

## Convenient General Preparation of Oxygenated Monofluoro- and *gem*-Difluoro-5 $\alpha$ -androstanes using Diethylaminosulphur Trifluoride

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**Summary** Hydroxy-ketones in the 5 $\alpha$ -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 5 $\alpha$ -androstanes having fluorine substituents at various positions of the steroid nucleus. Although a wide array of fluorosteroids has been described,<sup>1</sup> most of the reagents used in fluorina-

tions 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,<sup>2a</sup> but there are many instances of side-reactions

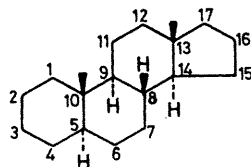
previous instances<sup>4</sup> of the use of DAST with steroids: 9 $\alpha$ -H,11-OH- and 9 $\alpha$ -F,11 $\beta$ -OH-steroids are dehydrated to  $\Delta^{9(11)}$  and 9 $\alpha$ -F, $\Delta^{11}$ -compounds, respectively, whereas 9 $\alpha$ -Cl,11 $\beta$ -OH-steroids give 9 $\alpha$ -Cl,11 $\beta$ -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 con-

TABLE. Reactions of oxygenated 5 $\alpha$ -androstanes (1) with diethylaminosulphur trifluoride (DAST).<sup>a</sup>

| $\begin{array}{c}   \\ \text{---C---C---} \\   \quad \quad    \\ \text{OH} \quad \quad \text{O} \end{array} \xrightarrow[30 \text{ min at } 20^\circ \text{C}]{\text{DAST-CH}_2\text{Cl}_2} \begin{array}{c}   \\ \text{---C---C---} \\   \quad \quad    \\ \text{F} \quad \quad \text{O} \end{array}$ | $\begin{array}{c}   \\ \text{---C---C---} \\   \quad \quad    \\ \text{OAc} \quad \quad \text{O} \end{array} \xrightarrow[2-48 \text{ h at } 80^\circ \text{C}]{\text{DAST (neat)}} \begin{array}{c}   \\ \text{---C---C---} \\   \quad \quad    \\ \text{OAc} \quad \quad \text{F} \end{array}$ |
|--|--|
| 3 $\beta$ -OH-17-CO $\longrightarrow$ { 3 $\alpha$ -F-17-CO (47%)<br>$\Delta^2$ -17-CO (44%)   | 17 $\beta$ -OAc-3-CO $\longrightarrow$ 17 $\beta$ -OAc-3,3-F <sub>2</sub> (86%)  |
| 3 $\beta$ -OH- $\Delta^5$ -17-CO $\longrightarrow$ 3 $\beta$ -F- $\Delta^5$ -17-CO (91%)   | 3 $\beta$ -OAc-6-CO $\longrightarrow$ { 3 $\beta$ -OAc-6,6-F <sub>2</sub> ** (29%)<br>3 $\beta$ -OAc- $\Delta^5$ -6-F** (33%)  |
| 3 $\alpha$ -OH-17-CO $\longrightarrow$ { 3 $\beta$ -F-17-CO (14%)<br>$\Delta^2$ -17-CO (83%)   | 17 $\beta$ -OAc-6-CO $\longrightarrow$ { 17 $\beta$ -OAc-6,6-F <sub>2</sub> **b (45%)<br>17 $\beta$ -OAc- $\Delta^5$ -6-F**b (45%)   |
| 6 $\alpha$ -OH-17-CO $\longrightarrow$ 6 $\alpha$ -F-17-CO** (86%)   | 3 $\beta$ -OAc-7-CO $\longrightarrow$ 3 $\beta$ -OAc-7,7-F <sub>2</sub> ** (70%)   |
| 11 $\alpha$ -OH-2,17-(CO) <sub>2</sub> $\longrightarrow$ { 9 $\alpha$ -F-2,17-(CO) <sub>2</sub> ** (16%)<br>$\Delta^{9(11)}$ -2,17-(CO) <sub>2</sub> ** (67%)  | 17 $\beta$ -OAc-7-CO $\longrightarrow$ 17 $\beta$ -OAc-7,7-F <sub>2</sub> ** (85%)   |
| 12 $\beta$ -OH-17-CO $\longrightarrow$ 12 $\beta$ -F-17-CO** (77%)   | 3 $\beta$ -OAc-11-CO $\longrightarrow$ No reaction   |
| 16 $\alpha$ -OH $\longrightarrow$ 16 $\beta$ -F** (88%)  | 3 $\beta$ -OAc-12-CO $\longrightarrow$ 3 $\beta$ -OAc-12,12-F <sub>2</sub> ** (90%)  |
| 16 $\beta$ -OH-2,7-(CO) <sub>2</sub> $\longrightarrow$ 16 $\alpha$ -F-2,7-(CO) <sub>2</sub> ** (72%)   | 17 $\beta$ -OAc-12-CO $\longrightarrow$ 17 $\beta$ -OAc-12,12-F <sub>2</sub> ** (95%)  |
| 17 $\beta$ -OH-3-CO $\longrightarrow$ 17 $\alpha$ -F-3-CO (39%)  | 3 $\beta$ -OAc-16-CO $\longrightarrow$ 3 $\beta$ -OAc-16,16-F <sub>2</sub> ** (51%)  |
| 17 $\alpha$ -OH-3-CO $\longrightarrow$ { $\Delta^{16}$ -3-CO<br>$\Delta^{13(17)}$ -17-Me-3-CO } (95%)  | 3 $\beta$ -OAc-17-CO $\longrightarrow$ 3 $\beta$ -OAc-17,17-F <sub>2</sub> (58%)   |
|  | 3 $\beta$ -OAc-20-CO $\longrightarrow$ 3 $\beta$ -OAc-20,20-F <sub>2</sub> ** (43%)  |

<sup>a</sup> Compounds are represented by abbreviated names, e.g. 16 $\beta$ -OH-2,7-(CO)<sub>2</sub> for 16 $\beta$ -hydroxy-5 $\alpha$ -androstan-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. <sup>b</sup> Fully characterised as the 17-ketones obtained by hydrolysis and oxidation.

occurring. (For example, with even the simple substrate 3 $\beta$ -hydroxy-5 $\alpha$ -androstan-17-one the desired 3 $\alpha$ -fluoro compound is accompanied by other products whose nature and proportions depend upon the conditions of the reaction and the work-up.<sup>2b</sup>) Sulphur tetrafluoride, the reagent employed most commonly for obtaining *gem*-difluorides from steroidal ketones,<sup>1b</sup> has the practical disadvantage of requiring specialised equipment.



(1)

We have investigated the reactions of a series of oxygenated 5 $\alpha$ -androstanes (1) with diethylaminosulphur trifluoride<sup>3</sup> (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

conditions suffice for the alcohol  $\rightarrow$  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 3 $\alpha$ -OH  $\rightarrow$  3 $\beta$ -F reaction is unsatisfactory with 5 $\alpha$ -H androstanes, the products are conveniently prepared by hydrogenating the 3 $\beta$ -F- $\Delta^5$ -compounds which are themselves readily obtained using DAST. The 11 $\alpha$ -alcohol studied here gives a 9 $\alpha$ -fluoro-compound as well as the expected  $\Delta^{9(11)}$ -olefin. 17 $\alpha$ -Alcohols give products formed by dehydration and rearrangement; fortunately, treatment of 17,17-difluoro-5 $\alpha$ -androstanes with alumina affords 17-fluoro- $\Delta^{16}$ -compounds which are easily reduced to 17 $\beta$ -fluorides.<sup>5</sup> For the ketone  $\rightarrow$  *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-5 $\alpha$ -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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