A MODIFIED ROUTE TO INTERMEDIATES IN PARTIAL SYNTHESES OF DIGITOXIGENIN AND XYSMALOGENIN

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3β-Hydroxy-5,14-pregnadien-20-one (*X*) was prepared *via* 6β-methoxy-3α,5-cyclo-5α-pregn-14-en-20-one (*VII*). The compound *X* and its acetate *XI* are known intermediates in partial syntheses of digitoxigenin and xysmalogenin, respectively. In the present paper, conversion of *X* into the cardenolide *XVII* is also described.

In the synthesis of digitoxigenin (*III*) from 3β-hydroxy-5,16-pregnadien-20-one (*I*), protection and deprotection of the 3β-hydroxyl and 5,6-double bond is necessary[1]. A promising route to simplification of the procedure seemed to be conversion of the 3β-hydroxy-5,6-unsaturated system into a 6β-methoxy-3α,5α-cyclosteroid since it involves simultaneous protection of both the 3β-hydroxyl and 5,6-double bond.

In the present paper we describe verification of this approach. The experiments also demonstrated that isolation of all intermediates in pure condition is not necessary.

The known 3α,5-cyclo-6β-methoxy-5α-pregn-16-en-20-one (*IV*) prepared[2] from 3β-hydroxy-5,16-pregnadien-20-one (*I*), was subjected to allylic bromination with N-bromosuccinimide, the crude 15-bromo derivative *V* was dehydrobrominated with lithium iodide and lithium carbonate in dimethyformamide, the 16,17-double bond in the crude dienone *VI* was selectively reduced with sodium in propanol and the product was reoxidized with pyridinium chlorochromate. Chromatography of the mixture separated the products of hydrogenolysis, *VIII* and *IX*, and gave the desired 6β-methoxy-3α,5-cyclo-5α-pregn-14-en-20-one (*VII*). Treatment with aqueous perchloric acid converted the cyclosteroid *VII* into 3β-hydroxy-5,14-pregnadien-20-one (*X*) in the overall 25% yield from *IV*. This compound is an intermediate in the synthesis of digitoxigenin reported by Fritsch and coworkers[1] and of xysmalogenin reported by Yoshii and coworkers[3]. Subsequent steps in the route to digitoxigenin (*III*) differed from those used in the procedure of the German authors[1]. Benzoylation of the 3β-hydroxyl in the alcohol *X* was followed by acetoxylation to give the 21-acetoxy derivative *XIII*. This diester was selectively hydrolyzed with perchloric

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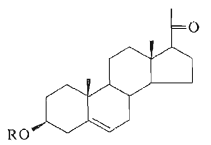

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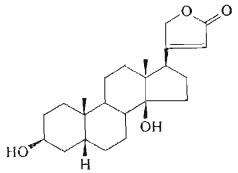
II, R = Ts



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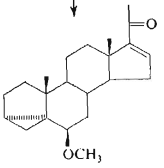

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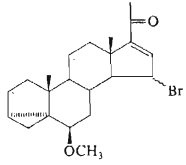

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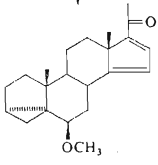
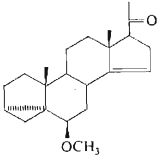


VI



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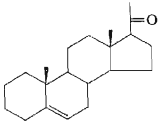
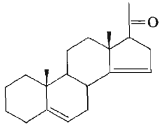
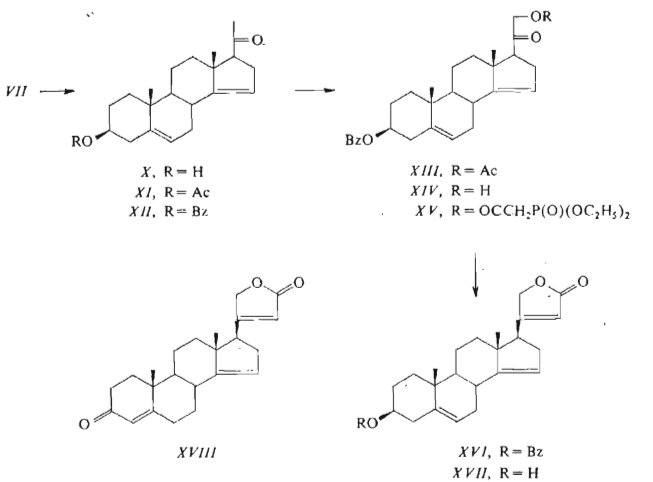


VIII



IX

acid in methanol to give the 21-hydroxy derivative *XIV* which was esterified with diethoxyphosphorylacetic acid in the presence of N,N'-dicyclohexylcarbodiimide. The ester *XV* thus obtained was cyclized with potassium tert-butoxide to yield the unsaturated lactone *XVI* which after alkaline hydrolysis gave anhydroxysmalogenin *XVII*. This compound constitutes a link to the α,β-unsaturated ketone *XVIII* which is another intermediate in the synthesis of digitoxigenin[1].



