AN ALTERNATIVE ROUTE TO OSLADINE AGLYCONE FROM SOLASODINE

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(22*S*,25*R*)-26-Acetylamino-3β,22-bistetrahydropyranyloxy-5-cholestene (*XIVa*), an intermediate in the partial synthesis of osladine aglycone reported in our previous paper, has been prepared by an alternative route *via* dihydrosolasodenol derivative *IIIa*.

In our preceding paper[1] we reported a partial synthesis of osladine aglycone from the steroid alkaloid solasodine. A characteristic feature of this synthesis was the opening of the spirosolane side chain by acetylation in a strongly acidic medium.

In the present paper an alternative route is reported whereby the E-ring of solasodine is opened by reduction with complex hydrides. Solasodine (*I*) was thus converted to dihydrosolasodenol A (*IIc*) on treatment with lithium aluminum hydride or sodium borohydride according to the reported procedure[2]. Further procedure required protection of the amino function and removal of the oxygen substituent at the 16--position. Acetylated derivatives *IIb* and *IIIb* are known[3,4]. However, if acetylation was used for protection of the amino group, hydrolysis of the acetamido group was extremely difficult at the later stage of the synthesis. Somewhat better results were achieved with formylation leading to the compound *IIa*. No difficulties were encountered in selective alkaline hydrolysis with potassium carbonate of O-acyl groups to yield *IIIa* or *IIIb*. Selective oxidation of the 16-hydroxyl group was performed according to a procedure reported[5] for the N-acetyl derivative *IIIb* to give the 16-oxo derivative *IVa* or the known[5] compound *IVb*. The thioketals *Va* and *Vb* were prepared and desulfurized with Raney nickel in the conventional manner. Difficulties were encountered in alkaline saponification of the acyl derivatives *VIa* and *VIb*. Even under vigorous conditions (refluxing with potassium hydroxide in ethylene glycol for 70 hours) 75% of unreacted N-acetyl derivative *VIb* was recovered, the yield of the desired dihydroisoverazine *VII* being 23%. Similar hydrolysis of the N-formyl derivative *VIa* yielded the base *VII* in 39% yield but no starting material could be recovered. Subsequent steps involved preparation of isoverazine (deoxotomatillidine) *IX via* the chloroamine *VIII*. A synthesis of isoverazine was reported by Bianchi and

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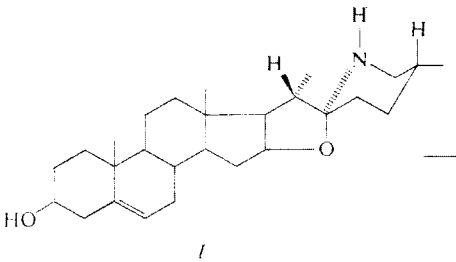
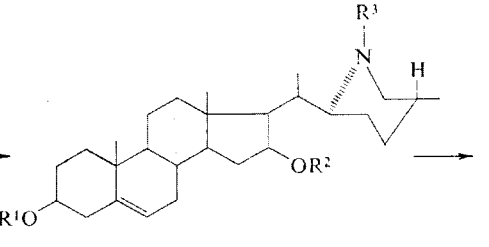
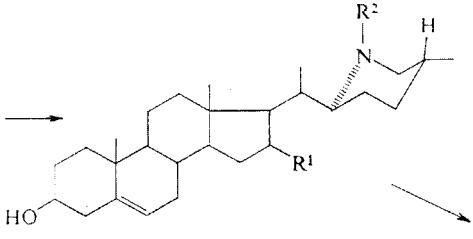


