R_3 = OH	;	R_4 = Ac	
6	R_1 = α-OH	;	R_2 = H(5β)	;	R_3,R_4 = O	;		
7	R_1 = β-F	;	R_2 = H(5β)	;	R_3,R_4 = O	;		
8	R_1 = $\Delta^{2,3}$	;	R_2 = H(5α)	;	R_3 = OH	;	R_4 = Ac	



11 R = OH

12 R = $\Delta^{9,11}$



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Complete inversion of the configuration at C-3 of the fluorinated product was also observed with 5β-androstan-3α-ol-17-on(6). 20ml of CH_2Cl_2 containing 0.48gr (1.6 mmol) of 6 were slowly added at -78° to 0.36gr (2.2 mmol) of DAST dissolved in 20 cc of CH_2Cl_2. The temperature was allowed to rise slowly to room temperature. The progress of the reaction was monitored by Tlc and when completed, the reaction mixture was poured into water washed with sodium carbonate and worked up in a usual manner.[10] 5β-Androstan-3β-fluoro-17-on (7) was isolated (170 mg - 35%, m.p.=131°; $[\alpha]_D$ = +86°; ν = 1725 cm^{-1}; M.W. = 292 (M.sp); NMR = δ = 4.85 (1H, H-3α, dm, J_{HF} = 48 Hz, W $\frac{h}{2}$ of each wing = 6 Hz); 0.98 (3H, Me-19, s); 0.85 (3H, Me-18, s); F^{19}MR:ϕ = 182.9 (four t, $J_{FH\ gem}$ = 48 Hz, J_{FaxHax} = 42 Hz, J_{FaxHeq} = 13 Hz.).Almost no fluorination occurs when trans diaxial elimination can easily take place. So, the main product from the reaction of 5α-pregnan-3α, 17α-diol-20-on (5), with DAST is the olefin 8 (m.p. 187°; yield 75%; ν=3500, 1720 cm^{-1}; M.W. = 316(M.Sp.) NMR: δ = 5.5 (2H, H-2 and 3, s); 2.21 (3H, Me-21, s); 0.75 (3H, Me-19, s); 0.7 (3H, Me-18,s).

While tertiary hydroxyls at C-17 (like in 5) are not affected by DAST, secondary hydroxyls at that position react quite rapidly. Testosteron serves as a good example. Two main products were isolated. One was 4-androsten-17α-fluoro-3-on (9) (40%, m.p. = 141°; $[\alpha]_D$ = 94°) while the other was identified as the rearranged olefin 10, which arose from the free carbonium ion (m.p. = 115°; yield = 32%).[1,2b]

When more hindered hydroxyls were reacted with DAST, the yield of the fluorides drops drastically. 4-Androsten-11β-ol-3,17-dion (11) under our conditions gives exclusively the dehydration product 12 (m.p. = 200°, yield 90% $[\alpha]_D$ = 217°)[11,12]. Similarly, reaction of DAST with methyl glycyrrhetate (13) which also contains a hindered hydroxyl group, gave the rearranged product 14 (55% yield), identical with an authentic sample[13].

The results above clearly demonstrate that fluorination proceeds with complete inversion of configuration. The fact that no racemization at C-3 or C-17 took place shows that free

carbonium ion is not involved in the production of the fluorine containing steroids. However, free carbonium ion is probably responsible for the production of olefins and rearranged products[14].

Notes and References

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14. All new compounds had the correct composition established by microanalysis. The NMR were taken in $CDCl_3$ with TMS and $CFCl_3$ as references for H^1 and F^{19} spectra. The $[\alpha]_D$ had been measured in $CHCl_3$ (c=1).

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