EXPERIMENTAL

Melting points were determined on a Kofler block. Analytical samples were dried at 50°C/26 Pa (0·2 Torr). Optical measurements were carried out in chloroform with an error of ±3°. The infrared spectra were recorded on a Zeiss UR 20 spectrometer in tetrachloromethane unless otherwise stated. The ^{1}H-NMR spectra were recorded on a Tesla BS 476 instrument (60 MHz) in deuteriochloroform at 30°C with tetramethylsilane as internal reference. Chemical shifts are given in ppm. Apparent coupling constants were obtained from the first order analysis. The mass spectra were recorded on a Jeol JMS D—100 spectrometer operating at 14—74 eV. The samples were introduced using a direct inlet at lowest temperature enabling evaporation. The elemental composition of ions was determined by accurate mass measurements. The identity of the 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 workup of an ethereal solution means washing the solution with 5% aqueous hydrochloric acid, water, a 5%

aqueous potassium hydrogen carbonate solution, water, drying with sodium sulfate and evaporation of the solvent *in vacuo*.

6β-Methoxy-3α,5-cyclo-5α-pregn-14-en-20-one (*VII*)

The 3α,5α-cyclosteroid[2] *IV* (13·4 g), N-bromosuccinimide (13·4 g), anhydrous potassium carbonate (40 mg) and azo-bis(isobutyronitrile) (40 mg) were refluxed and irradiated with a IR-lamp for 10 min. The flask was then chilled, the crystalline succinimide filtered off and the solvent removed under reduced pressure. The crude product was dissolved in dimethylformamide (100 ml), lithium iodide (6 g) and lithium carbonate (6 g) were added and the mixture heated at 90—100°C for 45 min. After being cooled, the mixture was diluted with water and the product taken up in ether, the solution was washed with water, potassium hydrogen carbonate, sodium thiosulfate and water, then dried with potassium carbonate and the solvent evaporated. The residue was dissolved in propanol (240 ml), heated to reflux temperature and sodium (12 g) was gradually added. After 2 h, the solution was diluted with propanol (120 ml) and sodium (12 g) was added to the boiling solution over a period of 3 h. After cooling, ice was added and the mixture neutralized with acetic acid, made weakly alkaline with potassium carbonate, taken up in ether, washed with water several times, dried with potassium carbonate and evaporated to dryness. The residue was repeatedly dissolved in benzene and the solvent evaporated. After the addition of dry sodium acetate (150 mg), the residue was dissolved in dichloromethane (200 ml) and oxidized with pyridinium chlorochromate (21 g) overnight with stirring. The solution was filtered through a layer of alumina (neutr.) and chromatographed on silica gel. Elution with a mixture of light petroleum and ether (95 : 5) furnished a non-polar fraction (1·5 g), followed by the main fraction (3·7 g) eluted with a mixture of the same solvents (90 : 10). A mixture of light petroleum and ether (95 : 15) eluted a more polar impurity (0·51 g). The main fraction was used in the subsequent step without purification. An analytical sample of *VII* was obtained from the main fraction by recrystallization from aqueous acetone in the presence of a drop of pyridine: m.p. 134 to 134·5°C, $[\alpha]_D^{20}$ +112° (*c* 1·8). ^{1}H-NMR spectrum: 0·88 (3 H, s, 18-H), 1·12 (3 H, s, 19-H), 2·37 (3 H, s, 21-H), 2·80 (1 H, m, $W = 10$ Hz, 6α-H), 3·56 (3 H, s, CH_3O), 5·40 (1 H, m, $W = 12$ Hz, 15-H). For $C_{22}H_{32}O_2$ (328·5) calculated: 80·44% C, 9·82% H; found: 80·21% C, 9·74% H.

