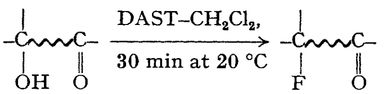
Convenient General Preparation of Oxygenated Monofluoro- and *gem*-Difluoro-5a-androstanes using Diethylaminosulphur Trifluoride

By T. Geoffrey C. Bird, Peter M. Fredericks, Sir Ewart R. H. Jones, and G. Denis Meakins*
(*Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford* OX1 3QY)

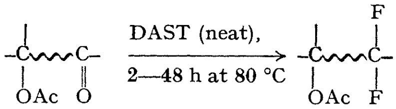
Summary Hydroxy-ketones in the 5α-androstane series are converted into fluoro-ketones by diethylaminosulphur trifluoride under mild conditions; acetoxy-ketones give acetoxydifluorides under more vigorous conditions.

In order to extend work on microbiological hydroxylation we required as substrates oxygenated 5α-androstanes having fluorine substituents at various positions of the steroid nucleus. Although a wide array of fluorosteroids has been described,[1] most of the reagents used in fluorinations suffer from disadvantages (such as difficulty of preparation, very high toxicity and reactivity, strong oxidising activity) and none appears to afford a satisfactory method for converting steroidal alcohols and ketones into their fluoro-analogues. *N*-(2-Chloro-1,1,2-trifluoroethyl)diethylamine is generally regarded as the best reagent for fluorinating alcohols,[2a] but there are many instances of side-reactions occurring. (For example, with even the simple substrate 3β-hydroxy-5α-androstan-17-one the desired 3α-fluoro compound is accompanied by other products whose nature and proportions depend upon the conditions of the reaction and the work-up.[2b]) Sulphur tetrafluoride, the reagent employed most commonly for obtaining *gem*-difluorides from steroidal ketones,[1b] has the practical disadvantage of requiring specialised equipment.

Table. Reactions of oxygenated 5α-androstanes (**1**) with diethylaminosulphur trifluoride (DAST).[a]

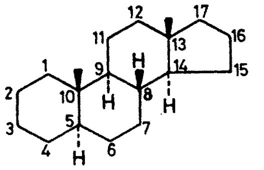


3β-OH-17-CO	→	3α-F-17-CO (47%) Δ^{2}-17-CO (44%)
3β-OH-Δ^{5}-17-CO	→	3β-F-Δ^{5}-17-CO (91%)
3α-OH-17-CO	→	3β-F-17-CO (14%) Δ^{2}-17-CO (83%)
6α-OH-17-CO	→	6α-F-17-CO** (86%)
11α-OH-2,17-$(CO)_2$	→	9α-F-2,17-$(CO)_2$** (16%) $\Delta^{9(11)}$-2,17-$(CO)_2$** (67%)
12β-OH-17-CO	→	12β-F-17-CO** (77%)
16α-OH	→	16β-F** (88%)
16β-OH-2,7-$(CO)_2$	→	16α-F-2,7-$(CO)_2$** (72%)
17β-OH-3-CO	→	17α-F-3-CO (39%)
17α-OH-3-CO	→	Δ^{16}-3-CO $\Delta^{13(17)}$-17-Me-3-CO (95%)



17β-OAc-3-CO	→	17β-OAc-3,3-F_2 (86%)
3β-OAc-6-CO	→	3β-OAc-6,6-F_2** (29%) 3β-OAc-Δ^{5}-6-F** (33%)
17β-OAc-6-CO	→	17β-OAc-6,6,-F_2**[b] (45%) 17β-OAc-Δ^{5}-6-F**[b](45%)
3β-OAc-7-CO	→	3β-OAc-7,7-F_2**(70%)
17β-OAc-7-CO	→	17β-OAc-7,7-F_2**(85%)
3β-OAc-11-CO		No reaction
3β-OAc-12-CO	→	3β-OAc-12,12-F_2** (90%)
17β-OAc-12-CO	→	17β-OAc-12,12-F_2** (95%)
3β-OAc-16-CO	→	3β-OAc-16,16-F_2** (51%)
3β-OAc-17-CO	→	3β-OAc-17,17-F_2 (58%)
3β-OAc-20-CO	→	3β-OAc-20,20-F_2** (43%)

[a] Compounds are represented by abbreviated names, *e.g.* 16β-OH-2,7-$(CO)_2$ for 16β-hydroxy-5α-androstane-2,7-dione. The structures of new products, those marked (**), were established by elemental analysis and spectrometric examination. The constants of starting materials and known fluoro-compounds agreed with the published values. [b] Fully characterised as the 17-ketones obtained by hydrolysis and oxidation.



(1)

We have investigated the reactions of a series of oxygenated 5α-androstanes (**1**) with diethylaminosulphur trifluoride[3] (DAST), a reagent which can be stored in plastic bottles at 0 °C for several months and is easily handled in conventional apparatus. (There appears to be only two previous instances[4] of the use of DAST with steroids: 9α-H,11-OH- and 9α-F,11β-OH-steroids are dehydrated to $\Delta^{9(11)}$ and 9α-F,Δ^{11}-compounds, respectively, whereas 9α-Cl,11β-OH-steroids give 9α-Cl,11β-F-compounds.) The selection of results presented here show that, with few exceptions, DAST is effective for the general transformations depicted in the upper part of the Table. Very mild conditions suffice for the alcohol → fluoride conversion; keto groups are not attacked under these conditions, and this selectivity obviates the need for carbonyl protection when hydroxy-ketones are to be fluorinated. Although the 3α-OH → 3β-F reaction is unsatisfactory with 5α-H androstanes, the products are conveniently prepared by hydrogenating the 3β-F-Δ^{5}-compounds which are themselves readily obtained using DAST. The 11α-alcohol studied here gives a 9α-fluoro-compound as well as the expected $\Delta^{9(11)}$-olefin. 17α-Alcohols give products formed by dehydration and rearrangement; fortunately, treatment of 17,17-difluoro-5α-androstanes with alumina affords 17-fluoro-Δ^{16}-compounds which are easily reduced to 17β-fluorides.[5] For the ketone→*gem*-difluoride conversion much more vigorous conditions are required. The reactivity of a keto-group varies appreciably according to its position in the steroid nucleus, and 11-oxo-5α-androstanes resist fluorination. Acetoxy-groups are not affected by this treatment. Thus, acetylation of a hydroxy-ketone, reaction with DAST, and hydrolysis gives the corresponding hydroxy-*gem*-difluoro-compound.

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