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C-10 SUBSTITUTED 19-NORSTEROIDS IX.[1] INTRODUCTION OF 10β SUBSTITUENTS*

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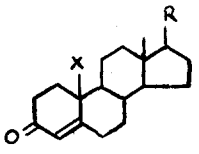
The introduction of substituents at C-10 in 19-norsteroids proceeds preferentially[2] or even exclusively[3] from the α-side. The 9α,10α compounds so obtained represent a class of interesting "unnatural" steroids difficult to obtain by other routes; 10β substituted steroids are more readily available by modification of an existing C-19 methyl group of natural products via the Barton reaction[4] or lead tetracetate oxidation.[5] Introduction of a C-10 substituent into 19-norsteroids in the "natural" β orientation is of practical importance, however, for preparation of steroids isotopically labeled with ^{14}C at this position. These compounds are important for studies of biochemical transformations affecting carbon 19 and in particular the stages in the biosynthesis of estrogens from androgens.

Recently, two laboratories[6,7] using essentially the same method have independently prepared testosterone-19-^{14}C (Ia R = OH). The radiochemical yield, however, was very low (4%, 0.5%) and the method was limited to the synthesis of the C-19 methyl compound. We now wish to report a procedure which permits the preparation of all the postulated precursors of estrogens (Ia-d) in good yield and

*This work was supported by grants from the American Cancer Society and the U. S. Public Health Service (Grants #CA 07304, FR-53). All new compounds described gave satisfactory microanalysis. The n.m.r. spectra were obtained at 60 megacycles in deuterochloroform. The melting points are corrected. Rotations were obtained in chloroform.

is eminently applicable to a radiochemical synthesis.



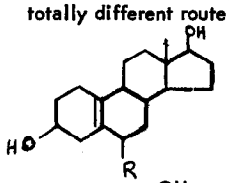
Ia X = CH_3
b X = CH_2OH
c X = CHO
d X = COOH

R = O, 

3β,17β-Dihydroxyestr-5(10)-en-6-one (IIb), m.p. 226-229°, obtained by activated manganese dioxide oxidation of 3β,6β,17β-trihydroxyestr-5(10)-ene (IIa)[8], reacts rapidly with potassium cyanide in boiling ethylene glycol to give one product only, isolated in 80-85% yield as the diacetate IIIa m.p. 259-61° $[\alpha]_D^{22}$ -56°. The orientation of the newly introduced cyano group was assigned as β from the n.m.r. spectrum in which the C-18 methyl resonance appeared at 53 cps consistent with long range deshielding by a 10β cyano group[2]. The orientation of the hydrogen at C-5 must clearly be affected by equilibration under the alkaline reaction conditions and from stability considerations may be expected to be α[9]. This was confirmed by the resonance of the 3α hydrogen as a broad multiplet at 280 cps indicative of axial character and consistent only with a trans A-B conformation. The stereospecific cyanide addition at C-10 is in sharp contrast to the result from the Δ1 (10)-2-keto system[2] where both 10α and 10β cyano compounds were obtained, the former predominant[10].

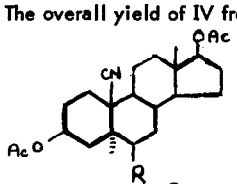
Reduction of the diacetate IIIa with $NaBH_4$ proceeded stereoselectively to yield mainly the triol diacetate IIIb m.p. 180-2° $[\alpha]_D^{22}$ - 70°. The axial nature and hence β orientation of the C-6 hydroxy group was suggested by the n.m.r. spectrum of the triacetate IIIc, where the 6α hydrogen appeared as a narrow multiplet (half-height

width 6 cps) at 302 cps. The C-6 alcohol in IIIb was smoothly dehydrated with thionyl chloride in pyridine to give 10β-cyanoestr-5-ene-3β,17β-diol diacetate (IV) m.p. 161-163°, identical in all respects with an authentic sample prepared by a totally different route[11,12]. The overall yield of IV from IIb was 50-60%.



IIa R = $\overset{OH}{\underset{H}{\diagup\!\!\diagdown}}$

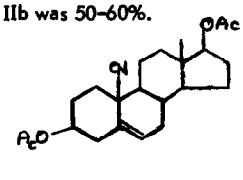
b R = O



IIIa R = O

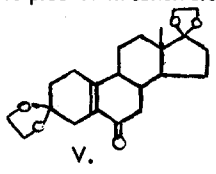
b R = $\overset{OH}{\underset{H}{\diagup\!\!\diagdown}}$

c R = $\overset{OAc}{\underset{H}{\diagup\!\!\diagdown}}$

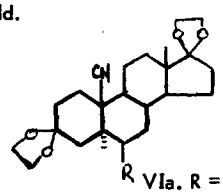


IV.