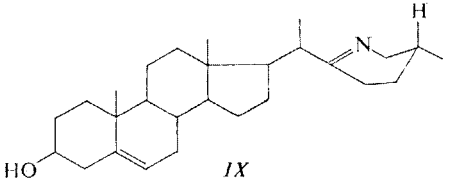
I



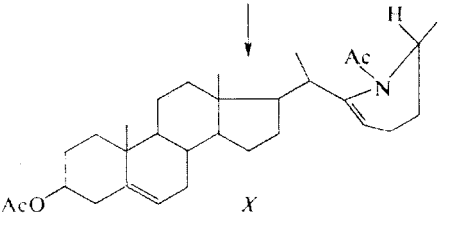
IIa; $R^1 = R^2 = R^3 = CHO$
IIb; $R^1 = R^2 = R^3 = Rc$
IIc; $R^1 = R^2 = R^3 = H$
IIIa; $R^1 = R^2 = OH$, $R^3 = CHO$
IIIb; $R^1 = R^2 = OH$, $R^3 = Rc$



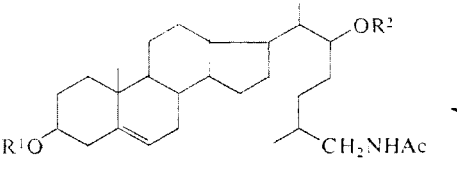
IVa; $R^1 =$  , $R^2 = CHO$
IVb; $R^1 =$, $R^2 = Ac$
Va; $R^1 =$  , $R^2 = CHO$
Vb; $R^1 =$, $R^2 = Ac$
VIa; $R^1 = H_2$, $R^2 = CHO$
VIb; $R^1 = H_2$, $R^2 = Ac$.
VII; $R^1 = H_2$, $R^2 = H$
VIII; $R^1 = H_2$, $R^2 = Cl$



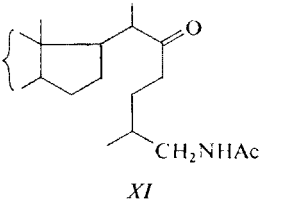
IX



X



XIIa; $R^1 = Ac$, $R^2 = H$, 22*S*
XIIb; $R^1 = Ac$, $R^2 = H$, 22*R*
XIIIa; $R^1 = R^2 = H$, 22*S*
XIIIb; $R^1 = R^2 = H$, 22*R*
XIVa; $R^1 = R^2 =$ THP, 22*S*
XIVb; $R^1 = R^2 =$ THP 22*R*



XI

Ac = CH_3CO, THP = tetrahydropyranyl

coworkers[6] using a different approach. The azomethine *IX* was then converted *via X* to the known[6] 22-oxocholestane derivative *XI* in the described manner. Reduction of the 22-oxo group with sodium borohydride led to a mixture of epimeric

22-hydroxy derivatives *XIIa* and *XIIb*. Saponification of the 3-acetoxy group followed by protecting the hydroxyls by treatment with dihydropyran led to compounds *XIVa* and *XIVb* already described in the preceding paper[1]. Since (22*S*)-epimer *XIVa* was converted[1] to osladine aglycone, the synthesis of *XIVa*, described in the present paper, represents a partical synthesis of this aglycone.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Unless stated otherwise, optical rotations were measured in chloroform. The infrared spectra were measured on a Zeiss UR 10 spectrophotometer. The ^{1}H-NMR spectra were measured on a Varian HA-100 instrument in deuteriochloroform using tetramethylsilane as an internal reference.

(22*S*,25*R*)-22,26-Formylepimino-5-cholestene-3β,16β-diol 3,16-diformate (*IIa*)

Dihydrosolasodenol A (*IIc*, 15 g) in pyridine (250 ml) was treated at 0°C with a solution of acetic--formic anhydride prepared from formic acid 99%, (290 ml) and acetic anhydride (120 ml) at 0°C. After standing at room temperature overnight, the mixture was poured on an ice-cooled sodium chloride solution and neutralized with aqueous ammonia. The precipitate was filtered with suction washed with water and dried. Chromatography over silica gel (1 000 g) in benzene–acetone (1 : 40) yielded the formyl derivative *IIa* (12·5 g), m.p. 185—189°C; repeated crystallization from benzene–-ligroin gave the product (10 g, 56%), m.p. 192—194°C, $[\alpha]_D^{20}$ — 8° (*c* 0·74). IR spectrum: 1 677 (CON—); 1 729, 1 178 (HCOO—C); 3 030 cm^{-1} (double bond). For $C_{30}H_{45}NO_5$ (499·7) calculated: 72·11% C, 9·08% H, 2·80% N; found: 72·15% C, 9·06% H, 3·07% N.

