NEW WAY TO DIGITOXIGENIN FROM 3β-ACETOXY-5-ANDROSTEN--17-ONE. STEREOSELECTIVE FREE RADICAL SUBSTITUTION OF IODIDE ATOM BY NITRILE GROUP AS A KEY STEP

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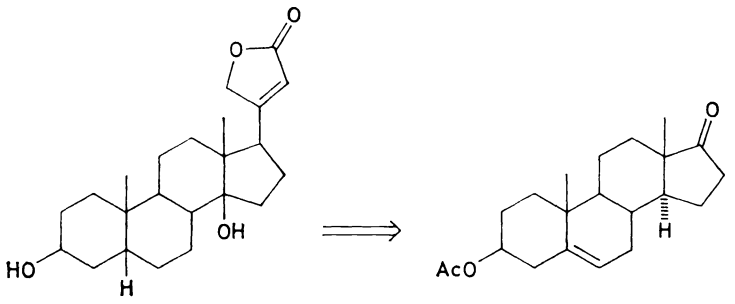
Dedicated to the memory of Professor František Šorm.

Digitoxigenin (*I*) was obtained from 17-oxoandrost-5-en-3β-yl acetate (*III*) using, as a key step, free radical stereoselective substitution of an iodine atom in *VI* by a nitrile group. Transformation of the nitrile group at C-17 into a pregnane side chain or a butenolide lactone ring took place without isomerization at C-17.

Since the discovery of the microbiological degradation[1] of the side chain of cholesterol and other steroids into androstane derivatives, the latter became convenient starting materials in the synthesis of many steroidal therapeutic agents.

Synthesis of digitoxigenin (*I*) (Scheme 1) and other cardenolides from Δ^5-androstane derivatives required solving three synthetic problems: *1*) hydrogenation of the 5(6)-double bond from the β-face in order to produce the *cis*-A/B ring junction, *2*)



