SYNTHESIS OF 4-(21-NOR-5-PREGNEN-20-YL)-1,3-THIAZOLE DERIVATIVES*

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The keto sulfoxide *IV*, prepared from the ester *III*, was reduced with amalgamated aluminium to give the ketone *V* which after enolization and silylation afforded the silyl enol ether *VI*. Oxidation of *VI* with osmium tetroxide and N-methylmorpholine N-oxide monohydrate yielded the α-hydroxy ketone *VII*. This was converted into the mesylate *IX* and further into the bromo ketone *XI* which on Hantzsch reaction with ethyl thioxamate furnished the steroidal thiazole *XII*. Compound *XII* was converted into the hemisuccinate *XIV*.

Within the framework of syntheses of heterocyclic analogues and models of cardiotonic steroids we described in our preceding paper[1] the preparation of 17β-[4-(2--ethoxycarbonyl-1,3-thiazolyl)]-5-androsten-3β-ol (*I*) and its derivatives in which the key intermediate, 21-hydroxy-3β-methoxymethoxy-5-pregnen-20-one was obtained by reaction of an enol ether (3β-methoxymethoxy-20-trimethylsilyloxy-5,20-pregnadiene) with the N-methylmorpholine N-oxide – osmium tetroxide system[1].

In the present communication we apply an analogous method to the synthesis of homologous derivatives, containing a methylene group interposed between the steroidal $C_{(17)}$ carbon atom and the $C_{(4')}$ carbon atom of the thiazole ring (*i.e.* steroidal thiazoles of the type *XII*).

Preparation of the α-hydroxy ketone *VII*, analogous to the previously described[1] procedure, represents a key step of the synthesis. This method appears to be much more versatile than the diazoketone route employed by Swiss authors[2] in the synthesis of 4'-[(3β-hydroxyandrost-5-en-17β-yl)methyl]-2'(5'*H*)-furanone.

The starting hydroxy ester *II* (ref.[3]) reacted with chloromethyl ether in the presence of N,N-dimethylaniline[4] to give the methoxymethoxy derivative *III* which was converted into the keto sulfoxide *IV* by reaction with sodium salt of dimethyl sulfoxide[5]. Compound *IV* was reduced with amalgamated aluminium in aqueous tetrahydrofuran[5,6] to the ketone *V*. The structure of the latter compound follows from the ^{1}H NMR spectrum, which displays a singlet at $\delta = 2{\cdot}12$ due to the methyl attached to the carbonyl group, and also from the IR spectrum, exhibiting carbonyl bands

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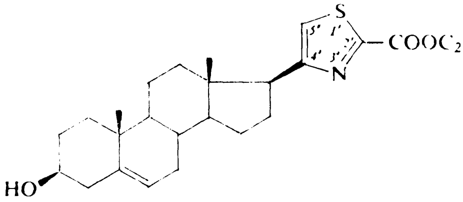
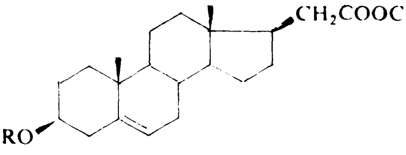
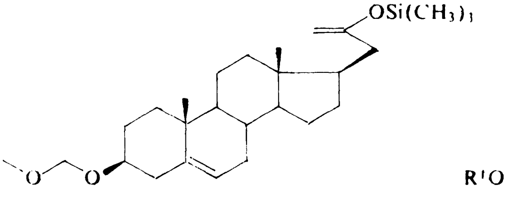
at 1 719 and 1 711 cm^{-1} and a band at 1 402 cm^{-1} due to a methylene group in the α-position to the carbonyl group. The attempted Pummerer rearrangement[7,8] of the keto sulfoxide *IV*, followed by desulfurization of the expected hemimercaptal acetate with Raney nickel, did not afford even traces of the described acetyl derivative of compound *VII*. We prepared therefore the hydroxy ketone *VII* analogously as described in the preceding communication[1], *i.e. via* the silyl enol ether *VI* as intermediate. Treatment with lithium diisopropylamide converted the ketone *V* into the enolate with terminal double bond which then reacted with chlorotrimethylsilane and triethylamine to give the trimethylsilyl enol ether *VI*. Its structure was proved by the ^1H NMR spectrum, particularly by a trimethylsilyl group signal at $\delta = 0{\cdot}16$ and a doublet of two olefinic protons at $\delta = 3{\cdot}87$. The enol ether *VI* was oxidized with a mixture of N-methylmorpholine N-oxide monohydrate[9] and osmium tetroxide[10] to the hydroxy ketone *VII* whose structure was confirmed by the ^1H NMR spectrum (the CH_2OH signal at $\delta = 4{\cdot}22$) and the IR spectrum (carbonyl and hydroxyl bands at 1 715 and 3 485 cm^{-1}, respectively). Removal of the methoxymethyl protecting group by *p*-toluenesulfonic acid monohydrate in a benzene–methanol mixture[1,11] afforded the known dihydroxy ketone *VIII* whose physical properties were identical with those reported in the literature[2].



