SYNTHESIS OF 14-DEOXY-14α-STROPHANTHIDOL

Pavel Kočovský and Václav Černý

Institute of Organic Chemistry and Biochemistry,
Czechoslovak Academy of Sciences, 166 10, Prague 6

Received May 14th, 1979

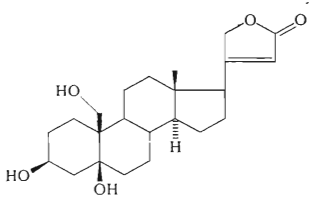
A thirteen-step synthesis of 3β,5,19-trihydroxy-5β,14α-card-20(22)-enolide (*I*, title compound) from 3β-acetoxy-5-pregnen-20-one (*V*) is described. A characteristic feature of this approach is the introduction of the 5β-hydroxyl group by hypobromous acid addition to the 5,6-unsaturated--19-acetoxy derivative *XV* which proceeds with 6(O)$^{\pi}$ ^{n} participation of the acetoxy group (*XV* → → *XVI* → *XVII*).

In our earlier papers[1,2] we described a novel route for the introduction of 5β-hydroxyl group into the steroid skeleton. This method is based on neighboring group participation between the $C_{(19)}$ substituent and the double bond in position 5, 6 and may be considered as potentially useful for the synthesis of 5β-hydroxycardenolides[3]. In order to verify this assumption we used this method for the preparation of 14--deoxy-14α-strophanthidol (*I*), a model compound that is closely related to the naturally occurring strophanthidol[4] (*II*). This paper presents a report on this synthesis.

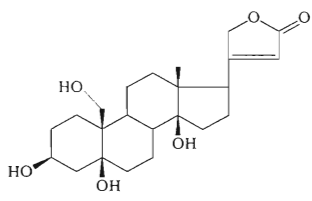
Pregnenolone acetate (*V*) was used as the starting compound. The functionalization at $C_{(19)}$ and $C_{(21)}$ was necessarily connected with the problem of differentiating the reactivity of the oxygen-containing functional groups at positions 3, 19 and 21 in the type-*III* compound. One possibility of protecting the (potential) hydroxyl group at $C_{(19)}$ was the introduction of the 5α-bromo-6β,19-epoxy moiety, provided the reaction was performed at the beginning of the reaction sequence (type *IV*). The problem of introducing the two remaining ester groups at $C_{(3)}$ and $C_{(21)}$ with different reactivity could then be readily solved.

Pregnenolone acetate (*V*) was converted into the epoxide *VII via* the bromohydrin *VI* in the conventional manner[5]. The compound *VII* could not be readily purified by crystallization and chromatography was necessary for obtaining the pure specimen.[6] However, alkaline hydrolysis of the crude product of $C_{(19)}$-functionalization *VII* gave the alcohol *VIII*; the good crystallization ability of *VIII* permitted its preparation from crude acetate *VII* without chromatography. The benzoate *IX* was prepared in the usual manner and its acetoxylation with lead tetraacetate in the presence of boron trifluoride etherate and methanol gave the 21-acetoxy derivative

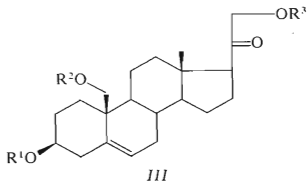
* Part CCXXVIII in the series On Steroids; Part CCXXII: This Journal *45*, 584 (1980).



