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# SYNTHESIS OF ECDYSONE—VI

## SYNTHESIS OF ECDYSONE FROM STIGMASTEROL

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**Abstract**—Ecdysone was synthesized from stigmasterol. The novel methods of synthesis of a 2β,3β-diol (A-ring structure), a 14α-hydroxy-7-en-6-one (B,C-ring structure) and a (22*R*)-22,25-dihydroxycholestane side chain previously reported were utilized.

ECDYSONE was the first insect moulting hormone isolated in a pure state[1] and identified[2] as (22*R*)-2β,3β,14α,22,25-pentahydroxy-5β-cholest-7-en-6-one (XXIX) by X-ray analysis. The synthesis of this hormone was reported by two groups[3,4] independently and by a different method in a preliminary communication,[5] the detailed description of which is now given.

In our program to synthesize ecdysone, its chemical formula was divided into three partial structures, A-ring (III), B,C-ring (VI) and the side chain (XII), and novel and improved methods for the preparation of these three structures were developed. In the first and second papers of this series, a novel synthesis of 2β,3β-dihydroxy-steroid from 3-oxo compound was described.[6] The autoxidation[7] of the A/B *trans*-fused 3-oxo-steroid (I) afforded a mixture of two possible enol forms of the 2,3-dione[8] (II), which without purification was reduced to the 2β,3β-dihydroxy-steroid (III) as a main product. In the third paper,[9] it was reported that the 14α-hydroxy-6-oxo-7-ene-steroid (VI) could be prepared from the 6-oxo-7-ene-steroid (IV) by enol acetylation into V followed by the oxidation. Synthesis of the side chain was described in the fourth paper.[10] Bisnorcholan-22-al (VII) easily obtainable from 22-ene-sterol was selected as the starting material. The reaction of VII with ethynyl-magnesium bromide gave 22-hydroxy-23-cholyne (VIII) as an epimeric mixture at C-22. The treatment of VIII with Grignard reagent followed by carbon dioxide afforded 22-hydroxy-25-homocholyn-25-oic acid (IX). IX was catalytically hydrogenated and (22*S*)- and (22*R*)-lactones (X and XI) were isolated. The side chain structure of ecdysone (XII) was constructed by treatment of (22*R*)-lactone (XI) with methyl-magnesium bromide.

It was reported that the B,C-ring and side chain structure of ecdysone (VI and XII) is not stable to acid even under mild conditions,[11] i.e. ecdysone has two unstable partial structures. The order of the preparation of these partial structures was, therefore, very important. The lactone structure (X or XI) was expected to be stable to reactions for the construction of the A-ring and B,C-ring structures described. In this connection, the most promising order of synthesis was considered to be (1) lactone, (2) A-ring, (3) B,C-ring, and (4) side chain.

