MODEL EXPERIMENTS IN THE SYNTHETIC APPROACH TO STROPHANTHIDIN: THE SYNTHESIS OF 3β,5-DIHYDROXY-5β-CHOLESTAN-19-AL*

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A five step synthesis of the title compound *XV* as a model substance for simple construction of the A/B ring part of strophantidin (*I*) is described. The key step of this synthetic approach is the hypobromous acid addition to the formate *V* which gives predominantly the diequoatorial bromohydrin *X* as a result of $6(O)^{\pi,n}$ participation of the 19-ester group in 5α,6α-bromonium ion *VII* cleavage. Treatment of *X* with Raney-Ni yields the 19-hydroxy derivative *XII* which on oxidation and hydrolysis gives the aldehyde *XV*.

The recent paper of Yoshii and coworkers[1] describing a synthesis of strophanthidin (*I*) prompted us to publish some model experiments presenting a novel way of introducing the β-oriented hydroxyl group into position 5 and describing a simple construction of the A/B ring part of the strophanthidin molecule.

To date, 5β-hydroxy steroids have been accessible from 4,5- or 5,6-unsaturated steroids via the corresponding 4β,5β-or 5β,6β-epoxides by reductive fission of the latter compounds[2-4]. The whole sequence does not give sufficient yields of the 5β--alcohols and, particularly for synthesis of strophanthidin, any improvement in accessibility of these compounds by an efficient and mild method is highly desirable. The new synthetic route to 5β-hydroxy steroids is based on our investigations of 19--acyloxy group participation in hypobromous acid addition to the 5,6-double bond[5]. Unlike 19-unsubstituted 5,6-unsaturated steroids (where the diaxial 5α-bromo-6β--hydroxy derivatives are formed predominantly[4]) the 19-acyloxy 5,6-unsaturated steroids give the diequatorial 5β-hydroxy-6β-bromo derivatives in excellent yields due to $6(O)^{\pi,n}$ participation (for notation *cf.*[5]) of the carbonyl group oxygen in the cleavage of the 5α,6α-bromonium ion *VI*.

In our experiments we started from 19-hydroxycholesteryl acetate (*III*) available from cholesterol. The simplest model was triol *XIII*. The latter was prepared from diacetate *IV* predominantly yielding the 5β-hydroxy-6α-bromo derivative *VIII* on hypobromous acid addition. Removal of the bromine atom from *VIII* was achieved

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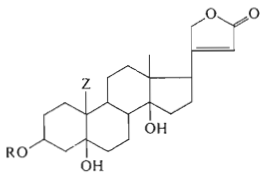
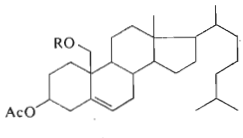
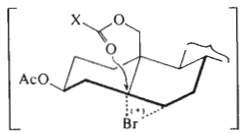
by treatment with Raney-nickel and afforded the triol diacetate *IX* (ref.[5]). Subsequent hydrolysis yielded the triol *XIII* representing a simple analogue of strophanthidol (*II*).



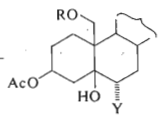
I, Z = CHO
II, Z = CH_2OH



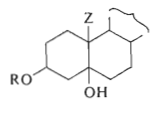
III, R = H
IV, R = Ac
V, R = HCO



VI, X = CH_3
VII, X = H



VIII, R = Ac, Y = Br
IX, R = Ac, Y = H
X, R = HCO, Y = Br
XI, R = HCO, Y = H
XII, R = H, Y = H



XIII, R = H, Z = CH_2OH
XIV, R = Ac, Z = CHO
XV, R = H, Z = CHO

For the synthesis of a model of strophanthidin (*I*) it was necessary to prepare a steroid containing an ester group at $C_{(19)}$ that could participate in the 5α,6α-bromonium ion cleavage and could then be easily hydrolyzed in the presence of the 3β-acetoxy group. The formyloxy group was found to meet both these conditions. 19-Hydroxycholesteryl acetate (*III*) was esterified by heating with 85% formic acid to yield the 19-formate *V*. On hypobromous acid addition this formate afforded the desired bromohydrin *X* (*via* the bromonium ion *VII*). This result demonstrates that the formate group can well participate by carbonyl oxygen in electrophilic addition. On reduction of the bromohydrin *X* with freshly prepared Raney-nickel both the bromine atom and the formate group were removed quantitatively to yield the pure triol monoacetate *XII*. On the other hand, reduction conducted with aged Raney-Ni

gave only a mixture of *XI* and *XII*. The compound *XII* was oxidized with chromium trioxide (Jones' or Corey's reagent[6]) to the aldehyde *XIV* which on hydrolysis of the 3β-acetoxy group afforded the dihydroxy aldehyde *XV*. This reaction sequence is a relatively simple route to construction of the A/B part of the strophanthidin molecule from a steroid precursor with a 3β-hydroxy-5,6-unsaturated structure.

