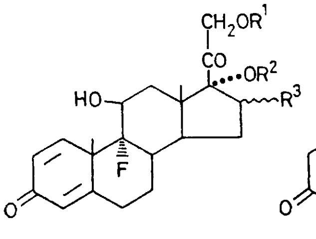
Synthesis of Δ^{11}-9α-Fluoro-steroids: *X*-Ray Crystal and Molecular Structure of 17α,21-Dipropionyloxy-9α-fluoro-16β-methylpregna-1,4,11-triene-3,20-dione

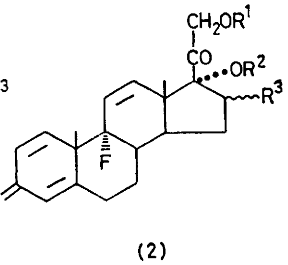
By Michael J. Green* and Ho-Jane Shue
(*Schering-Plough Research Division, Schering-Plough Corporation, Bloomfield, New Jersey* 07003)
Masato Tanabe* and Dennis M. Yasuda
(*Stanford Research Institute, Menlo Park, California* 94025)
and Andrew T. McPhail* and Kay D. Onan
(*Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina* 27706)

Summary Reaction of 9α-fluoro-corticosteroids with *NN*-dialkylaminosulphur trifluorides gives Δ^{11}-9α-fluoro-steroids (**2a,b**); a single-crystal *X*-ray analysis of (**2a**) is reported.

We here report the reaction of the recently described, potent fluorinating reagents, *NN*-dialkylaminosulphur trifluorides[1] with 9α-fluoro-corticosteroids and the preparation of novel Δ^{11}-9α-fluoro-steroids. The structure of one of the latter compounds was unequivocally established by single-crystal *X*-ray analysis.

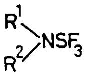
The 11β-hydroxy group of corticosteroids, *e.g.* hydrocortisone 21-acetate, is readily eliminated to yield the $\Delta^{9(11)}$ olefin by use of reagents such as $MeSO_2Cl$[2], $MeSO_2$-Cl–SO_2,[3] $SOCl_2$[4], *etc.* However, in the presence of a 9α-fluoro substituent the 11β-hydroxy group proves to be inert to these reagents[5] and, indeed, no example of a Δ^{11}-9α-halogeno steroid has previously been reported. We have found that the reaction of the 9α-fluoro-corticosteroids (**1a**) and (**1b**) with *NN*-diethylaminosulphur trifluoride (**3**) (1·1 equiv. in CH_2Cl_2 at −78 °C and then warmed to room temperature) gave, after chromatography, respectively, 53 and 57% of the elimination products (**2a**)† [m.p. 135—138 °C (from Et_2O), $[\alpha]_D^{26}$ +72·2° [dimethylformamide (DMF)], λ_{max} (MeOH) 238 nm (ε 18,200), n.m.r. ($CDCl_3$), δ 0·85 (3H, s, 13-Me), 1·27 (3H, s, 10-Me), 4·70 (2H, q, 21-H), 6·00 (1H, dd, *J* 10 and 2 Hz, 12-H), 6·27 (1H, d, *J* 2 Hz, 4-H), 6·38 (1H, dd, *J* 10 and 2 Hz, 2-H), 6·69 (1H, dd, *J* 10 and 5 Hz, 11-H), and 7·19 (1H, d, *J* 10 Hz, 1-H)] and (**2b**)† [m.p. 197—199 °C (from hexane–acetone), $[\alpha]_D^{26}$ +90·8 (DMF); u.v. and n.m.r. data similar to those for (**2a**)]. By use of piperidinosulphur trifluoride (**4**), the elimination product (**2a**) was obtained from (**1a**) in 62% yield. The 9-unsubstituted compound, prednisolone BMD[6] gave, as expected, the $\Delta^{9(11)}$ olefin in quantitative yield even at −78 °C.