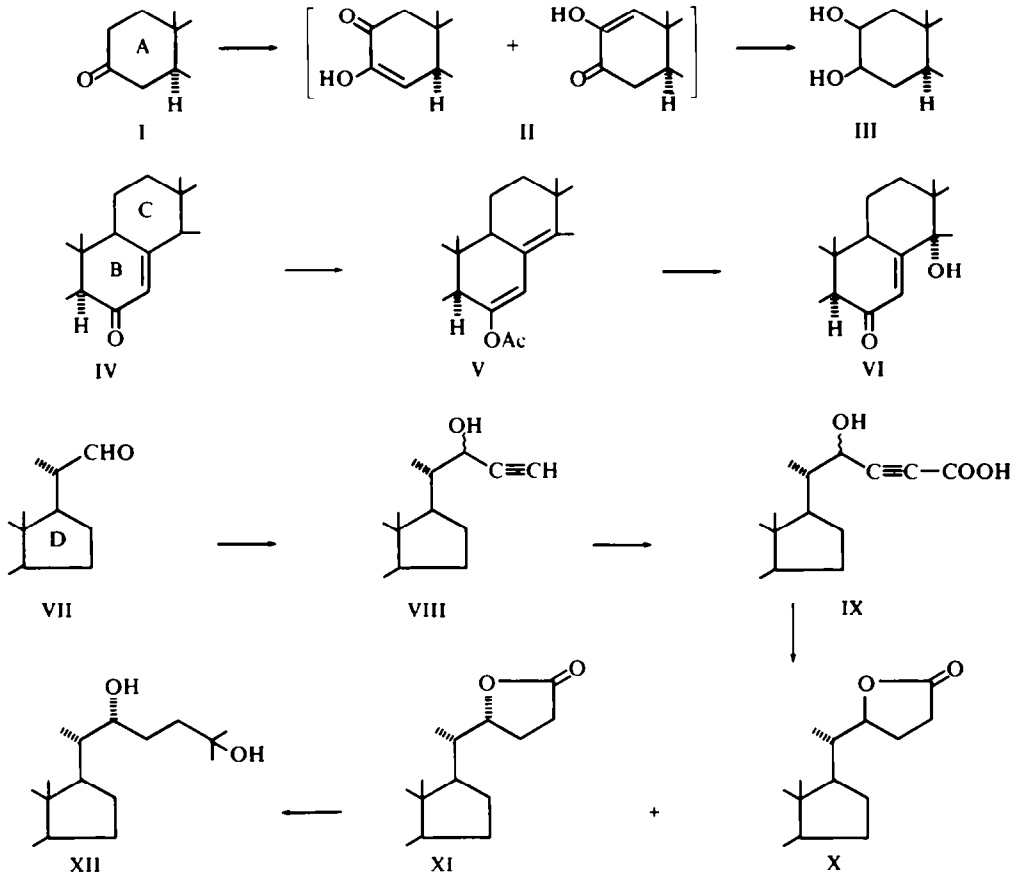



Chart 1

The dioxolactone (XIV), which was synthesized from stigmasterol (XIII)[10] was selected as starting material. The partial reduction of the dioxolactone (XIV) yielded a ketol-lactone which was assigned as 3β-hydroxy-6-oxolactone (XV) on the following grounds. A negative Cotton effect curve which is usually observed in a 6-oxo-steroid[12] was present in the ORD; this suggests that only the 3-oxo group was partially reduced. Configuration of the OH group introduced by the reduction was considered to be β, because it is generally accepted that the reduction of 3-oxo-steroid in the 5α-series gives 3β-OH compound with high stereospecificity.[13] XV was ketalized to the ketal (XVI) as an oily substance. The oxidation of this ketal (XVI)[14] afforded the 3-oxo compound (XVII), which showed a positive Cotton effect curve in ORD.[15]

The A,B-ring structure of XVII, 6,6-ethylenedioxy-3-one, was found to be suitable for the synthesis of the 2β,3β-dihydroxy-6-one by the method described. Thus, XVII was submitted to autoxidation in t-butanol in the presence of potassium t-butoxide to give the 2,3-dione (XVIII) as a mixture of two possible enol forms (2-hydroxy-1-en-3-one and 3-hydroxy-3-en-2-one). The IR spectrum showed that the lactone ring was opened to form the hydroxycarboxylic acid. This enol mixture was directly reduced to afford the trihydroxycarboxylic acid (XIX) as a mixture of epimers at C-2

