Stereoselective β-Face Catalytic Hydrogenation of Δ^4-9α-Fluoro-11β-hydroxycorticosteroids: Reappraisal

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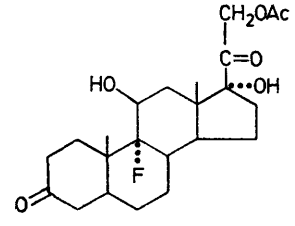
Summary At variance with previous reports, palladium-catalysed reduction of 9α-fluorohydrocortisone 21-acetate (**1a**) and 1,2-didehydro-9α-fluoro-16α-methylhydrocortisone 21-acetate (**2a**) yields the 5β-configuration.

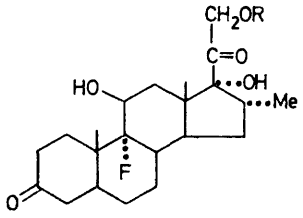
CATALYTIC (Pd–C) hydrogenation of the 4,5-double bond in the 4-en-3-one[1,2] and 1,4-diene-3-one[3] units of 9α-fluoro-11β-hydroxy steroids has been reported to yield only the 5α-isomer. We now report that such reductions of 9α-fluorohydrocortisone 21-acetate (**1a**) and 1,2-didehydro-9α-fluoro-16α-methylhydrocortisone 21-acetate (**2a**) occur stereospecifically to give the 5β-isomers (**1b**) and (**2b**), respectively.

In connection with another project we conducted a single-

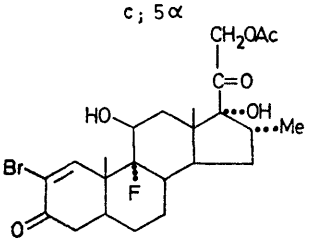
crystal *X*-ray analysis of a product[4] derived from the 2-bromo-Δ^1-4,5-dihydro-3-ketone (**3**)† and differing from it only at the 2-bromo-Δ^1 units. The 5α-configuration had been presumed for (**3**) because it had been obtained, albeit as a minor product [the major product was the $\Delta^{4,6}$-isomer of (**2a**)] *via* dibromination and dehydrobromination from the ring-A saturated compound (**2**; R = Ac), the Pd–C hydrogenation product of (**2a**). One conclusion from this *X*-ray analysis was that the A–B fusion was *cis*. Since the analysed product differed from (**3**) only at the Δ^1 unit, by implication (**3**) also had the 5β-configuration and, *ad extensio*, the ring-A saturated compound (**2**; R = Ac).



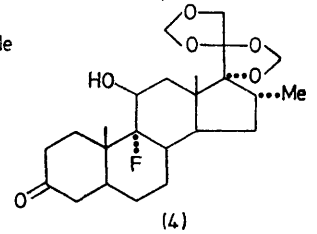
(1)
a; 4-ene
b; 5β
c; 5α



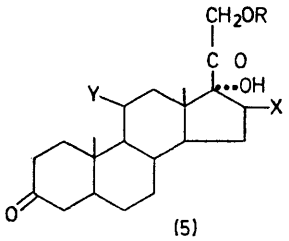
(2)
a; R = Ac, 1,4-diene
b; 5β, R = Ac
c; 5α, R = Ac
d; 5α, R = H
e; 5β, R = H



(3)

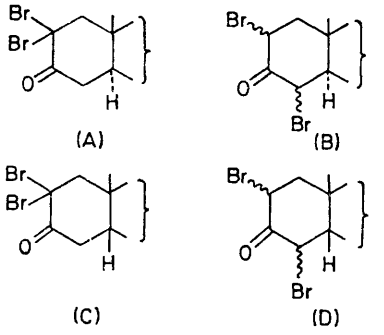


(4)
a; 5α
b; 5β
c; 1,4-diene



(5)
a; 5α, X = H, Y = OH, R = Ac
b; 5β, X = H, Y = OH, R = Ac
c; 5α, X = H, Y = OH, R = H
d; 5β, X = H, Y = OH, R = H
e; 5α, X = Me, Y = H, R = Ac
f; 5β, X = Me, Y = H, R = Ac