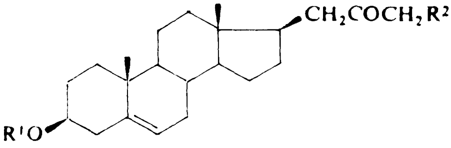
I



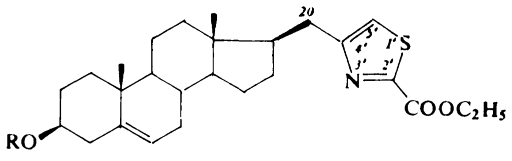
II, R = H
III, R = CH_2OCH_3



VI



IV, $R^1 = CH_2OCH_3$; $R^2 = S(O)CH_3$
V, $R^1 = CH_2OCH_3$; $R^2 = H$
VII, $R^1 = CH_2OCH_3$; $R^2 = OH$
VIII, $R^1 = H$; $R^2 = OH$
IX, $R^1 = CH_2OCH_3$; $R^2 = OSO_2CH_3$
X, $R^1 = CH_2OCH_3$; $R^2 = Cl$
XI, $R^1 = CH_2OCH_3$; $R^2 = Br$



XII, R = H
XIII, R = OCCH$_2$CH$_2$COOCH$_2$CCl$_3$
XIV, R = OCCH$_2$CH$_2$COOH

The hydroxy ketone *VII* was converted by the usual procedure[1,12–14] into the mesylate *IX*, characterized in the IR spectrum by bands at 1 359 and 1 179 cm^{-1} (—SO$_2$—) and at 1 740 and 1 730 cm^{-1} (C=O). Its ^{1}H NMR spectrum exhibited signals at $\delta = 4{\cdot}76$ (C$_{(22)}$—H), $\delta = 3{\cdot}22$ and $\delta = 4{\cdot}66$ (CH$_3$OCH$_2$O—) and $\delta = 3{\cdot}17$ (CH$_3$SO$_2$O—). As reported for similar mesylations[1], the reaction was accompanied by formation of the chloro derivative *X* which was isolated and characterized by its ^{1}H NMR spectrum (particularly by the signal at $\delta = 4{\cdot}07$ due to C$_{(22)}$—H and at $\delta = 3{\cdot}35$ and $\delta = 4{\cdot}65$ due to the CH$_3$OCH$_2$O grouping).

Treatment with an excess of lithium bromide in acetone[1,12,13] converted the mesylate *IX* into the bromo derivative *XI*. Its IR as well as ^{1}H NMR spectra have similar features (carbonyl bands for *X*: 1 734, 1 721 and 1 710 cm^{-1}, for *XI*: 1 731 and 1 716 cm^{-1}; the ^{1}H NMR spectra of *X* and *XI* differ only in the chemical shift of the C$_{(22)}$—H proton signals, in accord with the literature[1]).