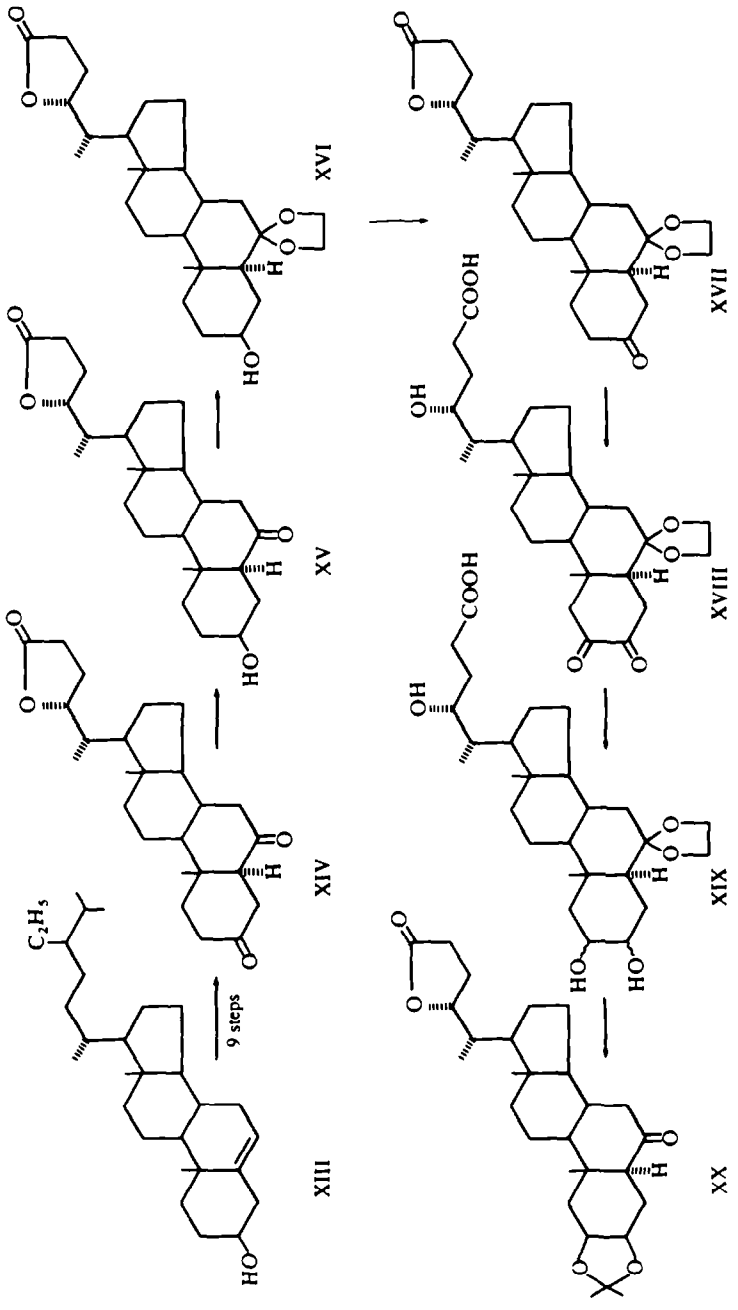
and C-3. The treatment of XIX with acetic acid followed by preparative TLC afforded the desired 2β,3β-dihydroxylactone (XXI) in 33·5% yield based on XVII. XXI was also isolated as the acetonide (XX) by the treatment of XIX with acetone and phosphomolybdic acid followed by chromatography. The hydrolysis of XX with phosphoric acid gave XXI. This supports the *cis* relationship of OH groups at C-2 and C-3. Acetylation of XXI yielded the diacetate (XXII). The assignment of 2β,3β-dihydroxyl structure in XX, XXI or XXII was mainly based on the analogy with similar reaction in cholestane series.[6b] The NMR spectrum of XXII also supports this structure. As shown in Table 1, the chemical shifts are consistent with those of 2β,3β-diacetoxy-5α-cholestan-6-one, the structure of which was fully established.[4b, 6b]

TABLE 1. NMR DATA OF XXIX, XXXI, XXXIII AND CORRESPONDING CHOLESTANE COMPOUNDS

| Compound | 18-$CH_3$ | 19-$CH_3$ | 7-H | 2,3-H |
|---|---|---|---|---|
| 2β,3β-Diacetoxy-5α-cholestan-6-one | 0·66 | 0·94 | | near 4·75<br>5·28 |
| XXIX | 0·71 | 0·94 | | near 4·73<br>5·27 |
| 2β,3β-Diacetoxy-5α-cholest-7-en-6-one | 0·59 | 1·01 | 5·74 (t)<br>$J$ = 2·5 | near 4·80<br>5·28 |
| XXXI | 0·65 | 1·01 | 5·81 (t)<br>$J$ = 2·5 | near 4·75<br>5·35 |
| 2β,3β-Diacetoxy-14α-hydroxy-5α-cholest-7-en-6-one | 0·67 | 1·00 | 5·90 (d)<br>$J$ = 2·5 | near 4·80<br>4·29 |
| XXXIII | 0·73 | 1·01 | 6·00 (d)<br>$J$ = 2·5 | near 4·75<br>5·36 |