We set out to determine the isomer ratio of (**2b**) to (**2c**) from the reduction of (**2a**). The ring A tetrahydro-reduction products (**4a**)[5] (Li–NH_3) and (**4b**) (5% Pd–C, EtOAc, 50 lb/in^2 H_2), both derived from (**4c**)[5] were shown to be different by t.l.c.‡ [(**4a**) slightly more polar than (**4b**)], n.m.r.,¶ c.d.,§ and mixed m.p. The molecular ellipticity [θ] of (**4b**) was more negative than that of (**4a**), an observation consistent with ring A,B *cis* and *trans* effects.[6] Careful analyses (t.l.c., c.d.) revealed no 5α-isomer (**4a**) in the crude palladium-catalysed reduction product from (**4c**). Treatment of (**4a**) and (**4b**) with aqueous formic acid (60%) at 60 °C, followed by base (KOH, MeOH, H_2O), generated the dihydroxyacetone side chain in (**2d**) and (**2e**), respectively, which t.l.c. showed to have a reversed order of polarity from (**4a**) and (**4b**). The [θ] value for (**2e**) was less positive than that of (**2d**), and the chemical shift of the 10-methyl signal in (**2d**) was upfield from that of the corresponding signal in (**2e**). Esterification (Ac_2O–pyridine) of (**2d**) and (**2e**) gave the 21-acetates (**2c**) and the more polar (t.l.c.) (**2b**), with the latter being identical to the hydrogenation product (Pd–C, EtOAc, 50 lb/in^2 H_2) obtained from (**2a**). Careful (t.l.c., c.d.) examinations of the crude palladium-catalysed reduction product from (**2a**) indicated the absence of any (**2c**).



(A) (B) (C) (D)

The relationship between (**3**) and (**2b**) was determined by hydrogenation of (**3**) [5% Pd–C; 250% Pd–C by wt. to (**3**), EtOAc, 1 atm H_2]. Complete reduction was effected and the product, identified as (**2b**) by t.l.c., c.d., n.m.r., and mixed m.p., was recovered in 56% yield.

The 5β-isomer (**1b**) was obtained by hydrogenation of (**1a**) at 1 atm in the presence of either 5% Pd–C in methanol

† All new compounds reported have analyses consistent with the proposed structures.

‡ Silica gel: $CHCl_3$–EtOAc (2 : 1) for (**2b**), (**2c**), (**4a**), and (**4b**); C_6H_6–EtOAc (1 : 1) for (**2b**) and (**2e**).

§ C.d. results were obtained on a Cary 61 instrument in MeOH: $[\theta]_{296}$ + 11,3000 (**1b**), $[\theta]_{296}$ + 10,300 (**2b**), $[\theta]_{292}$ + 16,200 (**2c**), $[\theta]_{291}$ + 14,400 (**2d**), $[\theta]_{294}$ + 7820 (**2e**), $[\theta]_{289}$ + 3190 (**4a**), $[\theta]_{288}$ − 2460 (**4b**), $[\theta]_{292}$ + 17,700 (**5a**), $[\theta]_{295}$ + 12,600 (**5b**), $[\theta]_{292}$ + 15,600 (**5c**), $[\theta]_{293}$ + 10,700 (**5d**), $[\theta]_{294}$ + 14,600 (**5e**), $[\theta]_{297}$ + 9640 (**5f**).

¶ All ^{1}H n.m.r. data were recorded at 100 MHz on a Varian XL-100-15 spectrometer in the Fourier transform mode in $(CD_3)_2SO$, except for (**5e**) and (**5f**) which were in $CDCl_3$, with Me_4Si as internal reference. The 9α-fluoro substituent causes a downfield shift of the 10-methyl signal in both the 5α and 5β- isomers with a larger effect in the latter: δ 1·26 in (**1b**), (**2b**), (**2e**), and (**4b**); 1·31 in (**2c**), (**2d**), and (**4a**); 1·19—1·20 in (**5a—f**), No diagnostically useful differences between α- and β-isomers were noted for the 13-methyl signals: δ 0·74 (**1b**), 0·84 (**2b**), 0·84 (**2c**), 0·82 (**2d**), 0·83 (**2e**), 1·08 (**4a**), 1·08 (**4b**), 0·75 (**5a**), 0·74 (**5b**), 0·72 (**5c**), 0·72 (**5d**), 0·82 (**5e**), and 0·81 (**5f**).