5-Pregnen-20-one (*VIII*) and 5,14-Pregnadien-20-one (*IX*)

A part (390 mg) of the non-polar fraction was rechromatographed on silica gel (35 g) impregnated with silver nitrate. Elution with a mixture of light petroleum and ether (97 : 3) gave a fraction (60 mg) recrystallization of which from ethanol yielded *VIII*, m.p. 136—137°C; literature[4] reports m.p. 133—135°C. Mass spectrum: M^+ 300. ^{1}H-NMR spectrum: 0·59 (3 H, s, 18-H), 0·94 (3 H, s, 19-H), 2·08 (3 H, s, 21-H), 5·28 (1 H, m, $W_{1/2} = 10$ Hz, 6-H). The fraction (280 mg) eluted with a mixture of light petroleum and ether (50 : 50) was recrystallized from ethanol to give the diene *IX* (170 mg), m.p. 149—149·5°C, $[\alpha]_D$ —34° (*c* 1·6). IR-spectrum: 1359, 1645, 1670, 1711 cm^{-1}. Mass spectrum: M^+ 298. ^{1}H-NMR spectrum: 0·84 (3 H, s, 18-H), 0·96 (3 H, s, 19-H), 2·11 (3 H, s, 21-H), 5·28 (1 H, m, $W_{1/2} = 10$ Hz, 6-H), 5·12 (1 H, m, $W_{1/2} = 8$ Hz, 15-H). For $C_{21}H_{30}O$ (298·4) calculated: 84·51% C, 10·13% H; found: 84·76% C, 10·13% H.

3β-Hydroxy-5,14-pregnadien-20-one (*X*)

The 3α,5α-cyclosteroid *VII* (200 mg) in acetone (10 ml) was treated with 0·4% aqueous perchloric acid (1 ml) at reflux temperature for 2 h. The reaction mixture was left standing overnight. The separated crystals of *X* (170 mg, 89%) were filtered with suction, m.p. 215·6—218°C, $[\alpha]_D$ —2°

(*c* 1·4); literature[1] reports m.p. 204—208°C. IR-spectrum: 1047, 1360, 1647, 1703, 3050, 3610 cm^{-1}. ^{1}H-NMR spectrum: 0·85 (1 H, s, 18-H), 1·00 (3 H, s, 19-H), 2·13 (3 H, s, 21-H), 3·50 (1 H, mt, $W_{1/2}$ = 28 Hz, 3-H), 5·18 (1 H, mt, $W_{1/2}$ = 7 Hz, 15-H), 5·40 (1 H, mt, $W_{1/2}$ = = 10 Hz, 6-H). For $C_{21}H_{30}O_2$ (314·4) calculated: 80·21% C, 9·62% H; found: 80·52% C, 9·65% H.

3β-Benzoyloxy-5,14-pregnadien-20-one (*XII*)

The alcohol *X* (800 mg) was dissolved in pyridine (10 ml) and treated with benzoyl chloride (0·5 ml) at room temperature overnight. The mixture was decomposed with ice and water, the product was taken up in ether and the ethereal solution was worked up as usual. The residue was crystallized from a mixture of dioxane, aceton, methanol and water to yield the benzoate *XII* (300 mg), m.p. 246—247°C, $[\alpha]_D^{20}$ +19° (*c* 1·9). ^{1}H-NMR spectrum: 0·87 (3 H, s, 18-H), 1·06 (3 H, s, 19-H), 2·14 (3 H, s, 21-H), 4·15 (1 H, m, *W* = 30 Hz, 3α-H), 5·17 (1 H, m, *W* = 10 Hz, 15-H), 5·50 (1 H, m, *W* = 15 Hz, 6-H). For $C_{28}H_{34}O_3$ (418·6) calculated: 80·35% C, 8·19% H; found: 80·24% C, 8·06% H.

3β-Benzoyloxy-21-acetoxy-5,14-pregnadien-20-one (*XIII*)

A solution of methanol (2·5 ml) in benzene (10 ml), a solution of boron trifluoride etherate (6 ml) in benzene (10 ml) and powdered lead tetraacetate (1·5 g) were added simultaneously at room temperature to a stirred solution of the ketone *XII* (800 mg) in benzene (100 ml) in the course of 4 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 (1 : 1) and filtered through a column of aluminum oxide. The filtrate was evaporated and the residue was chromatographed on silica gel (50 g) using a mixture of light petroleum, benzene and ether (65 : 25 : 10) which eluted the unreacted ketone *XII* (60 mg). The mixture of light petroleum, benzene, ether and acetone (60 : 25 : 10 : 5) eluted the acetoxy derivative *XIII* (410 mg), m.p. 206—207°C (acetone, n-heptane), $[\alpha]_D^{20}$ +21° (*c* 2·1). ^{1}H-NMR spectrum: 0·92 (3 H, s, 18-H), 1·20 (3 H, s, 19-H), 2·17 (3 H, s, CH_3CO_2), 4·69 (2 H, d, *J* = 2 Hz, 21-H), 5·20 (1 H, m, *W* = 14 Hz, 15-H), 5·47 (1 H, m, *W* = 15 Hz, 6-H). For $C_{30}H_{36}O_5$ (476·6) calculated: 75·60% C, 7·61% H; found: 75·44% C, 7·59% H.

