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HETEROCYCLIC STEROIDS - XX[1]

A FACILE APPROACH TO 10-AZA-STEROIDS

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In connection with our continued interest in the synthesis of heterocyclic steroids we wish to report a facile total synthesis of the 10-azasteroidal skeleton and some of its reductive transformations.

The synthesis of 10-aza-19-nor-testosterone has been described recently[3]. This synthetic sequence involves the preparation of an BCD tricyclic-intermediate, incorporating the future bridgehead nitrogen, followed by its elaboration to the steroid skeleton. Our own approach utilizes a pyridine system as potential ring A and depends upon the synthesis and ring-closure of 9,10-seco-steroid intermediate 1. The attractiveness of the latter scheme lies in the facile accessibility of 1 (three steps) from easily available starting materials. Furthermore, suitable substitution of the pyridine ring at the starting material level can, in principle, provide the corresponding ring A substituted 10-aza-steroids.

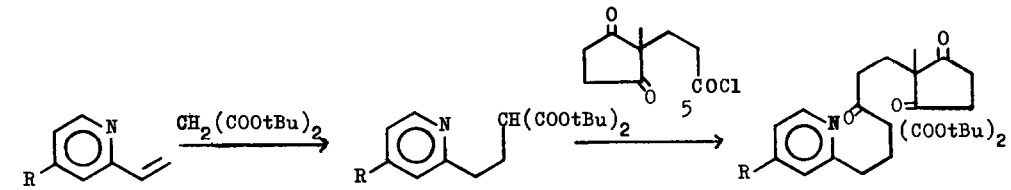
The feasibility of the scheme was tested by its application to the preparation of seco-steroid 2 , which required commercially available 2-vinylpyridine (3a) as the basic intermediate. A Michael addition of di-t-butyl malonate to 3a gave the corresponding adduct 4a in 80 p.c. yield. The malonate derivative 4a was readily acylated in benzene (NaH, 5°) with 2-[2',5'-dioxo-1'-methylcyclopentyl]propionyl chloride (5)[4] to yield the triketo product 6a. Treatment of 6a with anhydrous p-toluenesulfonic acid, in benzene, smoothly caused a simultaneous decarboxylation and cyclization to give crystalline 2, m.p. 78-79°, in about 80 p.c. yield; IR ($CHCl_3$): 1725, 1650, 1590, 1570 cm^{-1}; UV (EtOH): 251.1 nm (12,600); 210.5 nm (8,350).

The 4-methoxy-2-vinylpyridine (3b), required for synthesis of 1, was most conveniently prepared by the following sequence of reactions: commercially available 2-ethylpyri-

dine (7) was subjected to a conventional peroxide oxidation and the resulting N-oxide nitrated to give the 4-nitro derivative. Nucleophilic displacement of the nitro group with methoxide ion gave 4-methoxy-2-ethylpyridine-N-oxide (8) in good yield. N-oxide 8 was subsequently rearranged[5] with acetic anhydride and the thereupon formed α-acetoxy-2-ethyl-4-methoxypyridine was hydrolyzed and dehydrated to the desired vinylpyridine 3b (b.p. 112-114°/15 mm). The sequence 3b ⟶ 4b ⟶ 6b ⟶ 1 could be accomplished analogously as in the case of 3a; the overall yield of the three steps being 57 p.c. Optimum yields in the acylation of 4b were obtained when freshly prepared phenyllithium, in ether, was employed as a base and the reaction temperature was maintained at 0°. Seco-steroid 1 was obtained as a colourless oil after chromatography over a florisil column ($CHCl_3$-C_2H_5OH 19:1); IR ($CHCl_3$) 1745, 1665, 1600, 1575 cm^{-1}.

In order to attain ring-closure of 1, the 17-keto[6] function was first blocked by ketalization and the conjugated carbonyl group was reduced with lithium aluminium hydride. While the product of this reduction can, in principle, be a mixture of two isomeric alcohols (9a,b); the observation of a single C_{13}-CH_3 signal in the NMR spectrum of the reaction product suggests a predominantly stereospecific reduction. Steric considerations argue for approach of the hydride-complex from α-side of the molecule and the formation of a β-hydroxy product. When the reduction mixture, without purification, was treated with tosyl chloride and anhydrous potassium carbonate, in scrupulously dried acetonitrile, two crystalline salts, m.ps. 197-200° and 182-191° were obtained. The high melting product has been assigned the 9β-configuration (10b) in view of the magnetic nonequivalence of the ketal methylene groups. Molecular models indicate that in 10b these methylenes are unsymmetrically affected by the pyridinium ring. In 10a, on the other hand, the ketal group stands almost perpendicular to the plane of the steroid molecule. Consistent with these assignments the ketal protons in 10b appear as a multiplet around 3.8 δ and in 10a as a slightly broadened singlet at 3.9 δ. The larger proportion of 10b in the reaction mixture is in agreement with an SN_2 displacement of 9-β-tosylate, formed from the 9-β-alcohol. While an SN_1 reaction would appear to be responsible for the formation of 10a; it is not possible to exclude the involvement of this same mechanism for the generation of some of 10b.[7]