or EtOAc[1a] or 5% Pd–$BaSO_4$ in EtOAc.[1b] Strong indication for no formation of the 5α-product[7] came from careful t.l.c., n.m.r., and c.d. analyses of the crude reaction product as well as of the analytical sample of the hydrogenation product. Definitive assignment was made by single-crystal *X*-ray analysis. Crystals of (**1b**) are orthorhombic, space group $P2_12_12_1$, $a = 14{\cdot}41(1)$, $b = 19{\cdot}26(1)$, $c = 7{\cdot}73(1)$ Å, $Z = 4$. Intensities for reflections with $\theta < 67°$ were measured on an Enraf-Nonius CAD 3 diffractometer (Ni-filtered Cu-K_α radiation, $\lambda = 1{\cdot}5418$ Å) by the θ–2θ scanning procedure. The structure was solved by direct methods using MULTAN[8] and refined by full-matrix least-squares calculations (anisotropic C, O; isotropic H) to *R* 0·054 over 1791 statistically significant reflections.

The apparent exclusive formation of the 5β-isomer merits some comment. In neutral solvents or solvents containing acids[9] mixtures of 5α- and 5β-isomers are generally produced. Moreover, catalytic hydrogenations of 11β-hydroxyandrost-4-en-3-one substrates have been reported to yield 60β:40α mixtures.[10] Obviously the 9α-fluoro substituent has a dramatic effect on the course of reduction since our results reveal only *cis* A,B ring formation. It is significant that *X*-ray structural studies have shown the A ring in (**1a**) to be appreciably more folded towards the α-side than is the corresponding ring in hydrocortisone.[11] The β-face in (**1a**) should therefore be more accessible to the catalyst surface, a consideration which fits our findings well.

It has generally been accepted that the direction of enolization of the 3-carbonyl group is dictated by the configuration at C(5), the 5β-isomer allowing formation of more Δ^3 than Δ^2 product while a reversed situation obtains for the 5α-isomer, thus leading *via* bromination and dehydrobromination to formation of greater amounts of Δ^4 and Δ^1 products, rsepectively. For this reason, the α configuration was assigned to C(5) in (**1a**) following formation of the Δ^1 product after bromination and dehydrobromination.[12] Similarly, we could have concluded that the formation of the 2-bromo-Δ^1-grouping in (**3**) showed the configuration at C(5) to be α [*via* intermediates such as (A) or (B)]. However, our findings show this not to be the case, and indeed, accord well with the conclusion[10] that in the 5β-androstan-3-one series, the 11β-hydroxy substituent affects the relative ratio of Δ^2-*vs.* Δ^3-enol formation compared to the 11-deoxy-5β analogue. Thus, the 11β-hydroxy effect on the enolization ratio appears to be important in the formation of (**3**) [*via* intermediates such as (C) or (D)]. We point out, however, that the additional influence of the 9α-fluoro substituent for the formation of the dibromo precursor to (**3**) is not yet defined.

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[2] (a) U.S.P. 3,105,832 (*Chem. Abs.*, 1964, **60**, P3051f); U.S.P. 3,101,332 (*Chem. Abs.*, 1964, **60**, P3066e); (c) B.P. 814,070 (*Chem. Abs.*, 1959, **53**, 22100d); (d) B.P. 829,632 and 829, 633 (*Chem. Abs.*, 1960, **54**, 18602d); (e) U.S.P. 2,837,541 (*Chem. Abs.*, 1958, **52**, 20263i).

[3] U.S.P. 3,055,922 (*Chem. Abs.*, 1963, **58**, 5769d).

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[6] See, *e.g.* P. Crabbé, 'ORD and CD in Chemistry and Biochemistry,' Academic Press, New York, 1972, p. 37.

[7] Compound (**1c**) has been prepared by an alternative route by J. Elks, G.H. Phillips, and W. F. Wall, *J. Chem. Soc.*, 1958, 4001. The analytical constants for (**1c**) as reported therein are rather similar to those for the reduction product reported in refs. 1(a) and 1(b).

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[11] C. M. Weeks, W. L. Duax, and M. E. Wolff, *J. Amer. Chem. Soc.*, 1973, **95**, 2865.

[12] See footnote 12 in ref. 1(b).