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SYNTHESIS OF 14-DEOXY-14α-STROPHANTHIDIN

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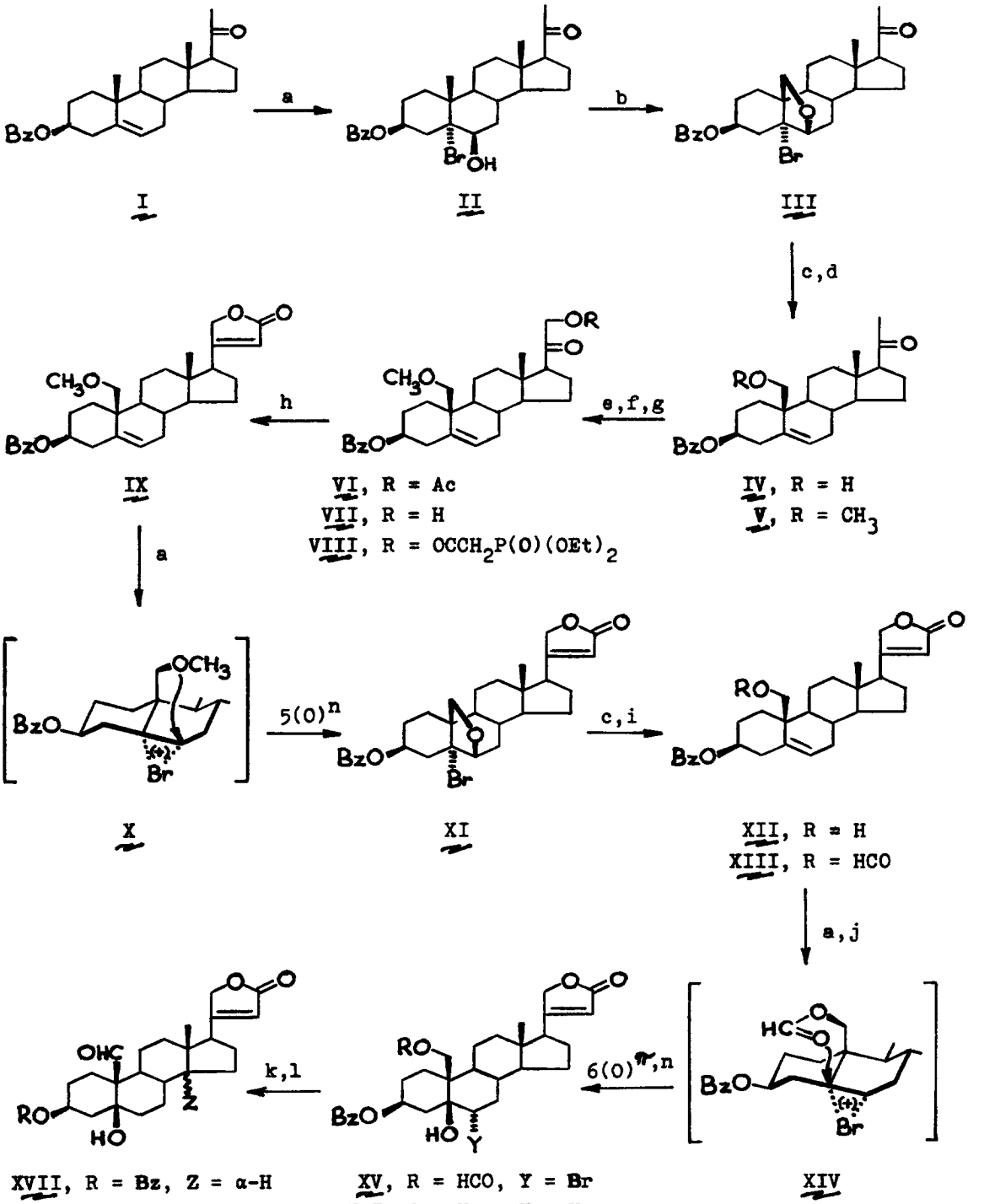
Abstract: Synthesis of the title compound (XVIII) from pregnenolone benzoate (I) is described. Characteristic features of this approach are the protection of the 19-hydroxyl as methyl ether and introduction of the 5β-hydroxyl by hypobromous acid addition with participation of the 19-substituent.

In the continuation of our work pursuing the goal of finding simpler partial synthetic routes to steroid cardiotonics, we turned our attention to the model experiments on the synthesis of strophanthidin (XIX). The aim of the present paper was to find a synthetic route for the construction of the substituted A/B-ring part of strophanthidin allowing, at the same time, synthesis of the side chain lactone ring. In the present paper we describe the synthesis of the model compound XVIII containing all these features. It differs from strophanthidin (XIX) by lacking the 14β-hydroxyl and by trans--junction of the rings C and D.