EXPERIMENTAL

Melting points were determined on a Kofler block. Analytical samples were dried at 50°C/0·2 Torr (26 Pa). Optical measurements were carried out in chloroform with an error of ±3°. The IR spectra were recorded on a Zeiss UR 20 spectrometer in tetrachloromethane. The ^{1}H-NMR spectra were recorded on a Tesla BS 467 instrument (60 MHz) in deuteriochloroform at 30° with tetramethylsilane as internal reference. Chemical shifts are given in ppm. Apparent coupling constants (in Hz) were obtained from a first order analysis. The identity of samples prepared by different routes was checked by mixture melting point determination, by thin layer chromatography (TLC) and by infrared and ^{1}H-NMR spectra. Usual work up of an ethereal solution means washing the solution with 5% aqueous hydrochloric acid solution, water, 5% aqueous potassium hydrogen carbonate solution, water, drying with sodium sulfate and evaporation of the solvent *in vacuo*.

Cholest-5-ene-3β,19-diol 3-Acetate 19-Formate (*V*)

The alcohol *III* (1 g) was treated with 85% formic acid (30 ml) at 70°C for 1 h. The mixture was cooled, diluted with water and the product extracted with ether. The ethereal layer was washed with water, 5% aqueous potassium hydrogen carbonate solution, water, dried with sodium sulfate and the solvent evaporated. The residue was crystallized from a mixture of acetone, methanol and water to yield the formate *V* (796 mg), m.p. 128—129°C. For $C_{30}H_{48}O_4$ (472·7) calculated: 76·23% C, 10·24% H; found: 76·02% C, 10·15% H.

6α-Bromo-5β-cholestane-3β,5,19-triol 3-Acetate 19-Formate (*X*)

The olefin *V* (760 mg) was dissolved in dioxane (15 ml) and treated with 10% perchloric acid (1·5 ml) and N-bromoacetamide (360 mg) at room temperature for 30 min. The mixture was then diluted with water and the product extracted with ether. The ethereal layer was washed with water, aqueous 5% potassium hydrogen carbonate solution, water, aqueous sodium thiosulfate solution, water, dried with sodium sulfate and the solvent was evaporated. The residue was chromatographed on a silica gel column (50 g) using a mixture of light petroleum and ether (93 : 7) for elution of lipophilic impurities and a mixture of light petroleum, ether and acetone (87 : 10 : 3) for elution of the desired compound. Corresponding fractions were collected and evaporated to yield the pure amorphous bromohydrin *X* (570 mg), $[\alpha]_D^{20}$ +26° (*c* 3·2). ^{1}H-NMR spectrum: 0·64 (3 H, s, 18-H), 4·46 (2 H, s, 19-H), 2·09 (3 H, s, CH_3CO_2), 8·11 (1 H, s, HCO_2), 5·26 (1 H, m, $W_{1/2}$ = 8 Hz, 3α-H), 4·62 (1 H, dd, $J_{6\beta,7\alpha}$ = 11 Hz, $J_{6\beta,7\beta}$ = 5 Hz, 6β-H). ^{1}H-NMR spectrum after TAI treatment: 3·26 (1 H, dd, J_{gem} = 16 Hz, $J_{4\beta,3\alpha}$ = 1 Hz, 4β-H), 5·37 (1 H, m, 6β-H), 8·43 (1 H, s, NH). For $C_{30}H_{49}BrO_5$ (569·6) calculated: 63·26% C, 8·67% H, 14·03% Br; found: 63·07% C, 8·53% H, 14·21% Br.

5β-Cholestane-3β,5,19-triol 3-Acetate 19-Formate (*XI*)

The bromohydrin *X* (70 mg) was dissolved in ethanol (2 ml), an aged Raney-Nickel preparation (100 mg) was added and the mixture was stirred at 70°C for 36 h (checked by TLC). The inorganic material was removed by filtration, washed with methanol and acetone, the filtrate was evaporated under reduced pressure, the residue dissolved in ether and the ethereal solution worked up as usual. The residue was chromatographed on one preparative silica gel plate (20 × 20 cm) using double development with a mixture of light petroleum, ether and acetone (80 : 10 : 10). The liphophilic zone was worked up to give the formate *XI* (29 mg), m.p. 122—123°C (aqueous acetone), $[\alpha]_D^{20}$ +42° (*c* 2·6). ^{1}H-NMR spectrum: 0·62 (3 H, s, 18-H), 4·52 (2 H, s, 19-H), 2·05 (3 H, s, CH_3CO_2), 8·25 (1 H, s, HCO_2), 5·23 (1 H, m, $W_{1/2}$ = 9 Hz, 3α-H). For $C_{30}H_{50}O_5$ (490·7) calculated: 73·43% C, 10·27% H; found: 73·27% C, 10·29% H. The polar zone gave after collection and elution the diol *XII* (18 mg).

