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D-NOROXASTEROID*

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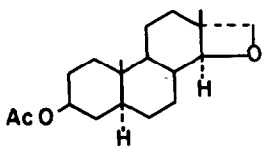
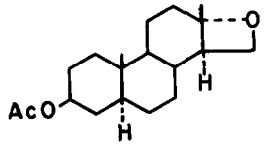
Extensive work has been published in the recent past on the synthesis of oxa and aza steroids (1). Also in recent years many research groups have successfully synthesized D-norsteroids (2). We have undertaken the synthesis of D-noroxasteroids to unravel the chemistry of an oxetane ring fused to a rigid cyclohexane system in trans fashion (1a, 1b), thereby opening a new class of steroids where interesting and novel biological and physicochemical properties might be expected.



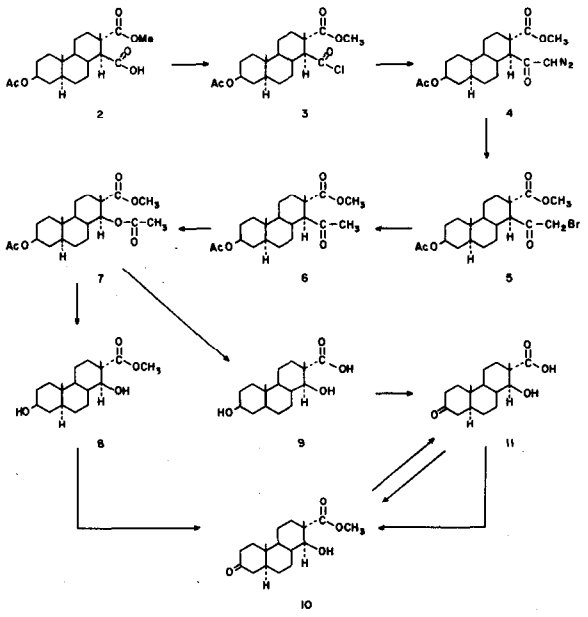
I a



I b

The starting material (3) in our synthesis was 3β-acetoxy-15,17-seco-D-norandrostane-15,17-dioic acid 17-methyl ester (2), which on treatment with oxalyl chloride in benzene at 55° for 1 1/2 hrs, gave a crystalline acid chloride 3, m.p. 94°. Reaction of 3 with diazomethane at 0° for 2 hrs gave 3β-acetoxy-15-oxo-16-diazo-16,17-secoandrostan-17-oic-acid 17-methyl ester (4), m.p. 138-40°. Gaseous hydrobromic acid was bubbled through the ether solution of 4 for a few minutes at room temperature, whereupon the yellow color of the diazoketone disappeared. Upon concentration of the solution, the bromoketone 5 crystallized. One recrystallization from methylene chloride-hexane gave material melting at 158-60°. The bromoketone 5 was reduced to 3β-acetoxy-16,17-seco-15-oxo-androstan-17-oic acid 17-methyl ester (6, m.p. 112-13°) by zinc dust in the presence of

*All new compounds reported here have been characterized by u.v., i.r., n.m.r., mass spectra and elemental analysis.



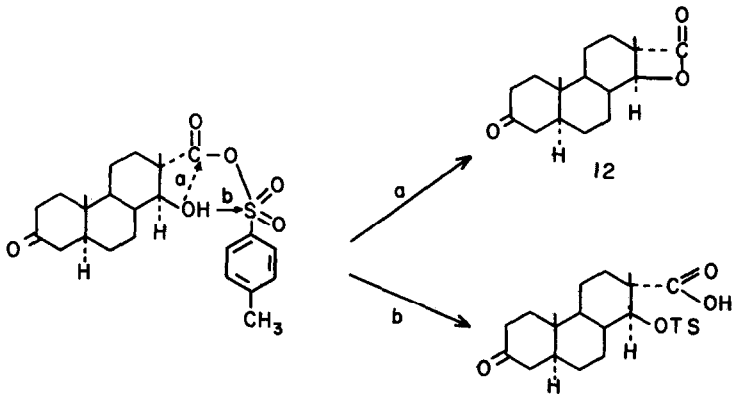
sodium iodide in glacial acetic acid. The overall yield of 6 from 2 was 75%.

Methyl ketone 6, upon Baeyer-Villiger oxidation with trifluoroperoxyacetic acid (4), gave 3β,14β-diacetoxy-14,17-seco-D-bisnorandrostan-17-oic acid 17-methyl ester (7, m.p. 172-73°) in 85% yield. Compound 7, when refluxed with 3% methanolic potassium hydroxide for 2 hrs gave, besides the desired product 8, m.p. 155-56°, a small amount of 9. Hydroxyester 8, upon oxidation with Jones reagent, gave almost quantitatively a monohydroxy ketone 10, m.p. 184-85°. 14β-Hydroxy-3-oxo-14,17-seco-D-bisnorandrostan-17-oic acid 17-methyl ester (10), on hydrolysis with 20% methanolic potassium hydroxide solution gave the corresponding acid 11, m.p. 226-28°, which was also obtained by the oxidation of 9 with Jones reagent.

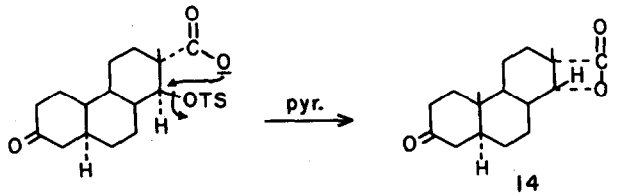
Hydroxyester 10 could not be oxidized to the corresponding diketone either with Jones reagent or chromium trioxide in pyridine. Furthermore, treatment with tosyl chloride and pyridine at room temperature gave starting material only. Acetylation requires drastic conditions, and the yield is poor. In contrast, 9 can readily be

acetylated under mild conditions, in a reaction probably involving intramolecular esterification.

When 11 was treated with 1 mole of p-toluenesulphonyl chloride and a catalytic amount of pyridine in methylene chloride, we were able to isolate a small amount of a tosyl derivative, but the main product was a sulfur free compound with the following properties: ν_{max}^{KBr} 5.55 (β-lactone) and 5.85 μ; mass spectrum $\frac{m^+}{e}$ = 276 (M), 261 (M-15) and 232 (M-44) base peak. All these criteria suggest that the compound 12 has a β-lactone moiety and the reaction could be visualized as follows:



However, it is also conceivable that instead of the trans β-lactone, the cis β-lactone could be obtained from the hydroxyacid in the following way:



The β-lactone, on treatment with methanol containing a catalytic amount of p-toluenesulphonic acid, gave a hydroxyester which is in all respects identical (i.r., n.m.r., mass spec., mixed m.p.) with compound 10. Therefore structure 14 must be eliminated.

The same β-lactone was also obtained when 11 was treated with dicyclohexylcarbodiimide

for 18 hrs at room temperature. So far we have been unable to prepare an analytically pure sample of 12, since it has always been contaminated with traces of hydroxy acid 11.

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