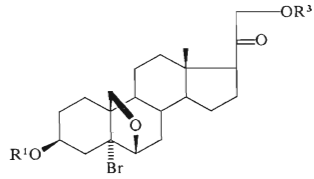
I



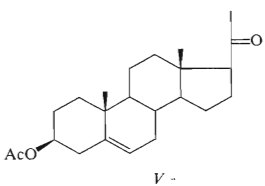
II



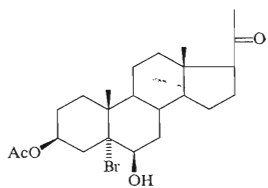
III



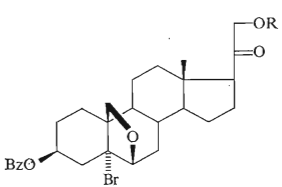
IV



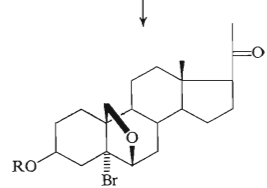
V



VI



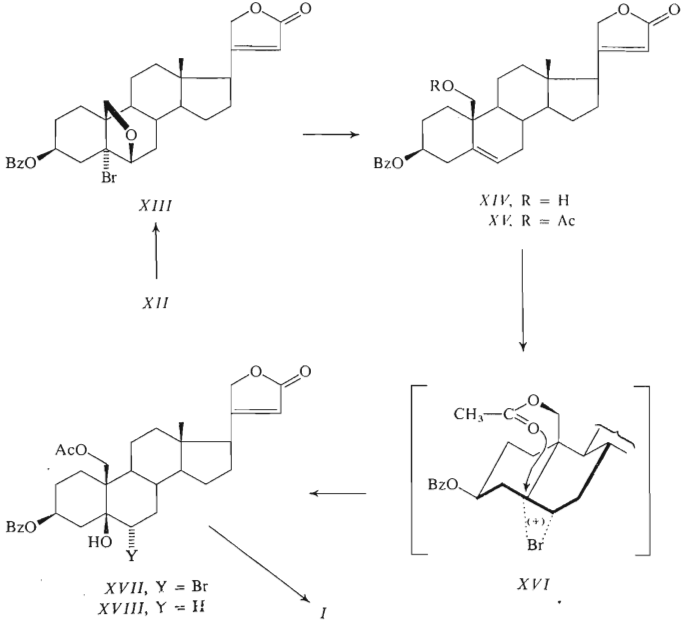
X, R = Ac
XI, R = H
XII, R = OC—CH_2—P(O)$(OC_2H_5)_2$



VII, R = Ac
VIII, R = H
IX, R = Bz

X in excellent yield. Selective hydrolysis with perchloric acid smoothly afforded the 21-hydroxy derivative *XI* which was esterified with diethyl phosphonoacetic acid in the presence of N,N'-dicyclohexylcarbodiimide[7]. On Wittig–Horner cyclization, the ester *XII* gave the cardenolide *XIII* in good yield.

Cleavage of the epoxide ring and removal of the bromine atom in *XIII* was achieved by treatment with zinc in acetic acid in the conventional manner.[6] This step and the following acetylation of the alcohol *XIV* proceeded without difficulty to give the compound *XV*. Addition of hypobromous acid to the olefin *XV* gave the diequatorial bromohydrin *XVII* in 60% yield. This unusual, but desired, reaction course is due to $6(O)^{\pi,n}$ participation[1–3] of the 19-acetoxy group in 5α,6α-bromonium ion cleavage, as depicted in formula *XVI*. The bromine atom in *XVII* was removed with Raney-Ni in 62% yield. In the last step, both ester groups were hydrolyzed with potassium hydrogen carbonate in a mild and smooth reaction to give the triol *I*. The easy hydrolysis of the axial benzoyloxy group is of interest and is obviously due to the accelerating influence of 5β-hydroxyl.



XIII

XII

XIV, R = H
XV, R = Ac

XVI

XVII, Y = Br
XVIII, Y = H

I

EXPERIMENTAL

Melting points were determined on a Kofler block. Analytical samples were dried at 53°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*.

3β,5,19-Trihydroxy-5β,14α-card-20(22)-enolide (*I*)

The diester *XVIII* (60 mg) in methanol (7 ml) and water (1 ml) was refluxed with potassium hydrogen carbonate (30 mg) for 30 min. The volume of the mixture was reduced to about 2 ml, 5% aqueous hydrochloric acid (5 ml) was added, the product was taken up in a mixture of chloroform and ether, the organic layer was washed with water, dried and evaporated. The residue was chromatographed on one preparative silica gel plate (20 × 20 cm) using a mixture of benzene, ether and acetone (70 : 10 : 20) as eluent. Corresponding zone was collected, washed with a mixture of benzene and ether and the filtrate was evaporated to yield the oily triol *I* (37 mg), $[\alpha]_D^{20}$ +26° (*c* 0·7). ^{1}H-NMR spectrum: 0·63 (3 H, s, 18-H), 4·30 (3 H, brd m, 19-H and 3α-H), 4·72 (2 H, brd s, 21-H), 5·82 (1 H, m, $W = 9$ Hz, 22-H). For $C_{23}H_{34}O_5$ (390·5) calculated: 70·74% C, 8·78% H; found: 70·59% C, 8·94% Br.