The diacetate (XXII) was brominated and the resulting 5α-bromo compound was rearranged to the 7α-bromo compound (XXIII) by warming the solution at 50° for 2 hr. The crude material was submitted to the next procedure, because it is fully established that such a treatment of 6-oxo-steroid yields 7α-bromo compound.[4c, 9, 16] Thus the dehydrobromination[17] gave the 7-en-6-oxo compound (XXIV). Its structure was established from UV, IR and NMR data (Experimental). In NMR spectrum, chemical shifts and patterns of 7-H, 19-$CH_3$, 2α-H and 3α-H support its structure as shown in Table 1.

The enol acetylation[18] of XXIV yielded the enol acetate (XXV), which was proved to be the 6,8(14)-diene by UV spectrum ($\lambda_{max}$ 250 mμ) and was submitted to the next procedure without purification. The crude enol acetate (XXV) was oxidized[19] to yield the 14α-OH compound (XXVI). Its structure was readily proved by IR, UV, and NMR spectra. In its IR spectrum, an OH and α,β-unsaturated oxo bands were observed at 3470 and 1667 $cm^{-1}$, respectively, and the maximum absorption appeared at 240 mμ in its UV spectrum. Both observations indicate that an OH group was introduced into the 7-en-6-oxo structure. In the NMR spectrum, the signal of 7-H in XXVI shows a doublet centered at 6·00 ppm, while a triplet is centered at 5·81 ppm in XXIV. It has been reported[16, 20] that the long-range coupling of 7-H with 9α-H and 14α-H was observed in an unsubstituted 7-en-6-oxo system, and accordingly,


9 steps
XIII
XIV
XV
XVI
XVII
XVIII
XIX
XX

RO
RO
H
O
XXI : R = H
XXII: R = Ac
AcO
AcO
Br
XXIII
XXIV
OAc
XXV
OH
OH
HO
HO
XXIX
XXVIII
XXVII
XXVI

Chart 2

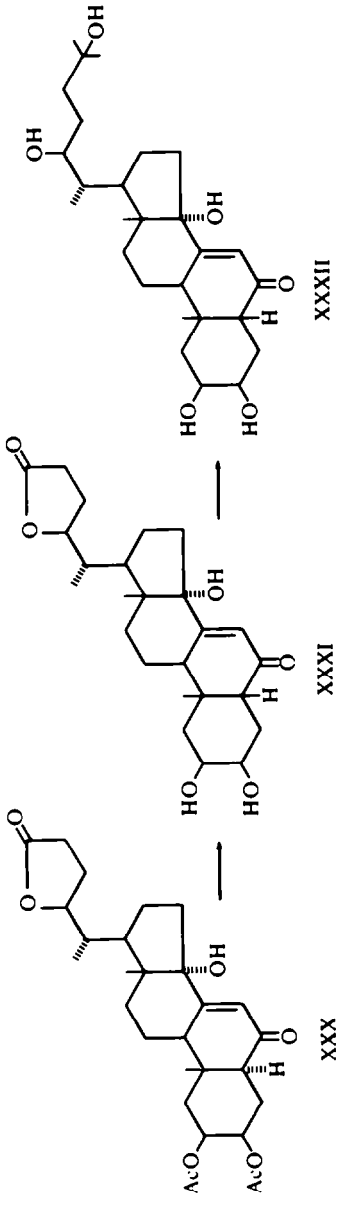


Chart 3

the 7-H proton shows a triplet as in XXIV. From this fact an OH group must have been introduced at C-9 or C-14. While the chemical shift of the 18-Me group in XXVI appeared in a lower field (0·08 ppm) compared with that of XXIV, no shift was observed in the 19-Me signal. This suggests strongly that an OH group was introduced at the 14α-position.[21]