The 1,3-thiazole derivative *XII* was synthesized in a 54% yield by the Hantzsch reaction[12,15] in which the bromo ketone *XI* reacted with ethyl thioxamate in boiling acetonitrile. Its structure was proved by comparison of its spectral properties with those published[1] for related derivatives. The pertinent data for the thiazoles *XII*,

TABLE I
IR Data for the thiazoles *XII*, *XIII* and *XIV* (in chloroform, wavenumbers in cm^{-1})

XII	*XIII*	*XIV*	Lit.[a]
3 115	3 120	3 115	3 100–3 130
1 521, 1 509	1 523, 1 510	1 507	1 500–1 522
1 305	1 304	1 304	1 301–1 315
1 096	1 094	1 096	1 040–1 096
1 021	1 022	1 022	1 000–1 035

[a] Characteristic thiazole bands are summarized in ref.[1], the band in the region 1 601–1 635 cm^{-1}, reported[1] for some thiazoles, was not observed in the spectra of our thiazoles *XII*–*XIV*.

XIII and *XIV* are given in Table I and II. Similarly, the derivatives *XII*–*XIV* were compared with the compound *I* using reversed phase high performance liquid chromatography characteristics (Table III).

The hemisuccinate *XIV* was prepared *via* the 4-(2,2,2-trichloroethoxy)-4-oxobutanoic acid derivative[1,16–18] *XIII* and its structure was evidenced by IR spectral bands due to carboxyl (3 400–2 400, 1 713 cm^{-1}), thiazole (see Table I), an ester group (1 726 and 1 174 cm^{-1}) and an ester on the thiazole nucleus (1 250 cm^{-1}). Also the ^{1}H NMR spectrum was in accord with the structure *XIV* (for the thiazole proton signal see Table II), particularly the signal of the —OOC—CH$_2$CH$_2$—COO— moiety at δ = 2·65.

TABLE II

^{1}H NMR Spectral data for the thiazoles *XII*–*XIV* in deuteriochloroform

Proton	*XII*	*XIII*	*XIV*	Lit.[a]
$C_{(5')}$—H in thiazole[b]	7·17	7·14	7·18	6·20–7·21
$C_{(20)}$—H i.e. in α-position to the thiazole ring[c]	2·83 (W = 21)	2·75[d] (W = 30)	2·80[d] (W = 50)	2·63–2·98 (W ≐ 20)

[a] Values observed for many steroidal thiazoles[1]; [b] singlet; [c] multiplet; [d] the signal overlapped with the multiplet of the succinic acid moiety.

TABLE III

Retention times (t_R, min) and capacity factors (k') in HPLC of steroidal thiazoles. Solvent: Methanol (A), methanol–water mixture 9 : 1 (v/v) (B), or tetrahydrofuran-methanol–water mixture 2 : 2 : 1 (v/v/v) (C). Flow rate: for A and B 2 ml/min (pressure 4·92 MPa or 7·03 MPa respectively), for C 1 ml/min (pressure 4·57 MPa). Column packing: Separon Si C_{18} (10 μm). Samples were applied in dichloromethane solution

Compound	A		B		C	
	t_R	k'	t_R	k'	t_R	k'
I	2·24	0·48	5·17	1·82	3·62	0·55
XII	2·33	0·54	5·75	2·14	3·70	0·59
XIII	3·05	1·01	16·81	8·17	8·58	2·68
XIV	2·78	0·84	5·56	2·03	4·25	0·82

It can be summarized that the synthesis of steroidal thiazoles *I* along the pathway ketone – enol ether – α-hydroxy ketone – bromo ketone was used successfully also with homologous derivatives, leading to the thiazole *XII* and its derivatives, prepared for structure – biological activity studies.