3β-Hydroxy-5-bromo-6β,19-epoxy-5α-pregnan-20-one (*VIII*)

A solution of the acetate[5] *VII* (15 g) and potassium hydroxide (10 g) in methanol (500 ml) was refluxed for 5 min, about one half of the solvent was removed *in vacuo*, water was added and the precipitated product was collected by suction. The solid material was dissolved in a mixture of ether and chloroform, the solution was washed with water, dried and the solvent was evaporated. The residue was crystallized from a mixture of chloroform and light petroleum to yield *VIII* (9·6 g), m.fl. 186—187°C, $[\alpha]_D^{20}$ +56° (*c* 1·9). ^{1}H-NMR spectrum: 0·65 (3 H, s, 18-H), 2·10 (3 H, s, 21-H), 3·67 (1 H, d, $J = 9$ Hz, 19-H), 3·97 (1 H, d, $J = 9$ Hz, 19-H), 4·05 (1 H, m, $W = 30$ Hz, 3α-H), 4·10 (1 H, m, $W = 7$ Hz, 6-H). For $C_{21}H_{31}BrO_3$ (411·4) calculated: 61·31% C, 7·60% H, 19·42% Br; found: 61·19% C, 7·46% H, 19·53% Br.

3β-Benzoyloxy-5-bromo-6β,19-epoxy-5α-pregnan-20-one (*IX*)

The alcohol *VIII* (9 g) in pyridine (50 ml) was treated with benzoyl chloride (6 g) at room temperature for 6 h. The excess reagent was decomposed with ice and water, the product taken up in chloroform and the solution worked up as usual. The residue was crystallized from a mixture of chloroform and methanol to yield *IX* (8·1 g), m.p. 251—252°C, $[\alpha]_D^{20}$ +54°, identical with the authentic sample[8].

3β-Benzoyloxy-5-bromo-6β,19-epoxy-21-acetoxy-5α-pregnan-20-one (*X*)

To a stirred solution of the ketone *IX* (10 g) in benzene (400 ml) the solution of methanol (19 ml) in benzene (60 ml), the solution of boron trifluoride etherate (26 ml) in benzene (60 ml), and powdered lead tetraacetate (12 g) were added simultaneously at room temperature in the course

of 3 h. The mixture was filtered, the filtrate was diluted with ether and water, and the ethereal solution was worked up as usual. The residue was dissolved in a mixture of light petroleum and benzene (3 : 1) and filtered through a column of aluminum oxide. The filtrate was evaporated and the residue was crystallized from a mixture of acetone, methanol and water to yield *X* (7·4 g), m.p. 172–173°C, $[\alpha]_D^{20}$ +61° (*c* 1·7). For $C_{30}H_{37}BrO_6$ (573·5) calculated: 62·83% C, 6·50% H, 13·93% Br; found: 62·71% C, 6·40% H, 14·08% Br.

3β-Benzoyloxy-5-bromo-6β,19-epoxy-21-hydroxy-5α-pregnan-20-one (*XI*)

The acetate *X* (7 g) was dissolved in a mixture of chloroform (100 ml) and methanol (300 ml) and treated with a solution of 70% perchloric acid (4 ml) in water (4 ml) at 50°C for 12 h (checked by TLC). The solution was concentrated *in vacuo*, diluted with chloroform and ether, washed with water, aqueous 5% potassium hydrogen carbonate solution, water, dried and the solvent evaporated. The residue was crystallized from a mixture of light petroleum and ether to yield *XI* (4·0 g), m.p. 206–209°C, $[\alpha]_D^{20}$ +46° (*c* 1·8). ^{1}H-NMR spectrum: 0·67 (3 H, s, 18-H), 3·72 (1 H, d, *J* = 9 Hz, 19-H), 4·03 (1 H, d, *J* = 9 Hz, 19-H), 4·16 (1 H, m, 6α-H, overlapped by the signals of 21-H), 4·17 (2 H, d, *J* = 5 Hz, 21-H), 5·40 (1 H, m, *W* = 35 Hz, 3α-H). For $C_{28}H_{35}BrO_5$ (531·5) calculated: 63·28% C, 6·64% H, 15·03% Br; found: 63·17% C, 6·49% H, 15·11% Br.

