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A SYNTHESIS OF 16β,17β-IMINOANDROSTANES

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The variable conformational and steric influences in the steroid nucleus necessitate a variation in the choice of reagents used for the synthesis of fused steroidal aziridines. Although iodine isocyanate readily reacts with Δ^2-steroids[1] it is inapplicable to most other steroid olefins and leads to very low yields of 16β, 17β-iminoandrostan-3β-ol from the corresponding 16-androstene. We wish to report a convenient method to fuse the interesting aziridine ring system[2] to the biologically important β-face of the steroidal D-ring.[3]

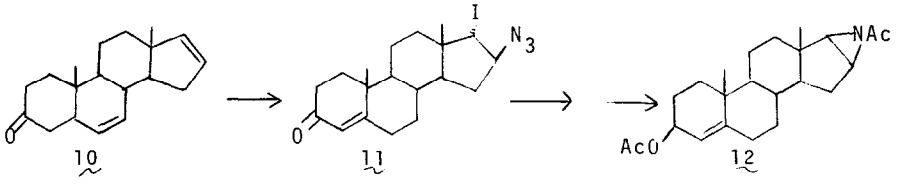
Iodine azide[4] attacks 3-β-acetoxy-16-androstene (1) from the α-side and regiospecifically[5] to give 90% yield 3β-acetoxy-16β-azido-17α-iodoandrostane (2) [mp 157-158°; ir 2100, 1740, 1250, and 1030 cm^{-1}; nmr τ5.33 (m broad, 2, $W_{\frac{1}{2}}$=18 Hz), 5.10 (d, 1, J=1.5Hz, 17α-H), 7.99 (s, 3, CH_3CO_2-), 9.02 (s, 3, H-18), and 9.18 (s, 3, H-19)].[6] Exposure of 2 to an excess of LAH in ether afforded analytically pure 16β,17β-iminoandrostan-3β-ol (3) in 62% yield (mp shows the crystalline forms to transpose at ca. 75° before melting at 154-155°) . A two step synthesis via the diborane reduction of 2 to the iodo amine 4 gives 3 but in lower yield. The presence of the aziridine ring is easily proved by acetylation with acetic anhydride and pyridine to 5 (mp 153-153.5°; ir 1730, 1695, 1395, 1375, 1285, 1250 and 1026 cm^{-1}; nmr τ5.38 (s broad, 1, $W_{\frac{1}{2}}$20Hz, 3α-H), 6.98 (t,1,J=ca. 5Hz, 16α-H), 7.23 (d, 1, J=5Hz, 17α-H), 7.95 (s,CH_3CON), 8.01 (s,3, CH_3CO_2), and (s,6, H-18 and H-19). The single amide band at 1695 cm^{-1} quickly identifies a tertiary amide and the triplet-doublet pattern for the 16 and 17 proton is identical to the pattern of the 16β,17β-epoxide.[7] These spectra are characteristically different from those of the iodo amide 6 which confirm the 17α-location of the iodo group

by the retention of a doublet for the 17-proton (mp 156-157°; ir 3300, 3070w, 1730, 1645, 1545, 1240, 1150, 1083, 1020, 958, and 901 cm^{-1}; nmr τ2.05 (d broad, 1, NH), 5.30 (m,2,$W_{1/2}$=25Hz), 5.98 (d, 1, J=2Hz. 17a-H), 7.99 (s,3, $CH_3CO_2^-$), 8.03 (s,3, CH_3CON), 9.03 (s,3,H-18), and 9.18 (s,3,H-19).

The unquestionable structure proof of the 16β,17β-aziridine stereochemistry was assured by the independent stereorational synthesis [1→7→8→9→5] in which the nitrogen function was introduced on the β-side by the trans-opening of the α-epoxide 7.

Selective addition (even in the presence of 2 equiv. of iodine azide) to the 16-double bond of $\Delta^{4,16}$-andorstadien-3-one (10) is possible and some selective addition to the 16-double bond of $\Delta^{5,16}$-dienes were observed. 16β-Azido-17α-iodo-Δ^4-androsten-3-one (11) was converted by LAH to the 3-hydroxy-16β,17β-aziridines. The major isomer was easily purified by crystallization in the form of the N,O-diacetyl derivative 12 (mp 145-147°, ir 1725, 1690, 1650 sh, 1370, 1265, 1255 and 1018 cm^{-1}; nmr τ6.74 (s, $W_{1/2}$=3Hz, 4-H, protruding out of a multiplet, $W_{1/2}$=18Hz), 6.93 (t broad, 1, J=4.5Hz, 16α-H), 7.21 (d,1,J=5Hz), 17a-H), 7.92 (s,3, CH_3CON), 7.98 (s,3,$CH_3CO_2^-$), 8.96 (H-19), and 9.16 (H-18).