Addition of hypobromous acid to the pregnenolone benzoate (I) led to the diaxial bromohydrin II which on reaction with lead tetraacetate was cyclized to the 6β,19-epoxy derivative III (m.p. 250-251°C, $[\alpha]_D^{20}$ +52°). Reduction of the latter with zinc in boiling acetic acid smoothly afforded the 19-alcohol IV (m.p. 216-217°C, $[\alpha]_D^{20}$ +52°) which was methylated using sodium hydride and methyl iodide to give the methyl ether V (m.p. 155-157°C, $[\alpha]_D^{20}$ +33°). The latter compound was acetoxylated in excellent yield with lead tetraacetate in the presence of boron trifluoride etherate to give the 21--acetoxy derivative VI (m.p. 134-135°C, $[\alpha]_D^{20}$ +32°. ^{1}H-NMR: 0.68 s 18-H; 2.13 s CH_3CO_2; 3.28 s CH_3O; 3.30 d and 3.64 d, J = 10 Hz, 19-H; 4.44 d and 4.78 d, J = 16 Hz, 21-H). The acetoxy group in VI was selectively hydrolyzed under acidic conditions to the 21-alcohol VII (m.p. 155-156°C, $[\alpha]_D^{20}$ +25°).


a
b
c,d
e,f,g
h
a
5(O)n
c,i
a,j
6(O)π,n
k,l
I
II
III
IV, R = H
V, R = CH3
VI, R = Ac
VII, R = H
VIII, R = OCCH2P(O)(OEt)2
IX
X
XI
XII, R = H
XIII, R = HCO
XIV
XV, R = HCO, Y = Br
XVI, R = H , Y = H
XVII, R = Bz, Z = α-H
XVIII, R = H , Z = α-H
XIX, R = H , Z = β-OH

Scheme - Reagents:

a NBA, $HClO_4$, Diox.; b $(AcO)_4Pb$, I_2, Bzn; c Zn, AcOH; d MeI, NaH, DME; e $(AcO)_4Pb$, $BF_3.Et_2O$, MeOH, Bzn; f $HClO_4$, MeOH, $CHCl_3$; g DCCI, $(EtO)_2P(O)CH_2CO_2H$, Bzn; h t-BuOK, DME; i HCO_2H; j Ra-Ni, EtOH; k CrO_3, Me_2CO; l K_2CO_3, MeOH.

The 21-alcohol VII was esterified with diethylphosphonoacetic acid in the presence of dicyclohexylcarbodiimide and the resulting ester VIII was cyclized without isolation with potassium tert.-butoxide to yield the unsaturated lactone IX (m.p. 220-222°C, $[\alpha]_D^{20}$ -28°, IR: 1278, 1628, 1712, 1749, 1768 cm^{-1}).

The hydroxyl group at position 19 was recovered by a two-step procedure: Treatment of the methoxy derivative IX with hypobromous acid afforded in high yield the bromoepoxide XI (m.p. 284-285°C, $[\alpha]_D^{20}$ -3°), which on reduction with zinc in hot acetic acid smoothly gave the 19-alcohol XII (m.p. 256-257 °C, $[\alpha]_D^{20}$ -15°). The reaction with hypobromous acid proceeds via the bromonium ion X which is opened with $5(0)^n$ participation by an attack of the 19-methoxyl group (for notation cf. ref.[1]). It is pertinent to note that we observed the easy and extremely mild recovery of unsaturated alcohols from the corresponding methyl ethers also in other cases[1-3]. We believe that this procedure is likely to become a general method for protection of unsaturated alcohols, provided the steric arrangement enables the $5(0)^n$ participation.

For introduction of the 5β-hydroxyl we used a novel simple method which we recently developed[4]: The alcohol XII was converted to the formate XIII (m.p. 215-218°C, $[\alpha]_D^{20}$ -40°) which was treated with hypobromous acid. The addition proceeds with $6(0)^{\pi,n}$ participation of the carbonyl oxygen in the cleavage of the intermediary bromonium ion XIV to give the diequatorial bromohydrin XV (m.p. 148-152°C, $[\alpha]_D^{20}$ +18°. ^{1}H-NMR: 0.62 s 18-H; 4.50 s 19-H; 4.58 m 6β-H overlapped by other signals; 4.73 brd s 21-H; 5.52 m, W = 15 Hz, 3α-H; 5.85 m, W = 8 Hz, 22-H; 8.15 s HCO_2). Subsequent treatment of the bromohydrin XV with Raney-Ni removed both the bromine atom and the formate group to give the diol XVI (m.p. 183-185°C; $[\alpha]_D^{20}$ +14°, IR: 1280, 1702, 1743,

1775, 3220, 3380 cm^{-1}) in the single step.

Oxidation of the 19-alcohol XVI with Jones' reagent furnished the 19-aldehyde XVII (m.p. 203-204°C, $[\alpha]_D^{20}$ +25°, IR: 1285, 1698, 1738, 1772, 2728, 3540 cm^{-1}) in which the benzoyloxy group was smoothly saponified with potassium hydrogen carbonate to afford the target compound XVIII, a deoxy analog of strophanthidin XIX as an amorphous foam ($[\alpha]_D^{20}$ +22°, IR: 1629, 1748, 1785, 2761, 3475, 3610 cm^{-1}).

The present synthesis shows that the construction of the A/B-ring part of strophanthidin molecule allowing at the same time synthesis of the side chain lactone ring can be conducted in a relatively simple way. The conversion of the compound XVIII and some intermediates of this synthesis to strophanthidin is in progress in this laboratory.

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