EXPERIMENTAL

Melting points were determined on a Boetius micro melting point apparatus (GDR), optical rotations on a Perkin-Elmer 141 MC polarimeter. IR spectra were taken on a UR-20 (Zeiss, Jena) spectrophotometer, wavenumbers are given in cm^{-1}. ^1H NMR spectra were measured on Tesla BS-467 (60 MHz) or Varian XL-200 (200 MHz) instruments in deuteriochloroform, with tetramethylsilane as internal standard, chemical shifts are given in ppm (δ-scale), coupling constants (*J*) and band widths (*W*) in Hz. All parameters were obtained by first-order analysis. Mass spectra were measured on an AEI-901 spectrometer, unless stated otherwise. Preparative chromatography was carried out on columns of silica gel (according to Pitra, 60—120 μm, Service Laboratories of this Institute), thin-layer chromatography (TLC) was performed on silica gel G according to Stahl (Woelm). Spots were detected by spraying with sulfuric acid followed by heating. For high performance liquid chromatography (HPLC) a stainless steel column (250 × 4 mm) packed with Separon Si C_{18} (10 μm, Laboratory Instruments, Czechoslovakia) and a UVM-4 UV detector (Development Workshops of Czechoslovak Academy of Sciences) were used. The fractions were detected at 230 nm. Experiments with organometallic reagents were conducted under argon. Solutions were dried over anhydrous sodium sulfate and taken down on a rotatory evaporator at bath temperature 40—50°C and pressure 2—2·5 kPa. Analytical samples were dried over phosphorus pentoxide at about 25 Pa.

Methyl 3β-Methoxymethoxy-5-pregnen-21-oate (*III*)

N,N-Dimethylaniline (1.10 ml; 8·68 mmol) and chloromethyl methyl ether (0·72 ml; 9·48 mmol) were added to a solution of the hydroxy derivative *II* (2 g; 5·77 mmol; ref.[3]) in dichloromethane (25 ml). After standing for 24 h at room temperature the mixture was diluted with ether (300 ml), washed successively with dilute hydrochloric acid, water, potassium hydrogen carbonate solution and water, dried and taken down. The residue was chromatographed on a column of silica gel (180 g) in benzene–ether (98 : 2), affording 2 g (89%) of the derivative *III*, m.p. 65—67°C, $[\alpha]_D^{25}$ $-60°$ (*c* 0·4, chloroform). IR spectrum (tetrachloromethane): 1 740 (COOR), 1 667 (C=C), 1 149, 1 106, 1 040 cm^{-1} (C—O—C). ^1H NMR spectrum: 5·35 m (1 H, $C_{(6)}$—H), 4·67 s (2 H, O—CH_2—O), 3·63 s (3 H, $COOCH_3$), 3·34 s (3 H, OCH_3), 1·00 s (3 H, $C_{(19)}$—H), 0·60 s (3 H, $C_{(18)}$—H). For $C_{24}H_{38}O_4$ (390·6) calculated: 73·81% C, 9·81% H; found: 73·57% C, 9·79% H.

3β-Methoxymethoxy-21,24-dinor-5-cholen-22-one (*V*)

A mixture of sodium hydride (3·27 g;136 mmol) and dimethyl sulfoxide (100 ml) was heated to 65°C for 2 h. After cooling, the solution was diluted with tetrahydrofuran (40 ml) and the ester *III* (5·34 g; 13·7 mmol) in tetrahydrofuran (40 ml) was added. The mixture was stirred for 2 h at room temperature, poured into water, neutralized with solid ammonium chloride and the product was extracted with ethyl acetate. The extract was washed six times with water, dried and taken down. The residue (7 g) was the practically pure (TLC in light petroleum–acetone 9 : 1) keto sulfoxide *IV*. ^1H NMR spectrum: 5·33 m (1 H, $C_{(6)}$—H), 4·66 s (2 H, O—CH_2—O), 3·75 s (2 H, $C_{(23)}$—H), 3·33 s (3 H, OCH_3), 2·66 s (3 H, $SOCH_3$), 1·00 s (3 H, $C_{(19)}$—H), 0·60 s (3 H, $C_{(18)}$—H). The crude *IV* (7 g) was dissolved in tetrahydrofuran (200 ml) and water (25 ml) and amalgamated aluminium[5] (3 g) was added during 30 min to the boiling stirred solution. The mixture was boiled and stirred for 90 min more, cooled and poured onto a column of silica gel (50 g), layered with Celite (20 g). Ethyl acetate eluted 4·5 g of a crude product which was chromatographed on a column of silica gel (450 g). Elution with benzene–ether (98·5 : 1·5) gave 3·55 g (69%) of the ketone *V*, m.p. 107—109°C (light petroleum - ether); $[\alpha]_D^{25}$ $-53°$ (*c* 0·2; chloroform). IR spectrum (tetrachloromethane): 1 719, 1 711 (C=O), 1 402 (CH_2—CO), 3 030, 1 668 (C=C—H). ^{1} H NMR spectrum: 5·34 m (1 H, $C_{(6)}$—H), 4·67 s (2 H, O—CH_2—O), 3·34 s (3 H, OCH_3), 2·21 s (3 H, $C_{(23)}$—H), 1·00 s (3 H, $C_{(19)}$—H), 0·59 s (3 H, $C_{(18)}$—H). Mass spectrum, *m*/*z*: 312 (M—$C_2H_6O_2$). For $C_{24}H_{38}O_3$ (374·6) calculated: 76·96% C, 10·23% H; found: 76·98% C, 9·98% H.