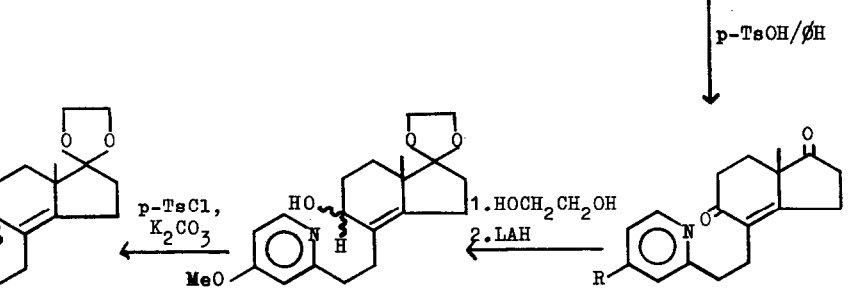
Reduction of 10a and 10b with sodium borohydride, in ethanol, proceded stereospecifically to give single isomers of the corresponding tetrahydro derivatives. Hydrolysis of the latter gave the corresponding isomeric 10-aza-19-nor-$\Delta^{8,14}$-androstane-3,17-diones,



3a R = H
b R = OMe

4a R = H
b R = OMe

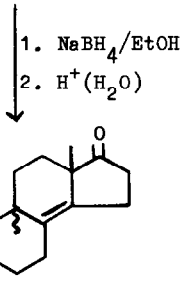
6a R = H
b R = OMe



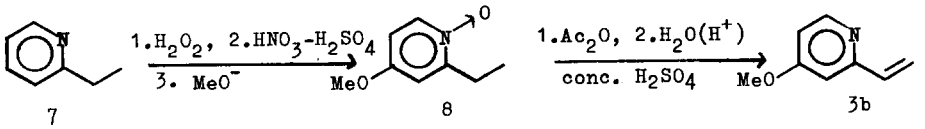
1 R = OMe, 2 R = H

9a α - OH
b β - OH

10a 9α (20%)
b 9β (47%)



11a 5α, 9α
b 5β, 9β



7 8 3b

(11a,b),m.ps. 159-161° and 134-137°, in good yield. M.p. 159-161° (11a); IR ($CHCl_3$): 2870, 2840, 2750, 2690 cm^{-1} (Bohlmann bands), 1740, 1725 (2 x C=O); NMR ($CDCl_3$): δ 1.19 (s, C_{13}-CH_3), δ 3.58 (octet, J=11, 6 and 2, C_9-H). M.p. 134-137° (11b); IR ($CHCl_3$): 2860, 2790, 2755, 2700 (Bohlmann bands), 1740, 1725 cm^{-1} (2 x C=O); NMR ($CDCl_3$): δ 1.11 (s, C_{13}-CH_3), 3.48 (m, $W_{\frac{1}{2}}$ = 19 c/s, C_9-H). The intense Bohlmann bands[8] observed in the IR spectra of 11a and 11b plead for the presence of nearly ideal transquinolizidine ring systems in both these compounds. Inspection of molecular models of isomeric 10-aza-19-nor-$\Delta^{8,14}$-3,17-diketo steroids - in the light of the abovementioned argument - allows the tentative assignment of 5α, 9α- and 5β, 9β- structures to the high melting (11a) and low melting (11b) products, respectively. An X-ray crystallographic investigation is currently underway to settle the stereochemical assignments unequivocally.

It is obvious that the principle embodied in the synthetic sequence leading to 1 and 2 is capable of extension to other ring A modified precursors. An assessment of the potentialities of this scheme is under investigation in this laboratory.

References

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1. Part XIX. The molecular structure of a 6-thiaestrogen. H. Schenk, W.M.B. Könst, W.N. Speckamp and H.O. Huisman, Tetrahedron Lett., in press.
2. Taken in part from the doctorate dissertation of H.J. Wille, University of Amsterdam, 1970.
3. D. Bertin and J. Perronnet, Bull.Soc.Chim.France, 117 (1969).
4. The acid chloride 5 was obtained in quantitative yield by treatment of the corresponding acid [ref. R.E. Brown, D.M. Lustgarten, R.J. Stanaback and R.I. Meltzer, J.Org.Chem. 31, 1489 (1966] with oxalyl chloride.
5. R. Bodalski and A.R. Katritzky, J.Chem.Soc. (B), 831 (1968) and references cited therein.
6. Steroid nomenclature is used for this and the following seco-steroidal systems.
7. Ring-closure of the cation derived from 9b (β-OH) could yield both 10a and 10b in a ratio which cannot be simply predicted.
8. J. Skolik and P.J. Krueger, Tetrahedron 24, 5439 (1968).