The cyano derivative IV provides access to the compounds of interest Ia-d via transformations which have already been described[12,13] and which are reported to proceed in satisfactory yield.

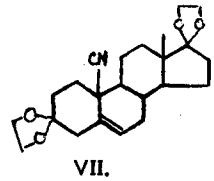


V.



VIa. R = O

b. R = $\overset{OH}{\underset{H}{\diagup\!\!\diagdown}}$



VII.

Some of the desired compounds Ia-d would be more readily available from a precursor already possessing a 3 keto group, and the hydrocyanation reaction was therefore repeated on the 3,17-bisdioxolane derivative V[14]. The reaction was again stereospecific and yielded the saturated 10β-cyano ketone IVa m.p. 226-229° $[\alpha]_D^{22}$ -101° in high yield. Reduction to the 6β-ol VIb m.p. 203-207° $[\alpha]_D^{22}$ - 36°,

and dehydration to the Δ5 compound VII m.p. 207-210° (vinyl proton at 340 cps) $[\alpha]_D^{22}$ - 148°, proceeded in an overall yield of 60-65%. The conversion of the bisdioxolane derivative VII to certain of the pertinent compounds Ia-d by described procedures[12,13] requires less chemical manipulation than from the corresponding diacetate IV and this sequence is preferable for some of the radiochemical applications.

The reaction sequences described represent acceptable means for the preparation of labeled hormones and intermediates of considerable biochemical interest. These applications will be reported in further studies.

REFERENCES

1. Part VIII. J. Fishman, M. Torigoe and J. A. Settepani Tetrahedron, 21: 3677 (1965).
2. M. Torigoe and J. Fishman Tetrahedron, 21: 3669 (1965).
3. J. A. Settepani, M. Torigoe and J. Fishman Tetrahedron, 21: 3661 (1965).
4. M. Akhtar and D. H. R. Barton J. Am. Chem. Soc., 84: 1496 (1962).
   T. Jen and M. E. Wolff J. Med. Pharm. Chem., 5: 876 (1962).
5. A. Bowers, R. Villotti, J. A. Edwards, E. Denot and O. Halpern J. Am. Chem. Soc., 84: 3204 (1962).
   K. Heusler, J. Kalvoda, Ch. Meystre, H. Ueberwasser, P. Wieland, C. Anner and A. Wettstein Experientia, 18: 464 (1962).
6. P. N. Rao and L. R. Axelrod Chem. and Ind. 1838 (1963); J. Chem. Soc. 1356 (1965).
7. S. Rakhit and M. Gut J. Am. Chem. Soc., 86: 1432 (1964).
8. M. Akhtar and D. H. R. Barton Ibid, 86: 1528 (1964).
   This triol is more conveniently prepared by the lead tetracetate fragmentation of androst-5-ene-3β,17β,19-triol 3,17 diacetate and subsequent $LiAlH_4$ reduction. See ref. 14 and also R. M. Moriarty and K. Kapadia Tetrahedron Letters, 1165 (1964).
9. In the corresponding situation with a 10β methyl substituent, 12% of the 5β, isomer is present at equilibrium. N. L. Allinger, M. A. DeRooge, and R. B. Herman J. Org. Chem., 26: 3626 (1961); a 10β chloromethyl group results in 30% of the 5β isomer. H. Carpio, A. Cruz-Bazan, M. G. Teran-Medina and J. A. Edwards Ibid, 30: 4154 (1965).
10. In the patent literature the 1,4 addition of methyl Grignard to the Δ^5 (10)-6-ketone system is reported to yield only 10α-methyl-5β compounds. A. Bowers and O. Halpern U. S. Patent 3,148,185 (1964).

11. R. Gardi and C. Pedralli Gazz. Chim. Ital., 91: 1420 (1961).
12. M. E. Wolff and T. Jen J. Med. Chem., 6: 726 (1963).
13. T. Jen and M. E. Wolff J. Org.Chem., 28: 1573 (1963).
14. M. Amorosa, L. Caglioti, G. Cainelli, H. Immer, J. Keller, H. Wehrli, M. Lj Mihailovic, K. Schaffner, D. Arigoni and O. Jeger Helv. Chim. Acta, 45: 2674 (1962).