23-Hydroxy-3β-methoxymethoxy-21,24-dinor-5-cholen-22-one (*VII*)

1-Butyllithium in hexane (3·57 ml; c 1·6 mol l^{-1}) was added at $-78°C$ to a stirred solution of diisopropylamine (607 mg; 6 mmol) in tetrahydrofuran (10 ml). After stirring for 30 min at $-78°C$ a solution of the ketone *V* (1·12 g; 3 mmol) in tetrahydrofuran (5 ml) was added in the course of 5 min and the mixture was stirred at $-78°C$ for 1 h. Triethylamine (0·697 ml; 5 mmol), followed by chlorotrimethylsilane (0·634 ml; 5 mmol) was added, the mixture was allowed to attain room temperature (1 h) and diluted with benzene (300 ml). The solution was washed with potassium hydrogen carbonate solution, dried over anhydrous potassium carbonate and taken down, the residue (1·28 g) being practically pure enol ether *VI* (according to TLC in light petroleum–acetone 9 : 1). ^{1}H NMR spectrum (tetrachloromethane, external lock): 5·26 m (1 H, $C_{(6)}$—H), 4·52 s (2 H, O—CH_2—O), 3·87 d (2 H, $C_{(23)}$—H, $J = 3·5$), 3·24 s (3 H, OCH_3), 0·98 s (3 H, $C_{(19)}$—H), 0·57 s (3 H, $C_{(18)}$—H), 0·16 s (9 H, O—$Si(CH_3)_3$).

A solution of osmium tetroxide (15 mg) in 2-methyl-2-propanol (1·5 ml) was added to a solution of N-methylmorpholine N-oxide[9] (426 mg; 3·15 mmol) in water (6 ml) and acetone (13·5 ml). The solution was cooled to $-5°C$ and a solution of *VI* (1·28 g) in acetone (5 ml), followed by tetrahydrofuran (10 ml), was added. After stirring for 6 h at 0°C and then for 6 h at room temperature, potassium pyrosulfate (500 mg) was added. The mixture was acidified with sulfuric acid (*c* 1 mol . . l^{-1}) and taken down *in vacuo*. The residue was partitioned between ethyl acetate and water, the aqueous phase was extracted with ethyl acetate and the combined organic layers were washed with dilute hydrochloric acid, water, potassium hydrogen carbonate and water. After drying and evaporation of solvent, the residue was chromatographed on a column of silica gel (100 g). Elution with light petroleum-acetone (98 : 2) gave 797 mg (68%) of the hydroxy ketone *VII*, m.p. 137—140°C (light petroleum–acetone), $[\alpha]_D^{25}$ $-53°$ (*c* 0·1, chloroform). IR spectrum (chloroform): 3 485 (OH), 1 715 (C=O), 1 668 (C=C). ^{1}H NMR spectrum: 5·34 m (1 H, $C_{(6)}$—H), 4·67 s (2 H, O—CH_2—O), 4·22 d (2 H, $C_{(23)}$—H, $J_{23,OH} = 4·5$), 3·34 s (3 H, OCH_3), 3·10 t (1 H, —OH, $J_{23,OH} = 4·5$), 1·00 s (3 H, $C_{(19)}$—H), 0·60 s (3 H, $C_{(18)}$—H). For $C_{24}H_{38}O_4$ (390·6) calculated: 73·81% C, 9·81% H; found: 73·87% C, 9·70% H.