3β-Benzoyloxy-5-bromo-6β,19-epoxy-5α,14α-card-20(22)-enolide (*XIII*)

A solution of the alcohol *XI* (4·0 g), diethylphosphonoacetic acid (4·0 g) and N,N′-dicyclohexylcarbodiimide (3·5 g) in benzene (250 ml) and pyridine (0·1 ml) was stirred at room temperature for 6 h. N,N′-Dicyclohexylurea was filtered off, the solution evaporated to yield the crude phosphonate *XII*. The phosphonate was dissolved in 1,2-dimethoxyethane (40 ml) and stirred with potassium tert-butoxide (1 g) at room temperature for 1 h. The mixture was diluted with ether, acidified with 5% aqueous hydrochloric acid, the solution was washed with water, dried, and the solvent evaporated. The residue was dissolved in benzene and filtered through a column of alumina. The filtrate was evaporated to yield the crude *XIII* (3·2 g). A sample was crystallized from a mixture of acetone and n-heptane to yield the pure lactone *XIII*, m.p. 285–286°C, $[\alpha]_D^{20}$ −5° (*c* 2·0), ^{1}H-NMR spectrum: 0·67 (3 H, s, 18-H), 3·75 (1 H, d, *J* = 9 Hz, 19-H), 4·05 (1 H, d, *J* = 9 Hz, 19-H), 4·10 (1 H, m, *W* = 9 Hz, 6α-H), 5·45 (1 H, m, *W* = 30 Hz, 3α-H), 5·87 (1 H, m, *W* = 8 Hz, 22-H). For $C_{30}H_{35}BrO_5$ (555·5) calculated: 64·86% C, 6·35% H, 14·38% Br; found: 64·59% C, 6·28% H, 14·45% Br.

3β-Benzoyloxy-19-hydroxy-14α-carda-5,20(22)-dienolide (*XIV*)

A solution of the epoxide *XIII* (2·0 g) in a mixture of acetic acid (50 ml) and methanol (5 ml) was stirred with powdered zinc (5 g) at 90°C for 5 min. The hot mixture was filtered to separate, the inorganic material, diluted with water and set aside overnight. The crystalline material was collected by suction, washed with aqueous methanol and air dried to yield *XIV* (1·1 g), m.p. 256–257°C, $[\alpha]_D^{20}$ −15° (*c* 1·1). ^{1}H-NMR spectrum: 0·70 (3 H, s, 18-H), 3·26 (1 H, d, *J* = 12 Hz, 19-H), 3·95 (1 H, d, *J* = 12 Hz, 19-H), 4·76 (2 H, brd s, 21-H), 5·10 (1 H, m, *W* = 30 Hz, 3α-H), 5·81 (1 H, m, *W* = 14 Hz, 6-H), 5·83 (1 H, m, *W* = 8 Hz, 22-H). For $C_{30}H_{36}O_5$ (476·6) calculated: 75·60% C, 7·61% H; found: 75·43% C, 7·56% H.

3β-Benzoyloxy-19-acetoxy-14α-carda-5,20(22)-dienolide (*XV*)

The alcohol *XIV* (300 mg) was acetylated with acetic anhydride (0·5) in pyridine (3 ml) at room temperature for 4 h. The excess reagent was decomposed with ice and water, the product taken up in ether and the ethereal solution was worked up as usual. The residue was crystallized from

a mixture of methanol, acetone and water to yield *XV* (270 mg), m.p. 175–177°C, $[\alpha]_D^{20}$ −43°. ^{1}H-NMR spectrum: 0·67 (3 H, s, 18-H), 2·05 (3 H, s, CH_3CO_2), 4·00 (1 H, d, J = 12 Hz, 19-H), 4·60 (1 H, d, J = 12 Hz, 19-H), 4·77 (2 H, brd s, 21-H), 4·90 (1 H, m, W = 30 Hz, 3α-H), 5·71 (1 H, m, W = 15 Hz, 6-H), 5·89 (1 H, m, W = 7 Hz, 22-H). For $C_{32}H_{38}O_6$ (518·7) calculated: 74·11% C, 7·39% H; found: 74·02% C, 7·47% H.