3β-Benzoyloxy-21-hydroxy-5,14-pregnadien-20-one (*XIV*)

The diester *XIII* (600 mg) was dissolved in a mixture of chloroform (15 ml) and methanol (30 ml) and treated with a solution of 72% perchloric acid (1 ml) in water (1 ml) at room temperature for 2 days. The volume of the mixture was reduced to about 1/10 *in vacuo*, diluted with ether and water and the ethereal layer was washed with water, 5% aqueous potassium hydrogen carbonate, water, then dried and the solvent evaporated. The residue was chromatographed on silica gel (30 g) using a mixture of light petroleum, ether and acetone (80 : 10 : 10) as eluent. Corresponding fractions were evaporated to yield the alcohol *XIV* (550 mg). A sample was crystallized from a mixture of chloroform and n-heptane, m.p. 236—237°C, $[\alpha]_D^{20}$ +19° (*c* 2·3). ^{1}H-NMR spectrum: 0·88 (3 H, s, 18-H), 1·08 (3 H, s, 19-H), 4·23 (2 H, brd s, 21-H), 4·90 (1 H, m, *W* = = 30 Hz, 3α-H), 5·22 (1 H, m, *W* = 11 Hz, 15-H), 5·48 (1 H, m, *W* = 16 Hz, 6-H). For C_{28}. .$H_{34}O_4$ (434·6) calculated: 77·39% C, 7·89% H; found: 77·13% C, 7·86% H.

3β-Benzoyloxy-carda-5,14,20(22)-trienolide (*XVI*)

A solution of the alcohol *XIV* (200 mg), diethoxyphosphoryloacetic acid (200 mg) and N,N'-dicyclohexylcarbodiimide (180 mg) and pyridine (0·01 ml) in benzene (12 ml) was stirred at room

temperature for 6 h. N,N'-Dicyclohexylurea was filtered off and the solution was evaporated to yield the crude phosphonate *XV*. The phosphonate was dissolved in 1,2-dimethoxyethane (4 ml) and stirred with potassium tert-butoxide (50 mg) at room temperature for 1 h. The mixture was diluted with ether, acidified with 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 and the residue was chromatographed on two preparative silica gel plates (20 × 20 cm) using a mixture of light petroleum, ether and acetone (75 : 15 : 15) as eluent. Corresponding zones were collected, eluted with a mixture of benzene and ether (1 : 1) and the filtrate was evaporated. The residue was crystallized from a mixture of acetone and n-heptane to give the lactone *XVI* (86 mg), m.p. 233—235°C, $[\alpha]_D^{20}$ —2° (*c* 1·7). ^{1}H-NMR spectrum: 0·82 (3 H, s, 18-H), 1·08 (3 H, s, 19-H), 4·75 (2 H, m, $W = 7$ Hz, 21-H), 4·90 (1 H, m, $W = 30$ Hz, 3α-H), 5·27 (1 H, m, $W = 10$ Hz, 15-H), 5·48 (1 H, m, $W = 15$ Hz, 6-H) 5·88 (1 H, m, $W = 10$ Hz, 22-H). For $C_{30}H_{34}O_4$ (458·6) calculated: 78·57% C, 7·47% H; found: 78·42% C, 7·51% H.

3β-Hydroxy-carda-5,14,20(22)-trienolide (*XVII*)

The benzoate *XVI* (60 mg) in methanol (6 ml) and water (0·6 ml) was refluxed with potassium carbonate for 5 h. The volume of the mixture was reduced *in vacuo* 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 phase 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. The respective zone was collected, washed with a mixture of benzene and ether (1 : 1) and the filtrate was evaporated. The residue was crystallized from a mixture of chloroform and light petroleum to yield the alcohol *XVII* (24 mg), m.p. 226—227°C, $[\alpha]_D^{20}$ —3° (*c* 2·0) in accordance with the literature[3].

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