It should be added that the recent development of a high yield regioselective synthesis of 16-androstenes[8] greatly enhances the potential of this synthetic method. Thus we were able to obtain the 16-olefins 1 and 10 by treatment of 17-tosylhydrazones with methyl lithium in glyme without any interferring rearrangement of the neopentyl system.



10 11 12

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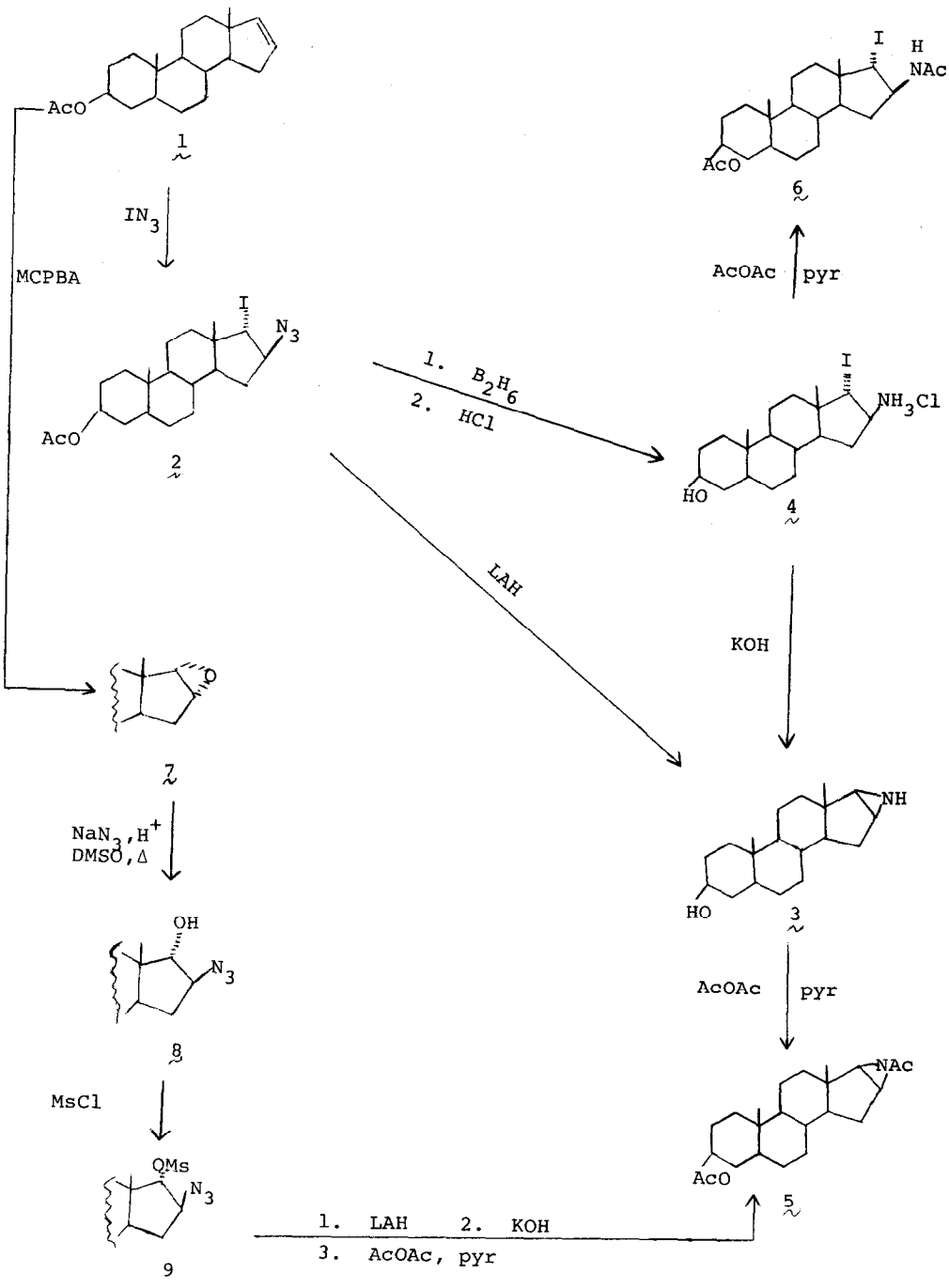
AcO
1
IN_3
MCPBA
I
N_3
AcO
2
1. B_2H_6
2. HCl
I
NH_3Cl
HO
4
LAH
KOH
I
H
NAc
AcO
6
AcOAc
pyr
O
7
NaN_3, H^+
DMSO, Δ
OH
N_3
8
MsCl
OMs
N_3
9
NH
HO
3
AcOAc
pyr
NAc
AcO
5
1. LAH 2. KOH
3. AcOAc, pyr

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6. Satisfactory analyses were obtained for all fully characterized compounds; ir spectra were taken in KBr.

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