Synthesis of 3β-Methoxy-5α,14α-card-20(22)-enolide from 3β-Methoxy-5α-androstan-17-one. A Method for the Construction of the Cardenolide Side-chain

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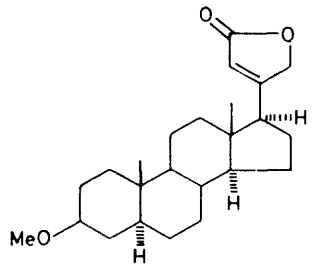
Summary The cardenolide side-chain has been constructed on the androstane skeleton *via* Knoevenagel condensation of the 17-oxo-derivative (**2a**) with ethyl cyanoacetate, three-step transformation of the resultant product (**2b**) to the protected hydroxy-aldehyde (**4**), followed by the formation of the cyanohydrin (**5a**), hydrolytic butenolide ring closure, and dehydration.

THE construction of the butenolide side-chain at the 17β-position of the androstane skeleton is a major problem in the synthesis of cardenolides and attracts considerable attention.[1] All methods recently developed for this purpose,[2] with one exception,[3] are based on 20-oxy-pregnane derivatives as starting materials. We now report a simple method for cardenolide synthesis starting from easily available 17-oxo-androstane derivatives, exemplified by the synthesis of compound (**1**).

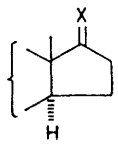
The condensation[4] of 3β-methoxy-5α-androstan-17-one (**2a**) with ethyl cyanoacetate gave the cyano-ester† (**2b**) as a mixture of *E*- and *Z*-isomers[5] [96% yield; major isomer, m.p. 174—176 °C; λ_{max} (EtOH) 238 nm, ϵ 12,300], which was used for the next step without purification. Treatment of (**2b**) with an excess of sodium borohydride in ethanol–tetrahydrofuran resulted[6] in saturation of the double bond, reduction of the ester group, and furnished the hydroxy-nitrile (**3a**) [97%; *m/e* 359 (M^+); δ ($CDCl_3$) 3·70 (2H, d, *J* 6 Hz, CH_2OH); ν_{max} (KBr) 3500 and 2250 cm^{-1}] as a mixture of isomers.‡ The stereochemistry of this product was elucidated as follows. The mixture of alcohol isomers (**3a**) was acetylated (acetic anhydride–pyridine), and the acetates (**3b**) were heated in dimethylformamide (DMF) in the presence of lithium carbonate (150 °C; 6 h). Pyrolysis gave the homogeneous α,β-unsaturated nitrile (**7a**) [93%, m.p. 112—113 °C; *m/e* 341 (M^+); δ ($CDCl_3$) 6·02 and 5·78 (2H, 2s, $C=CH_2$); ν_{max} (CCl_4) 2250 and 1600 cm^{-1}]. Oxidation of compound (**7a**) with potassium permanganate–tetrabutylammonium chloride–benzene[7] afforded the known[8] carboxylic acid (**7c**) [identified as the methyl ester (**7d**), m.p. 157—159 °C; *m/e* 348 (M^+)]. These experiments showed that (**3a**) is a mixture of compounds which are stereoisomeric only at C-20, and also that the side-chain at C-17 has the β-orientation.

† All new compounds obtained in homogenous form or as a mixture of stereoisomers had the expected spectral data and satisfactory combustion analysis or high-resolution mass spectra.

‡ No separation of isomers on t.l.c. plates was noted (hexane–ethyl acetate or benzene–acetone as eluant).



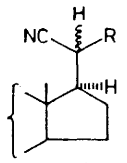
(1)



(2)

a; X = O

b; X = C(CN)CO$_2$Et

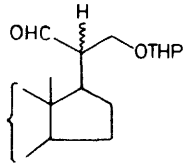


(3)

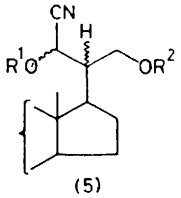
a; R = CH_2OH

b; R = CH_2OAc

c; R = CH_2OTHP



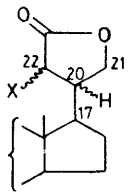
(4)



(5)

a; R^1 = H, R^2 = THP

b; R^1 = Ac, R^2 = THP

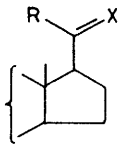


(6)

a; X = OH

b; X = OAc

c; X = Cl



(7)

a; R = CN, X = CH_2

b; R = CHO, X = CH_2

c; R = OH, X = O

d; R = OMe, X = O

The cyano-alcohol (**3a**) was converted into the tetrahydropyranyl ether (**3c**), which upon treatment[9] with 3·5 equiv. of di-isobutylaluminium hydride (hexane–toluene; −78 °C; 1 h), followed by standard work-up gave the aldehyde (**4**) [70—85% from (**3a**), *m/e* 446 (M^+); δ ($CDCl_3$) 9·80 (1H, m); ν_{max} (film) 1720 cm^{-1}]. On filtration of this product through a silica gel (MN 100—200 mesh ASTM) column a small amount (*ca.* 5%) of the α,β-unsaturated aldehyde (**7b**) [m.p. 123—126 °C; *m/e* 344 (M^+)] was formed and separated off.

The crude aldehyde (**4**) was treated in methanol with hydrogen cyanide generated *in situ* from an excess of potassium cyanide and conc. hydrochloric acid (room temp.; 30 min). The unstable, diastereoisomeric cyanohydrins (**5a**) formed in this way could not be fully characterised; however, the corresponding acetates (**5b**) showed the expected properties [*m/e* 515 (M^+); δ ($CDCl_3$) 5·70 (1H, m, 22-H in diastereomeric compounds)].

At this stage of the synthesis the side-chain contains all the structural elements necessary for the hydrolytic ring closure to give the cardenolide ring. For this purpose the crude cyanohydrin (**5a**) was dissolved in ethanol containing hydrochloric acid, and the mixture was refluxed for 20 min. Structure (**6a**) was ascribed to the product, isolated in 76% yield, on the basis of its i.r. [ν_{max} (KBr) 3500 (OH) and 1785 (C=O) cm^{-1}] and n.m.r. spectra, and the spectral data of its acetate (**6b**) [ν_{max} ($CHCl_3$) 1785 and 1740 cm^{-1}; δ ($CDCl_3$) 5·39 and 5·21 (1H, 2 d, *J* 10 Hz, 22-H)].

The hydroxy-lactone (**6a**) upon treatment with thionyl chloride in pyridine (reflux; 1 h) gave the chloride (**6c**), which was dehydrochlorinated (DMF; lithium carbonate; 150 °C; 1·5 h) without purification. In this reaction the chiral centres at C-20 and C-22 were destroyed, and the butenolide (**1**) [m.p. 147—148 °C; *m/e* 372 (M^+); δ ($CDCl_3$) 5·90 (1H, br. s), 4·88 (2H, s), 3·34 (3H, s), 3·10 (1H, m), 0·80 (3H, s), and 0·60 (3H, s); ν_{max} (KBr) 1790, 1750, and 1630 cm^{-1}; λ_{max} (EtOH) 217 nm] was formed (90% from (**6a**)].

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