The remaining processes for the synthesis of ecdysone were hydrolysis of the 2β,3β-diacetoxyl group accompanied by isomerization at C-5 and Grignard reaction of the lactone group in the side chain. Suitable reaction conditions for such processes were fully established by experiments on a model compound.[9,10] Isomerization at C-5 including hydrolysis was realized by treatment of the 2β,3β-diacetoxy-14α-hydroxy-5α-7-en-6-oxo-steroid with boiling 90% methanol containing potassium carbonate, and the ratio of the 5α- to 5β-compounds was usually 1:4–5. This isomerization was possible because of the interaction of the 2β-OH and 19-Me groups (1:3-diaxial interaction) in the 5α-series. Fortunately, the ring structure of ecdysone (2β,3β,14α-trihydroxy-5β-7-en-6-oxo group) is relatively inactive to Grignard reagents. This inertness made it possible to effect only a two-steps synthesis of 22-isoecdysone from XXX[16] as shown in Chart 3 (XXX → XXXI → XXXII).

On the basis of these observations, the synthesis of ecdysone from XXVI should also be realized in two steps. The treatment of XXVI with potassium carbonate in 90% methanol gave a mixture of XXVII and XXVIII, from which the two compounds were separated in a pure state by preparative TLC. The ratio of isomers (5α:5β = 1:4) was consistent with that observed on a model compound such as 2β,3β,14α-trihydroxy-5α-cholest-7-en-6-one.[9,16] The reaction of XXVIII with methylmagnesium bromide afforded the desired ecdysone. Its IR spectrum was identical with that reported for the natural product[22] and all other physical properties (m.p., UV, optical rotation, NMR, and MS) were also consistent with those of natural ecdysone.

## EXPERIMENTAL

All m.ps are uncorrected. Optical rotations were measured in $CHCl_3$ soln unless otherwise stated. IR spectra were recorded on a Hitachi EPI-G2 spectrometer as KBr pellets unless otherwise stated, and UV spectra on a Hitachi EPS-3 spectrometer in EtOH soln. ORD were measured on a Shimadzu ORD apparatus. NMR spectra were measured at 60 MHz on a Hitachi H-60 spectrometer and at 100 MHz on a Japan Electron Optics 4H-100 spectrometer using $CDCl_3$ as solvent unless otherwise stated. Chemical shifts are given in ppm downfield from internal TMS and coupling constants ($J$) in Hz. Abbreviations: s = singlet, d = doublet and m = multiplet.

(22R)-3β,22-*Dihydroxy*-6-*oxo*-25-*homo*-5α-*cholan*-25-*oic acid* 25 → 22-*lactone* (XV)

To a soln of XIV (1·18 g) in $CH_2Cl_2$ (60 ml) and EtOH (60 ml) was added powdered $NaBH_4$ (0·115 g) at −7 ~ −10°. The mixture was stirred for 30 min at the same temp and then cooled to −30°. After addition of AcOH and 10% HCl, the product isolated with $CH_2Cl_2$–ether mixture and crystallized from MeOH to give XV (0·965 g). An analytical sample was obtained by preparative TLC followed by crystallization from MeOH as colourless prisms, m.p. 222–223°; $[\alpha]_{578}^{20}$ −7° ($c$, 0·607); ORD ($c$, 0·240; $CHCl_3$): $[\alpha]_{700}$ −22°, $[\alpha]_{589}$ −29°, $[\alpha]_{314}$ −750°, (trough), $[\alpha]_{276}$ +749° (peak), $[\alpha]_{260}$ +578°. (Found: C, 74·59; H, 9·62. $C_{25}H_{38}O_4$ requires: C, 74·59; H, 9·52%).

(22R)-6,6-*Ethylenedioxy*-22-*hydroxy*-3-*oxo*-25-*homo*-5α-*cholan*-25-*oic acid* 25 → 22-*lactone* (XVII)

A portion of the benzene in a soln of XV (0·205 g) in benzene (60 ml) and ethylene glycol (10 ml) was removed by distillation. After addition of *p*-toluenesulfonic acid (0·06 g), distillation was continued for 5 hr during which benzene was added to maintain a constant volume. After cooling, pyridine and then

$CH_2Cl_2$–ether were added, and the soln was washed with $H_2O$, and dried ($Na_2SO_4$). Evaporation of the solvent left XVI as an oily substance.