3β,23-Dihydroxy-21,24-dinor-5-cholen-22-one (*VIII*)

p-Toluenesulfonic acid monohydrate (100 mg; 0·53 mmol) was added to a solution of the ether *VII* (100 mg; 0·26 mmol) in a mixture of benzene (3 ml) and methanol (7 ml). After warming to 45°C for 10 h the solvents were evaporated *in vacuo* and the residue was partitioned between water and ether. The ethereal layer was washed with a potassium hydrogen carbonate solution and water, dried and taken down. Chromatography of the residue on a preparative plate of silica gel (20 × 20 cm) in chloroform–benzene–methanol (6 : 4 : 1) afforded 50 mg (56%) of the hydroxy derivative *VIII*, m.p. 155—158°C (acetone), $[\alpha]_D$ $-54°$ (*c* 2·0, chloroform). Reported[2] m.p.

158–160°C, $[\alpha]_D^{25}$ −55·27°. The mass and IR spectra (the latter in chloroform) agreed with those described[2].

23-Methanesulfonyloxy-3β-methoxymethoxy-21,24-dinor-5-cholen-22-one (*IX*)

Methanesulfonyl chloride (0·97 ml, 1·44 g; 12·58 mmol) was added under cooling (ice bath) to the alcohol *VII* (1·63 g; 4·17 mmol) in pyridine (30 ml). After stirring at 0°C for 3 h the mixture was poured onto an ice–water mixture (200 ml) and extracted with chloroform (5 × 50 ml). The combined chloroform extracts were washed with 5% hydrochloric acid (3 × 100 ml) and saturated potassium carbonate solution (1 × 100 ml), dried over magnesium sulfate, filtered through charcoal and taken down. The residue was chromatographed on silica gel (100 g). Elution with benzene (2 l) gave the derivative *X* (see the following experiment). The fraction, obtained by elution with benzene–ether (3 : 2) was taken down and the residue was crystallized from dichloromethane–ether–light petroleum, yielding 800 mg (40%) of the mesylate *IX*, m.p. 135–136°C, $[\alpha]_D^{25}$ −38·2° (*c* 0·31, chloroform). IR spectrum (chloroform): 1 359, 1 179 (SO_2), 1 150, 1 106, 1 043, 1 015, 972 (C—O—C), 1 740, 1 730 shoulder (C=O), 1 668 cm^{-1} (C=C). ^{1}H NMR spectrum: 5·32 bd (1 H, $C_{(6)}$—H, *J* = 5), 4·76 s (2 H, $C_{(22)}$—H), 4.66 s (2 H, —O—CH_2—O—), 3·41 m (1 H, $C_{(3)}$—H), 3·32 s (3 H, CH_3—O), 3·17 s (3 H, CH_3SO_2—O—), 2·32 m (4 H, $C_{(20)}$—H + + $C_{(7)}$—H), 1·00 s (3 H, $C_{(19)}$—H), 0·60 s (3 H, $C_{(18)}$—H). For $C_{25}H_{40}O_6S$ (468·6) calculated: 64·07% C, 8·60% H, 6·84% S; found: 64·36% C, 8·63% H, 6·47% S.

23-Chloro-3β-methoxymethoxy-21,24-dinor-5-cholen-22-one (*X*)

The benzene fraction from chromatography in the preceding experiment was evaporated and the residue was crystallized from dichloromethane–ether–light petroleum to give 250 mg (15%) of the chloro derivative *X*, m.p. 144–145°C, $[\alpha]_D^{25}$ −41·6° (*c* 0·32, chloroform). IR spectrum (chloroform): 1 734, 1 721, 1 710 sh (C=O), 1 150, 1 043, 1 014, 972 (C—O—C), 1 668 cm^{-1}(C=C). ^{1}H NMR spectrum: 5·34 bd (1 H, $C_{(6)}$—H, *J* = 4·5), 4·65 s (2 H, O—CH_2—O), 4·07 s (2 H, $C_{(22)}$—H), 3·35 s (3 H, CH_3—O), 2·47 m (4 H, $C_{(20)}$—H + $C_{(7)}$—H). For $C_{24}H_{37}ClO_3$ (409·0) calculated: 70·48% C, 9·12% H, 8·67% Cl; found: 70·44% C, 9·20% H, 8·60% Cl.