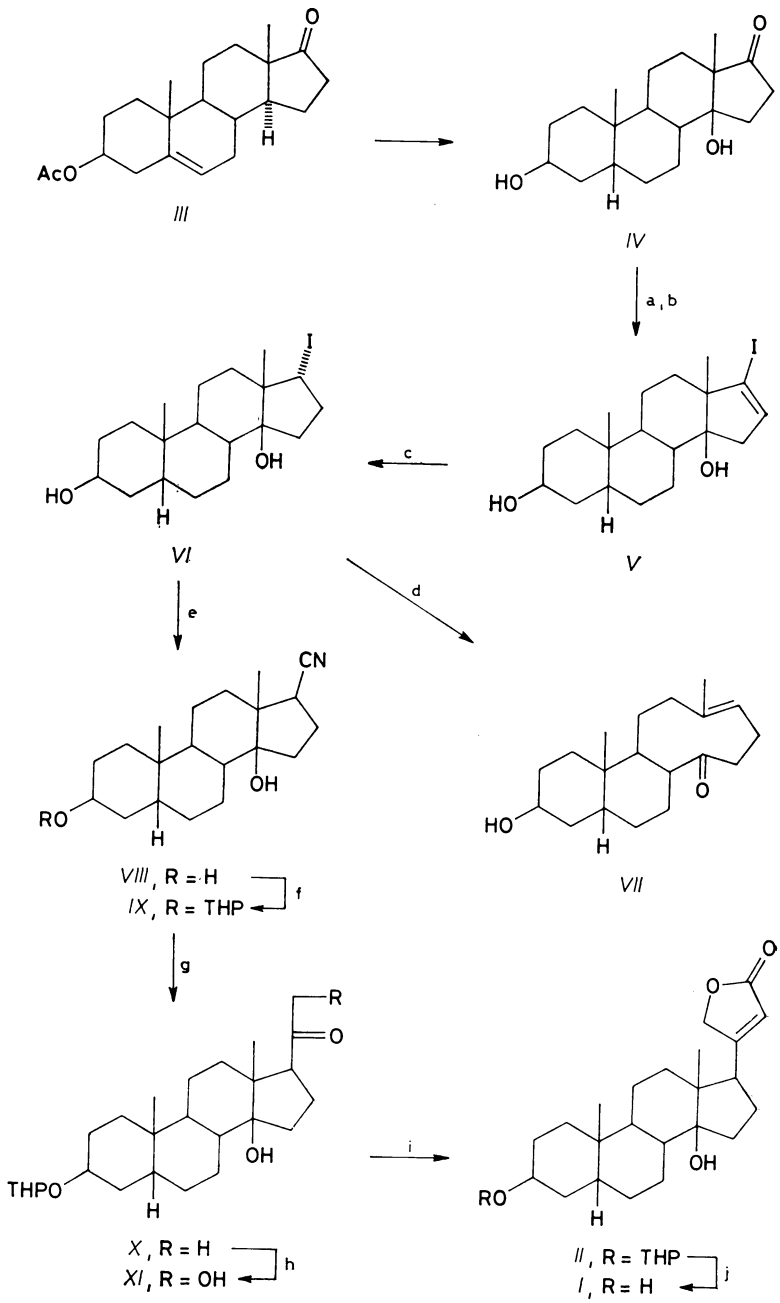
I *III*

SCHEME 1

formation of the butenolide lactone ring with the 17β-configuration, *3*) introduction of the 14β-hydroxyl group. Since the first problem has been resolved[2] satisfactorily, the remaining two required sophisticated stereoselective strategies. In most of the known approaches, the butenolide ring was constructed[3] before 14β-hydroxylation. This strategy allowed control of the stereochemistry at C-17. There are only two syntheses where the 14β-hydroxyl group was introduced before formation of the 17β-lactone. One of these methods[4] took the advantage of the 14β-OH for intramolecular control of the stereochemistry at C-17. The other, reported[5] by us, total synthesis of *rac*-9(11)-dehydrodigitoxigenin was based on free radical substitution at C-17. This process was controlled by the *cis*-C/D ring junction. However, transformation of the 17β-nitrile group into a hydroxy-methylketone function could conceivably have led, by enolization, to the corresponding 17α-product.

In the present work we showed clearly, by obtaining the natural digitoxigenin (*I*), that the methyl ketone *X* (Scheme 2) and its hydroxy derivative *XI* did not isomerize under the described conditions into the thermodynamically more stable 17α-derivatives. The synthesis of the title compound *I* was carried out using our earlier described[5-7] methodology. In the early stage of the synthesis, 17-oxoandrost-5-en-3-yl acetate (*III*) was transformed[2,6,7] into the known ketone *IV*. Then, compound *IV* was converted by the Barton method[8] into vinyl iodide *V*, and subsequently by hydrogenation with diimide to saturated iodide *VI*. The S_N2 type substitution of 17α-iodide *VI* by cyanide (potassium cyanide, dimethylsulfoxide) produced predominantly elimination product *VII*. Other nucleophiles such as lithium or copper acetylide did not lead to displacement products. This failure prompted us to investigate free radical substitution reaction using the tert-butyl isonitrile/tri-n-butyltin chloride/sodium cyanoborohydride system[9]. This reaction cleanly converted iodide *VI* into homogeneous nitrile *VIII* in 80% yield. After selective protection of the 3β-hydroxyl group, the THP-ether *IX* was treated with methyllithium in benzene to afford methyl ketone *X* as a single product (70% yield). Hydroxylation of *X* with lithium diisopropylamide[oxodiperoxymolybdenum(pyridine) (hexamethylphosphoric triamide)][10] in tetrahydrofuran and hexamethylphosphoric triamide gave in 34% yield hydroxymethyl ketone *XI* accompanied by unchanged *X* (44%). The target cardenolides *II* and *I* were obtained from *XI* by employing the Bestmann reagent[11] ((triphenylphosphoranylidene)ketene). Compound *II* was identical with the tetrahydropyranyl ether of digitoxigenin obtained from natural digitoxigenin. Also, hydrolysis of *II* in ethanol with pyridinium *p*-toluenesulfonate afforded *I*, identical with an authentic sample of digitoxigenin.

In conclusion, we have shown that digitoxigenin (*I*) was obtained from 17-oxoandrost-5-en-3β-yl acetate (*III*), via pregnanes *X* and *XI*, using fully stereocontrolled free radical reaction at C-17. This unique sequence of reactions allowed the synthesis 17β-substituted derivatives from compounds having a *cis*-C/D ring junction.