A soln of XVI in pyridine (4 ml) was added to a pyridine–$CrO_3$ complex prepared from pyridine (4 ml) and $CrO_3$ (0·4 g) at 0°, and the mixture was kept at room temp overnight. Ether–$CH_2Cl_2$ (1:1) was added and the ppt was removed by filtration with the aid of celite. The filtrate was washed with $H_2O$ and passed through a Florisil (2 g) column. Removal of the solvent afforded a solid (0·184 g), which was sufficiently pure for the next reaction. An analytical sample was obtained by crystallization from MeOH containing a trace of pyridine, colourless prisms, m.p. 224–228°; $[\alpha]_{578}^{20}$ +28° (*c*, 0·966); IR $\nu_{max}$: 1768 (lactone); 1702 $cm^{-1}$ (C=O); ORD (*c*, 0·397; $CHCl_3$): $[\alpha]_{700}$ −4°, $[\alpha]_{589}$ 0°, $[\alpha]_{312}$ +566° (peak), $[\alpha]_{272}$ −715°(trough), $[\alpha]_{260}$ −630°. (Found: C, 72·76; H, 9·43. $C_{27}H_{40}O_5$ requires: C, 72·94; H, 9·07%).

(22R)-2β,3β,22-*Trihydroxy*-6-*oxo*-25-*homo*-5α-*cholan*-25-*oic acid* 25 → 22-*lactone* (XXI)

(a) *From the ketal* (XVII). A soln of XVII (1·8 g) in THF (40 ml) was added to t-BuOH (200 ml) in which K metal (6·0 g) was dissolved beforehand, and the soln was shaken in $O_2$ atmosphere for 10 min, and poured into ice-water. After the pH was adjusted to 2·0 by addition of 10% HCl, the product was isolated with ether–$CH_2Cl_2$.

The product obtained was dissolved in MeOH (200 ml) and $NaBH_4$ (2·0 g) was added. The soln was allowed to stand at room temp for 30 min and refluxed for 30 min. After addition of 50% AcOH (200 ml), the soln was refluxed for 2 hr, and poured into $H_2O$. The product was isolated with ether–$CH_2Cl_2$ to give a crystalline residue. This was submitted to preparative TLC, and the material from the main fraction was crystallized from MeOH to afford XXI (0·568 g). An analytical sample was obtained by further crystallization from MeOH, colourless leaflets, m.p. 254–258°; $[\alpha]_{578}^{20}$ 0° (*c*, 0·595). (Found: C, 71·72; H, 9·18. $C_{25}H_{38}O_5$ requires: C, 71·74; H, 9·15%).

(b) *From the acetonide* (XX). A soln of XX (0·048 g) in EtOH (5 ml) and 10% $H_3PO_4$ (1 ml) was refluxed for 2 hr, and poured into $H_2O$. The product was isolated with ether-$CH_2Cl_2$ to give a crystalline solid, m.p. 243–248°, the IR spectrum of which was identical with that of the sample described.

(22R)-22-*Hydroxy*-2β,3β-*isopropylidenedioxy*-6-*oxo*-25-*homo*-5α-*cholan*-25-*oic acid* 25 → 22 *lactone* (XX)

The triol mixture (XIX) obtained from XVII (0·18 g) by the procedure described was dissolved in $Me_2CO$ (30 ml) and 5% phosphomolybdic acid in $Me_2CO$ (2·25 ml) was added. The soln was allowed to stand for 15 min at room temp and 30% $NH_4OH$ was added. The product was isolated with ether–$CH_2Cl_2$ to give a crystalline residue, which was chromatographed on Florisil (4 g). The acetonide XX (0·048 g) was eluted with ether. An analytical sample was obtained by crystallization from MeOH as colourless prisms, m.p. 238–241°, $[\alpha]_{578}^{20}$ +17° (*c*, 0·483). (Found: C, 72·60; H, 9·52. $C_{28}H_{42}O_5$ requires: C, 73·32; H, 9·23%).