23-Bromo-3β-methoxymethoxy-21,24-dinor-5-cholen-22-one (*XI*)

A mixture of the mesylate *IX* (661 mg; 1·41 mmol), acetone (30 ml) and anhydrous lithium bromide (1·24 g) was heated to 50°C for 30 min and applied on a column of silica gel (50 g). Elution with light petroleum–ether (2 : 1, 250 ml), followed by crystallization from dichloromethane–ether–light petroleum, furnished the bromo derivative *XI* (466 mg; 73%), m.p. 115·5 to 118°C, $[\alpha]_D^{25}$ −46·1° (*c* 0·2, chloroform). IR spectrum (chloroform): 1 731 sh, 1 716 (C=O), 1 140, 1 106, 1 031, 1 019, 942, 914 cm^{-1} (C—O—C). ^{1}H NMR spectrum: 5·33 bd (1 H, $C_{(6)}$—H, *J* = 4·5), 4·65 s (2 H, —O—CH_2—O—), 3·87 s (2 H, $C_{(22)}$—H), 3·34 s (3 H, CH_3 O—), 3·39 m (1 H, $C_{(3)}$—H, *W* = 25), 2·45 m (4 H, $C_{(20)}$—H + $C_{(7)}$—H), 1·00 s (3 H, $C_{(19)}$—H), 0·61 s (3 H, $C_{(18)}$—H). For $C_{24}H_{37}BrO_3$ (453·5) calculated: 63·57% C, 8·22% H, 17·62% Br; found: 63·78% C, 8.52% H, 17·31% Br.

20-[4-(2-Ethoxycarbonyl-1,3-thiazolyl)]-21-nor-5-pregnen-3β-ol (*XII*)

A solution of the bromo ketone *XI* (617 mg; 1·36 mmol) and ethyl thioxamate (186 mg; 1·4 mmol) in acetonitrile (20 ml) was refluxed for 32 h. Further portions (50 mg) of ethyl thioxamate were added in 4 h intervals. The mixture was taken down in the presence of silica gel and chromatographed on a silica gel column (125 g) in light petroleum – ether (2 : 1; 4 l). The product from the main fraction was crystallized from dichloromethane–ether–light petroleum, affording 326 mg (54%) of the thiazole *XII*, m.p. 169—171°C; $[\alpha]_D^{25}$ $-50{\cdot}7°$ (*c* 0·25; chloroform). IR spectrum (chloroform): 3 115, 1 521 sh, 1 509, 1 305, 1 096, 1 021 sh (thiazole), 3 610 (OH), 1 670 (C=C), 1 731, 1 713, 1 261 ($COOC_2H_5$). ^{1}H NMR spectrum: 7·17 s (1 H, $C_{(5')}$—H), 5·35 bd (1 H, $C_{(6)}$—H, $J = 4{\cdot}5$), 4·48 q (2 H, CH_3CH_2—O—, $J = 7$), 3·46 m (1 H, $C_{(3)}$—H, $W = 35$), 2·83 m (2 H, $C_{(20)}$—H, $W = 20$), 2·37 bd (2 H, $C_{(7)}$—H, $J = 8{\cdot}5$), 1·45 t (3 H, CH_3CH_2—O—, $J = 7$), 1·03 s (C 3 H, $C_{(19)}$—H), 0·56 s (3 H, $C_{(18)}$—H). For $C_{26}H_{37}NO_3S$ (443·6) calculated: 70·39% C, 8·41% H, 3·16% N, 7·23% S; found: 70·45% C, 8·74% H, 2·88% N, 7·03% S.