SCHEME 2

a $N_2H_4.H_2O$, Et_3N, EtOH; b I_2, Et_3N, THF; c $N_2H_4.H_2O$, C_2H_5COOH, air; d KCN, DMSO; e $(CH_3)_3C—NC$, Bu_3SnCl, $NaBH_3CN$, AIBN; f dihydropyran, pyridinium *p*-toluenesulfonate,

EXPERIMENTAL

The organic solutions were dried with anhydrous sodium sulfate or magnesium sulfate and evaporated under reduced pressure by means of a rotary evaporator. All reactions were monitored by TLC using hexane–ethyl acetate or benzene–acetone–methanol solvent systems. TLC chromatograms were developed by spraying with a solution of phosphomolybdic acid and cerric sulfate in 10% sulfuric acid, and then were heated to 150°C. For column chromatography, Merck silicagel 60 (230–400 mesh) was used. The melting points were measured with Boetius apparatus and were not corrected. The spectroscopic data were taken using the following instruments: IR — Beckman 4240 (in chloroform, wavenumbers in cm^{-1}), MS — Finnigan 8200 (energy of ionizing electrons 70 eV), HR — MS-Varian 731, ^1H NMR — Bruker AM 500 (chemical shifts in ppm (δ-scale), coupling constants in Hz).

Compound *IV* was synthesized from *III* accordingly to the literature[2,6,7]. Compounds *II*, *V*, *VI*, *VIII*, *IX*, *X*, and *XI* were obtained in an analogous way to compounds described[5] by us earlier.

17α-Iodo-5β,14β-androstan-3β,14-diol (*VI*)

Starting from compound *IV* (2·20 g, 7·23 mmol) crude compound *V* (2·25 g, 75%) was obtained which without further purification was subjected to hydrogenation reaction, according to literature[5], affording compound *VI* (1·51 g, 67%), m.p. 169–171°C (hexane–ether). IR spectrum: 3 640, 3 560. ^1H NMR spectrum: 0·95 s and 0·97 s, 2 × 3 H (3 × H-18, 3 × H-19); 4·12–4·15 m, 1 H (H-3); 4·43 t, 1 H (H-17, $J = 9·5$). Mass spectrum, *m/z* (%): 400 ($M^+ - 18$, 0·5), 291 (47), 273 (100), 255 (61). HR MS, *m/z*: for $C_{19}H_{29}IO$ calculated 400·1263, found 400·1263; for $C_{18}H_{31}O_2$ calculated 291·2324, found 291·2324; for $C_{19}H_{29}O$ calculated 273·1239, found 273·1239.

3β,14-Dihydroxy-5β,14β-androstan-17β-yl cyanide (*VIII*)

Starting from iodide *VI* (2·0 g, 4·8 mmol) compound *VIII* (1·21 g, 80%) was obtained, m.p. 210–218°C (chloroform–ether). IR spectrum: 3 650, 2 260. ^1H NMR spectrum: 0·97 s, 3 H (3 × H-19); 1·26 s, 3 H (3 × H-18); 2·59 t, 1 H (H-17, $J = 6·35$); 4·10–4·15 m, 1 H (H-3). Mass spectrum, *m/z* (%): 317 (M^+, 30), 299 (100), 281 (30), 266 (22), 250 (90), 203 (30), 176 (40), 161 (21), 149 (49), 135 (27), 121 (38), 108 (63). HR MS, *m/z*: for $C_{20}H_{31}NO_2$ calculated 317·2345, found 317·2345.

14-Hydroxy-3β-tetrahydropyranyloxy-5β,14β-androstan-17β-yl cyanide (*IX*)

Starting from compound *VIII* (2·5 g, 7·9 mmol) compound *IX* (2·21 g, 70%) was obtained, m.p. 160–180°C (ether–pentane). IR spectrum: 3 620, 2 250. ^1H NMR spectrum: 0·95 s, 3 H (3 × H-19); 1·26 s, 3 H (3 × H-18); 2·58 t, 1 H (H-17, $J = 6·05$); 3·45–3·53 m, 1 H; 3·86–3·92 m, 1 H; 3·92–3·98 m, 1 H (H-3); 4·60–4·65 m, 1 H (OCHO). Mass spectrum, *m/z* (%): 401 (M^+, 17), 383 (27), 300 (45), 282 (100), 85 (58). HR MS, *m/z*: for $C_{25}H_{39}NO_3$ calculated 401·2930, found 401·2930.