(22R)-2β,3β-*Diacetoxy*-22-*hydroxy*-6-*oxo*-25-*homo*-5α-*cholan*-25-*oic acid* 25 → 22-*lactone* (XXII)

A soln of XXI (0·568 g) in $Ac_2O$ (30 ml) was refluxed for 2 hr and poured into $H_2O$. The product was isolated with ether–$CH_2Cl_2$ to give a crystalline residue, which on crystallization from MeOH afforded XXII (0·543 g). An analytical sample was obtained by further crystallization from MeOH as colourless needles, m.p. 230–233°, $[\alpha]_{578}^{20}$ +4° (*c*, 0·908); IR $\nu_{max}$: 1774 (lactone); 1740 (OAc); 1708 $cm^{-1}$ (C=O); NMR: 0·71 (18-$CH_3$, 3H, s); 0·94 (19-$CH_3$, 3H, s); 0·87 (21-$CH_3$, 3H, d, $J$ = 6·0); 1·99 (OAc, 3H, s); 2·07 (OAc, 3H, s); 4·73 (3α-H, and 22-H, 2H, very broad m); 5·27 (2α-H, 1H, d like signal, half-band width 7·5). (Found: C, 69·22; H, 8·47. $C_{29}H_{42}O_7$ requires: C, 69·29; H, 8·42%).

(22R)-2β,3β-*Diacetoxy*-22-*hydroxy*-6-*oxo*-25-*homo*-5α-*chol*-7-*en*-25-*oic acid* 25 → 22-*lactone* (XXIV)

To a soln of XXII (0·48 g) in AcOH (10 ml) was added 3% HBr in AcOH (one drop) and $Br_2$ (0·152 g) in AcOH (1 ml). The soln was stirred at 50° in $N_2$ atmosphere for 2 hr and poured into $H_2O$. The product was isolated with ether–$CH_2Cl_2$ to give crystalline XXIII which was submitted directly to the following reaction.

A soln of the crude XXIII in DMF (5 ml) was refluxed with $Li_2CO_3$ (0·25 g) for 2 hr in $N_2$ atmosphere. After addition of 10% HCl, the product was isolated with ether–$CH_2Cl_2$ and crystallized from MeOH to give XXIV (0·244 g). An analytical sample was obtained by further crystallization from MeOH–$CH_2Cl_2$ as colourless needles, m.p. 271–274°, $[\alpha]_{578}^{20}$ +20° (*c*, 0·662); IR $\nu_{max}$: 1770 (lactone); 1740 (OAc); 1666 (C=O); 1615 $cm^{-1}$ (C=C); NMR: 0·65 (18-$CH_3$, 3H, s); 0·95 (21-$CH_3$, 3H, d, $J$ = 6·0; 1·01 (19-$CH_3$, 3H, s); 5·81 (7-H, 1H, t, $J$ = 2·5); UV $\lambda_{max}$: 244 mμ (ε, 14,200). (Found: C, 69·03; H, 8·45. $C_{29}H_{40}O_7$ requires: C, 69·57; H, 8·05%).

(22R)-2β,3β-*Diacetoxy*-14α,22-*dihydroxy*-6-*oxo*-25-*homo*-5α-*chol*-7-*en*-25-*oic acid* 25 → 22-*lactone* (XXVI)

A soln of XXIV (0·188 g) in 0·001 M $HClO_4$ in EtOAc (18 ml) and $Ac_2O$ (2 ml) was allowed to stand at room temp for 30 min. $H_2O$ was added and the mixture was stirred at room temp for 30 min to decompose $Ac_2O$. The product was isolated with ether–$CH_2Cl_2$ to give an oily material.

To a soln of this oily material in ether (10 ml) and THF (10 ml) was added a soln of monoperphthalic acid (0·089 g) in ether (0·74 ml), and the soln was allowed to stand at dark place overnight. The product was isolated with ether–$CH_2Cl_2$ and crystallized from MeOH to give XXVI (0·073 g). The material obtained from the mother liquor was submitted to preparative TLC followed by crystallization from MeOH to give more XXVI (0·016 g). An analytical sample was obtained by crystallization from MeOH–$CH_2Cl_2$ as colourless needles, m.p. 269–272°, $[\alpha]_{578}^{20}$ +70° (*c*, 0·611); IR $\nu_{max}$: 3470 (OH); 1757 (lactone); 1662 (C=O); 1616 $cm^{-1}$ (C=C); NMR: 0·73 (18-$CH_3$, 3H, s); 0·94 (21-$CH_3$, 3H, d, $J$ = 6·0); 1·01 (19-$CH_3$, 3H, s); 6·00 (7-H, 1H, d, $J$ = 2·5); UV $\lambda_{max}$: 240 mμ (ε, 12,700). (Found: C, 67·39; H, 8·05. $C_{29}H_{40}O_8$ requires: C, 67·42; H, 7·80%).