20-[4-(Ethoxycarbonyl-1,3-thiazolyl)]-21-nor-5-pregnen-3β-ol 3-[4-(2,2,2-Trichloroethoxy)-4-oxobutanoate] (*XIII*)

A mixture of the alcohol *XII* (170 mg; 0·38 mmol), 4-(2,2,2-trichloroethoxy)-4-oxobutanoic acid[19] (178 mg; 0·71 mmol), N,N'-dicyclohexylcarbodiimide (87·5 mg; 0·43 mmol), 4-dimethylaminopyridine (2 mg) and benzene (10 ml) was stirred for 3 h at room temperature, applied on a column of silica gel (50 g) and eluted with ether. After evaporation, the residue was chromatographed on silica gel (50 g) in benzene–ether (4 : 1). Crystallization of the principal product from ether–light petroleum afforded 130 mg (51%) of the succinate *XIII*, m.p. 64—66°C. $[\alpha]_D^{25}$ $-39{\cdot}9°$ (*c* 0·14; chloroform). IR spectrum (chloroform): 3 120, 1 523, 1 510, 1 304, 1 094, 1 022 (thiazole), 1 261 (ester on the thiazole ring), 1 749, 1 731, 1 712, 1 157 (esters). ^{1}H NMR spectrum: 7·14 s (1 H, $C_{(5')}$—H), 5·33 m (1 H, $C_{(6)}$—H), 4·71 s (2 H, Cl_3CCH_2—O—), 4·45 q (2 H, CH_3CH_2—O—, $J = 7$), 2·75 m (6 H, $C_{(20)}$—H + —OCO—CH_2CH_2—COO—, $W = 30$), 2·27 bd (2 H, $C_{(7)}$—H, $J = 8$), 1·47 t (3 H, CH_3CH_2—O—), 0·99 s (3 H, $C_{(19)}$—H), 0·68 s (3 H, $C_{(18)}$—H). For $C_{32}H_{42}Cl_3NO_6S$ (675·1) calculated: 56·93% C, 6·27% H, 15·75% Cl, 2·07% N, 4·75% S; found: 57·02% C, 5·94% H, 15·94% Cl, 1·87% N, 4·51% S.

20-[4-(2-Ethoxycarbonyl-1,3-thiazolyl)]-21-nor-5-pregnen-3β-ol 3-(3-Carboxypropanoate) (*XIV*)

Water (1 ml), acetic acid (5 ml) and zinc dust (50mg) were added to a solution of the succinate *XIII* (150 mg; 0·31 mmol) in tetrahydrofuran (8 ml). The mixture was stirred in an ice-bath for 6 h, 30 mg portions of zinc dust being added every 30 min, and filtered through Celite. After evaporation, the residue was coevaporated with toluene and ethanol–toluene mixture (3 × 50 ml), and dissolved in methanol–benzene. The solution was taken down in the presence of silica gel and applied on a column of silica gel (50 g). The principal fraction after elution with benzene–ether (4 : 1), evaporation and crystallization from dichloromethane–ether–light petroleum afforded 55 mg (29%) of the hemisuccinate *XIV*, m.p. 143—145°C, $[\alpha]_D^{25}$ $-41{\cdot}5°$ (*c* 0·22; chloroform). IR spectrum (chloroform): 3 400—2 400, 1 713 sh (—COOH), 3 115, 1 507, 1 304, 1 096, 1 022 (thiazole), 1 726, 1 174 (—COOR), 1 726, 1 260 (—COOR on the thiazole ring). ^{1}H NMR spectrum (200 MHz, Varian XL-200 FT): 7·18 s (1 H, $C_{(5')}$—H), 5·37 bd (1 H, $C_{(6)}$—H, $J = 4{\cdot}3$), 4·63 m (1 H, $C_{(3)}$—H, $W = 30$), 4·48 q (2 H, CH_3CH_2O—, $J = 7{\cdot}1$), 2·8 m (6 H, $C_{(20)}$—H + —OOC—CH_2CH_2—COO—), 2·32 bd (2 H, $C_{(7)}$—H, $J = 7{\cdot}8$), 1·47 t (3 H, CH_3CH_2O—, $J = 7{\cdot}1$), 1·02 s (3 H, $C_{(19)}$—H), 0·71 s (3 H, $C_{(18)}$—H). For $C_{30}H_{41}NO_6S$ (543·7) calculated: 66·27% C, 7·60% H, 2·58% N, 5·90% S; found: 66·57% C, 7·94% H, 2·32% N, 5·71% S.

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