5β-Cholestane-3β,5,19-triol 3-Monoacetate (*XII*)

The bromohydrin *X* (550 mg) was dissolved in ethanol (10 ml) and stirred with freshly prepared Raney-Nickel (300 mg) at 70°C for 7 h (checked by TLC). The mixture was worked up as given for *XI* to yield the pure oily diol *XII* (430 mg), $[\alpha]_D^{20}$ +44° (*c* 2·1). ^{1}H-NMR spectrum: 0·58 (3 H, s, 18-H), 2·05 (3 H, s, CH_3CO_2), 5·16 (1 H, m, $W_{1/2}$ = 9 Hz, 3α-H). The signal of 19-H is overlapped by the signals of other protons. ^{1}H-NMR spectrum after treatment with trichloroacetyl isocyanate: 4·68 (2 H, s, 19-H). For $C_{29}H_{50}O_4$ (462·7) calculated: 75·28% C, 10·89% H; found: 75·44% C, 10·81% H.

5β-Cholestane-3β,5,19-triol (*XIII*)

A solution of the diacetate *IX* (100 mg) and potassium carbonate (100 mg) in methanol (5 ml) and water (1 ml) was refluxed for 1 h. About 3/4 h of the solvents were removed under reduced pressure, the mixture was treated with ether and water, the ethereal layer was washed with water, dried with sodium sulfate and the solvent was evaporated. The residue was crystallized from aqueous methanol to yield the triol *XIII* (60 mg), m.p. 146—147°C, $[\alpha]_D^{20}$ +37° (*c* 1·7). ^{1}H-NMR spectrum: 0·62 (3 H, s, 18-H), 4·25 (3 H, brd m, 19-H and 3α-H overlapped.) For $C_{27}H_{48}O_3$ (420·7) calculated: 77·09% C, 11·50% H; found: 76·98% C, 11·32% H.

3β-Acetoxy-5-hydroxy-5β-cholestan-19-al (*XIV*)

Method A: The alcohol *XII* (200 mg) was dissolved in dichloromethane (10 ml) and oxidized, while stirring, with Corey's oxidant[6] (300 mg) at room temperature for 30 min. The mixture was filtered through a column of aluminum oxide, the solvent was evaporated and the residue was chromatographed on a silica gel column (20 g) using a mixture of light petroleum and ether (93 : 7) for elution of lipophilic impurities and with a mixture of light petroleum, ether and acetone (88 : 10 : 2) for elution of the desired compound. Corresponding fractions were collected and evaporated. The residue was crystallized from aqueous methanol to yield the aldehyde *XIV* (74 mg), m.p. 134—135°C, $[\alpha]_D^{20}$ +48° (*c* 1·7). ^{1}H-NMR spectrum: 0·62 (3 H, s, 18-H), 10·17 (1 H, s, 19-H), 2·06 (3 H, s, CH_3CO_2), 5·23 (1 H, m, $W_{1/2}$ = 8 Hz, 3α-H). IR spectrum: 1242, 1714, 1742, 2760, 3589 cm^{-1}. For $C_{29}H_{48}O_4$ (460·7) calculated: 75·61% C, 10·50% H; found: 75·43% C, 10·62% H.

Method B: The alcohol *XII* (100 mg) was dissolved in acetone (3 ml) and treated with excess Jones' reagent at room temperature for 5 min. The excess of reagent was decomposed with

methanol, the mixture was diluted with ether and water, the ethereal solution was washed with water and 5% aqueous potassium hydrogen carbonate solution, dried and the solvent was evaporated. The residue was crystallized from aqueous methanol to yield the aldehyde *XIV* (71 mg), m.p. 134—135°C.

3β,5-Dihydroxy-5β-cholestan-19-al (*XV*)

A solution of the acetate *XIV* (40 mg) and potassium carbonate (50 mg) in methanol (4 ml) and water (1 ml) was refluxed for 1 h. About 3/4 of the solvent were removed under reduced pressure, the residue was treated with ether and water, the ethereal layer was washed with water, dried with sodium sulfate and the solvent was evaporated. The residue was crystallized from aqueous methanol to yield *XV* (28 mg), m.p. 235—240°C (aq. methanol), $[\alpha]_D^{20}$ +44° (*c* 2·0). IR spectrum (chloroform): 1711, 2760, 3475, 3610 cm^{-1}. For $C_{27}H_{46}O_3$ (418·7) calculated: 77·46% C, 11·07% H; found: 77·21% C, 10·96% H.

The analyses were carried out in the Analytical Laboratory of this Institute (head Dr J. Horáček). The IR spectra were recorded by Mrs K. Matoušková and Mr P. Formánek and interpreted by Dr S. Vašíčková. The ^{1}H-NMR *spectra were recorded and interpreted by Dr M. Synáčková.*

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