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CH_2Cl_2; g CH_3Li, benzene; h lithium diisopropylamide, [oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)], HMPA, THF; i $(C_6H_5)_3P{=}C{=}C{=}O$, Et_3N, benzene; j pyridinium *p*-toluenesulfonate, EtOH

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

Starting from compound *IX* (750 mg, 1·9 mmol) compound *X* (594 mg, 75%) was obtained, m.p. 140—148°C (ether). IR spectrum: 3 400, 1 695. ^{1}H NMR spectrum: 0·94 s and 0·97 s, 2 × 3 H (3 × H-18, 3 × H-19); 2·23 s, 3 H (CH_3CO); 2·87—2·92 dd, 1 H (H-17, J = 4·1; J' = 9·5); 3·44—3·50 m, 1 H; 3·85—3·93 m, 1 H; 3·94—3·98 m, 1 H (H-3); 4·61—4·64 m, 1 H (OCHO). Mass spectrum, *m/z* (%): 418 (M^+, 8), 400 (16), 390 (16), 317 (62), 299 (43), 288 (46), 230 (42), 85 (100). HR MS, *m/z*: for $C_{26}H_{42}O_4$ calculated 418·3086, found 418·3086.

14,21-Dihydroxy-3β-tetrahydropyranyloxy-5β,14β-pregnan-20-one (*XI*)

Starting from compound *X* (209 mg, 0·5 mmol) compound *XI* (73·8 mg, 34%) and recovered *X* (92 mg, 44%) were obtained. Compound *XI*, m.p. 160—167°C (ether). IR spectrum: 3 430, 1 695. ^{1}H NMR spectrum: 0·91 s and 0·94 s, 2 × 3 H (3 × H-18, 3 × H-19); 2·70—2·74 dd, 1 H (H-17, J = 3·8; J' = 8·8); 3·45—3·50 m, 1 H; 3·87—3·93 m, 1 H; 3·94—3·99 m, 1 H (H-3); 4·27 dd, 1 H (H-21, J(AB) = 20·8, J(AX) = 4·6); 4·31 dd, 1 H (H-21′, J(AB) = 20·8, J(BX) = = 4·6); 4·62—4·63 m, 1 H (OCHO). Mass spectrum, *m/z* (%): 434 (M^+, 3), 416 (8), 403 (19), 350 (23), 301 (28), 85 (100). HR MS, *m/z*: for $C_{26}H_{42}O_5$ calculated 434·3032, found 434·3032.

14-Hydroxy-3β-tetrahydropyranyloxy-5β-card-20(22)-enolide (*II*)

Starting from compound *XI* (43·4 mg, 0·1 mmol) compound *II* (27 mg, 59%) was obtained, m.p. 129—135°C (ether–pentane). The same compound was obtained by tetrahydropyranylation of digitoxigenin, using dihydropyrane and pyridinium *p*-toluenesulfonate as catalyst in methylene chloride. The compound *II* obtained from digitoxigenin had the same m.p., ^{1}H NMR, and MS spectra. ^{1}H NMR spectrum: 0·87 s and 0·94 s, 2 × 3 H (3 × H-19, 3 × H-18); 2·76 to 2·80 bt, 1 H (H-17, J = 5·5; J' = 8·8); 3·45—3·50 m, 1 H; 3·87—3·92 m, 1 H; 3·95—3·99 m, 1 H (H-3); 4·61—4·65 m, 1 H (OCHO); 4·81 dd, 1 H (H-21, J(AB) = 18·1, J(AX) = 1·0); 4·99 dt, 1 H (H-21, J(AB) = 18·1, J(BX) = 1·8); 5·87 d, 1 H (H-22, J = 1·5). Mass spectrum, *m/z* (%): 458 (M^+, 6), 440 (12), 356 (100), 339 (61), 246 (41), 203 (70). HR MS, *m/z*: for $C_{28}H_{42}O_5$ calculated 458·3032, found 458·3032.

Digitoxigenin (*I*)

A mixture of compound *II* (20 mg, 0·044 mmol), ethanol (2 ml) and pyridinium *p*-toluenesulfonate (2 mg) was maintained at 60°C for 1 h. Evaporation of solvent and chromatography afforded digitoxigenin (*I*) (14 mg, 85%). Compound *I* was identical in all respect with the natural digitoxigenin.

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