(22R)-2β,3β,14α,22-*Tetrahydroxy*-6-*oxo*-25-*homo*-5α-*chol*-7-*en*-25-*oic acid* 25 → 22-*lactone* (XXVII) *and* (22R)-2β,3β,14α,22-*tetrahydroxy*-6-*oxo*-25-*homo*-5β-*chol*-7-*en*-25-*oic acid* 25 → 22-*lactone* (XXVIII)

A soln of XXVI (0·085 g) in 0·6% $K_2CO_3$ in 90% MeOH (18 ml) was allowed to stand at room temp for 30 min, and refluxed for 30 min. After addition of $H_2O$, the pH was adjusted to 2·0 by addition of 10% HCl. The product was isolated with n-BuOH and dissolved in MeOH (20 ml). After addition of *p*-toluenesulfonic acid (0·025 g), the soln was allowed to stand at room temp for 30 min. $H_2O$ was added and the product was isolated with n-BuOH–ether and submitted to preparative TLC (Merck $GF_{254}$: developing solvent, $CH_2Cl_2$–$Me_2CO$–EtOH (80:20:5)). The chromatogram consists of two main fractions except minor patterns. From a polar fraction, XXVIII was obtained. Crystallization from MeOH afforded colourless prisms (0·037 g), m.p. 264–266°, $[\alpha]_{578}^{20}$ +79° (*c*, 0·043; EtOH); UV $\lambda_{max}$ 243 mμ (ε, 10,600). (Found: C, 69·52; H, 8·43. $C_{25}H_{36}O_6$ requires: C, 69·42; H, 8·39%).

From a nonpolar fraction, XXVII was obtained. Crystallization from MeOH afforded colourless needles (0·007 g), m.p. 243° (dec); $[\alpha]_D^{25}$ +32° (*c*, 0·297; EtOH); UV $\lambda_{max}$ 240·5 mμ (ε, 11,200). (Found: C, 69·22; H, 8·44. $C_{25}H_{36}O_6$ requires: C, 69·42; H, 8·39%).

(22R)-2β,3β,14α,22,25-*Pentahydroxy*-5β-*cholest*-7-*en*-6-*one* (*Ecdysone*) (XXIX)

To a soln of XXVIII (0·043 g) in THF (20 ml) was added dropwise the Grignard reagent prepared from Mg (0·50 g), MeBr (0·20 g) and THF (20 ml) at 0° and the mixture was stirred for 30 min at 0°. The mixture was cooled at −30° and ice was added to decompose excess Grignard reagent. After addition of 10% $NH_4Cl$, the product was extracted with n-BuOH and the organic layer was washed with 10% $NH_4Cl$ and $H_2O$. The solvent was removed by distillation *in vacuo*, and the residue was submitted to preparative TLC (silica gel Merck $GF_{254}$; developing system $CHCl_3$–MeOH (9:1)). Ecdysone (XXIX) was obtained from the main fraction. Crystallization from MeOH–EtOAc gave colourless prism (0·015 g), m.p. 238–239°, $[\alpha]_{578}^{20}$ +62° (*c*, 0·355, EtOH); NMR ($C_5D_5N$): 0·74 (18-$CH_3$, 3H, s); 1·08 (19-$CH_3$, 3H, s); 1·29 (21-$CH_3$, 3H, d, $J$ = 6·0); 1·39 (26,27-$CH_3$, 6H, s); 6·25 (7-H, 1H, d, $J$ = 2·5); UV $\lambda_{max}$ 243 mμ (ε, 11,600); MS *m/e*: 464 ($M^+$), 446 ($M^+$-18), 431 (446–15), 428, 413, 410, 395, 348, 330, 327, 315, 300, 279, 250, 99, 81, 69, 55.

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