(1)


(2)

a; $R^1 = R^2 = COEt, R^3 = \beta\text{-Me}$

b; $R^1 = COMe, R^2, R^3 =$ 


$R^1R^2NSF_3$

(3) $R^1 = R^2 = Et$

(4) $R^1, R^2 = -[CH_2]_5-$

The observation that *NN*-dialkylaminosulphur trifluorides react with (**1**) when the usual dehydrating agents do not is due firstly to the very electrophilic nature of these reagents which allows them to react with the highly hindered 11β-hydroxy group. Secondly the reaction not only generates an intermediate 11β-$OSF_2NR^1R^2$ substituent, which can further dissociate to the excellent leaving group $-OSF{=}\overset{+}{N}R^1R^2F^-$, but also liberates fluoride ion which can act as a base to remove the axial 12α-H. Some analogy can be drawn here to the reported use of tetramethylammonium fluoride[7] in elimination reactions. Substitution at C(11) in an S_N2 manner is inhibited by repulsion of the approaching fluoride ion by the 9α-fluoro substituent. It should be noted that even though *NN*-dialkylaminosulphur trifluorides are extremely reactive, they are also very selective; in the above transformations no reaction occurred with either the unsaturated ketone system in ring A or with the substituted dihydroxyacetone side chain.

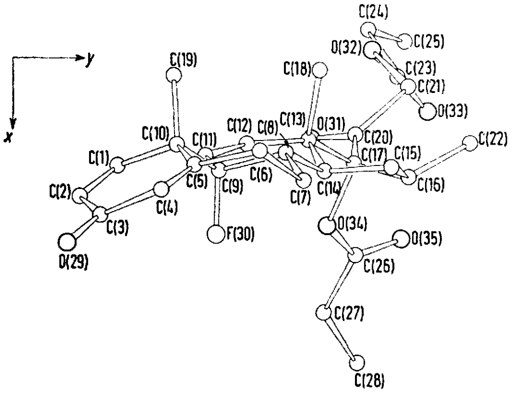


FIGURE. Structure of (**2a**).

The structure of the product from the reaction of (**1a**) with (**3**) was confirmed by single-crystal *X*-ray analysis of (**2a**) which crystallizes in the orthorhombic system, space group $P2_12_12_1$, a = 12·176(5), b = 18·124 (7), c = 11·722(5) Å, Z = 4. Intensities for all unique reflections with $\theta < 55°$ were measured on an Enraf-Nonius CAD-3 automated diffractometer (Ni-filtered Cu-K_α radiation, λ = 1·5418 Å; θ—2θ scans). The structure was solved by direct methods using MULTAN[8] and refined by full-matrix least-squares calculations (anisotropic C, F, O; isotropic H) to R 0·082 over 1047 statistically significant $[I > 2{\cdot}0\sigma(I)]$ reflections. A view of the solid-state conformation is shown in the Figure. Ring A, with $\Sigma|\omega|$‡ = 13·4°, is almost planar, ring B adopts a chair conformation, ring C is intermediate between an 8β, 14α-half-chair (C_2) form and a 14α-envelope (C_s) form, and ring D lies closer to a 13β, 14α-half-chair conformation than to a 14α-envelope form.§

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† Both (**2a**) and (**2b**) gave elemental analyses (C, H, F) correct to within ±0·3% of the calculated values.

‡ Endocyclic torsion angles, ω_{ij}(°), about bonds between atoms C(i) and C(j) are, for ring A: $\omega_{1,2}$ −1·1, $\omega_{1,10}$ 3·7, $\omega_{2,3}$ −1·0, $\omega_{3,4}$ 0·0, $\omega_{4,5}$ 3·0, $\omega_{5,10}$ −4·6; for ring B: $\omega_{5,6}$ −54·8, $\omega_{6,7}$ 53·9, $\omega_{7,8}$ −57·2, $\omega_{8,9}$ 61·0, $\omega_{9,10}$ −54·8, $\omega_{10,5}$ 51·7; for ring C: $\omega_{8,9}$ −38·9, $\omega_{9,11}$ 10·7, $\omega_{11,12}$ −4·0, $\omega_{12,13}$ 25·4, $\omega_{13,14}$ −54·7, $\omega_{14,8}$ 63·2; for ring D: $\omega_{13,14}$ 46·0, $\omega_{14,15}$ −40·2, $\omega_{15,16}$ 17·5, $\omega_{16,17}$ 10·3, $\omega_{17,13}$ −33·9.

§ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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