3β-Benzoyloxy-5-hydroxy-6α-bromo-19-acetoxy-5β,14α-card-20(22)-enolide (*XVII*)

A solution of the olefin *XV* (250 mg) in dioxane (5 ml) and water (0·5 ml) was treated with 10% aqueous perchloric acid (0·5 ml) and N-bromoacetamide (100 mg) at room temperature for 30 min. The mixture was diluted with water, the product taken up in ether, the ethereal layer was washed with water, 5% aqueous potassium hydrogen carbonate, aqueous sodium sulfate solution, and water, dried, and the solvent was evaporated. The residue was chromatographed on three preparative silica gel plates (20 × 20 cm) using a mixture of benzene, ether and acetone (85 : 10 : 5) as eluent. Corresponding zones were collected, eluted with a mixture of benzene and ether and the filtrate was evaporated to yield the foam of the bromohydrin *XVII* (180 mg), $[\alpha]_D^{20}$ +47° (*c* 1·4). ^{1}H-NMR spectrum: 0·62 (3 H, s, 18-H), 2·07 (3 H, s, CH_3CO_2), 4·42 (2 H, s, 19-H), 4·51 (1 H, m, 6β-H, overlapped by other signals), 4·74 (2 H, brd s, 21-H), 5·51 (1 H, m, W = 15 Hz, 3α-H), 5·85 (1 H, m, W = 7 Hz, 22-H). For $C_{32}H_{39}BrO_7$ (615·6) calculated: 62·44% C, 6·39% H, 12·98% Br; found: 62·23% C, 6·21% H, 13·04% Br.

3β-Benzoyloxy-5-hydroxy-19-acetoxy-5β,14α-card-20(22)-enolide (*XVIII*)

The bromohydrin *XVII* (150 mg) in ethanol (10 ml) was stirred and refluxed with freshly prepared Raney-Ni (200 mg) for 7 h. The inorganic material was filtered off, the solution was evaporated *in vacuo*, the residue dissolved in a mixture of chloroform and ether, the solution washed with water, dried and evaporated. The residue was chromatographed on a column of silica gel (20 g) with a mixture of benzene, ether and acetone (94 : 5 : 1). Corresponding fractions were collected and evaporated to yield the oily *XVIII* (81 mg), $[\alpha]_D^{20}$ +23° (*c* 5·8). ^{1}H-NMR spectrum: 0·63 (3 H, s, 18-H), 2·02 (3 H, s, CH_3CO_2), 4·45 (2 H, s, 19-H), 4·72 (2 H, brd s, 21-H), 5·50 (1 H, m, W = 16 Hz, 3α-H), 5·85 (1 H, m, W = 8 Hz, 22-H). For $C_{32}H_{40}O_7$ (536·7) calculated: 71·62% C, 7·51% H; found: 71·46% C, 7·39% H.

The analyses were carried out in the analytical laboratory of this Institute (under the direction of Dr J. Horáček). The IR *spectra were recorded by Mrs K. Matoušková and Mr P. Formánek and interpreted by Dr S. Vašíčková.* ^{1}H-NMR *spectra were measured by Mrs J. Jelínková.*

REFERENCES

1. Kočovský P., Černý V., Synáčková M.: This Journal *44*, 1487 (1979).
2. Kočovský P., Černý V.: This Journal *44*, 1500 (1979).
3. Kočovský P.: This Journal *44*, 2156 (1979).
4. Vystrčil A. in the book: *Chemie steroidních sloučenin* (V. Černý, Ed.), p. 909. Published by Nakladatelství ČSAV, Prague 1960.
5. Kalvoda J., Heusler K., Ueberwasser H., Anner G., Wettstein A.: Helv. Chim. Acta *46*, 1361 (1963).
6. Kočovský P., Černý V.: This Journal *44*, 2275 (1979).
7. Lehman H. G., Wiechert R.: Angew. Chem. Int. Ed. Engl. *7*, 300 (1968).
8. Kočovský P.: Tetrahedron Lett. *21*, 555 (1980).

Translated by the author (V. Č.).