(22*S*,25*R*)-22,26-Formylepimino-5-cholestene-3β,16β-diol (*IIIa*)

A solution of the triformyl derivative *IIa* (14 g) in methanol (1·5 l) was treated with an aqueous solution (60 ml) of potassium carbonate (11 g) at 34°C overnight. The solution was concentrated to one half of the original volume, diluted with water, the precipitate was filtered, washed with water and dried. Chromatography over silica gel (1 200 g) in benzene–chloroform–acetone (2 : 2 : 1) gave the diol *IIIa* (10·5 g), after repeated crystallization from aqueous methanol m.p. 146—147°C (7·8 g, 63%), $[\alpha]_D^{20}$ — 21°. IR spectrum: 1 658 (HCO—N); 3 610, 1 045, 1 021 cm^{-1} (OH). For $C_{28}H_{45}NO_3$ (443·7) calculated: 75·80% C, 10·22% H, 3·16% N; found: 75·79% C, 10·01% H, 3·17% N.

(22*S*,25*R*)-22,26-Formylepimino-3β-hydroxy-5-cholesten-16-one (*IVa*)

The title compound was prepared analogously as N-acetyl derivative *IVb* (ref.[5]): Oxidation of the diol *IIIa* (3·2 g) followed by crystallization from benzene–ligroin and from aqueous methanol, yielded the 16-oxo derivative *IVa* (1.02 g, 32%), m.p. 234—235°C, $[\alpha]_D^{20}$ — 85° (*c* 0·74). IR spectrum: 1 732 (CO); 1 660 (HCON); 3 600 cm^{-1} (OH). ^{1}H-NMR spectrum :0·835 d, J = 7 Hz, 3 H, (27-CH_3); 0·870 d, J = 6·5 Hz, 3 H, (21-CH_3); 0·990 s, 3 H, (18-CH_3); 1·040 s, 3 H, (19-CH_3); 4·670 mt, 1 H (CHOH); 1·640 br s, quenched on addition of D_2O (OH); 5·35 mt, 1 H (olefinic); 8·040 mt, 1 H (N—CHO). For $C_{28}H_{43}NO_3$ (441·6) calculated: 76·15% C, 9·81% H, 3·17% N; found: 76·35% C, 9·83% H, 3·36% N.

(22*S*,25*R*)-22,26-Acetylepimino-3β-hydroxy-5-cholesten-16-one 16-ethylenethioketal (*Vb*)

Dry hydrogen chloride was passed through a solution of the 16-oxo derivative *IVb* (2 g) in ethanedithiol (25 ml) for one hour, the mixture was set aside at room temperature overnight, then treated with excess potassium carbonate and extracted with chloroform. The extract was washed with potassium hydroxide (10%), dried with potassium carbonate and evaporated to dryness under reduced pressure. Chromatography over silica gel (100 g) in benzene–chloroform–acetone (2 : 2 : 1) and crystallization from benzene–ligroin yielded the thioketal (1·8 g, 77%), m.p. 234—237°C, $[\alpha]_D^{20}$ — 65° (*c* 0·79). IR spectrum: 1618 (N—$COCH_3$); 3605 cm^{-1} (OH). For $C_{31}H_{49}NO_2S_2$ (531·8) calculated: 70·00% C, 9·29% H, 2·63% N, 12·06% S; found: 69·83% C, 9·12% H, 2·31% N, 11·57% S.

(22*S*,25*R*)-22,26-Formylepimino-3β-hydroxy-5-cholesten-16-one 16-ethylenethioketal (*Va*)

The same procedure applied to the 16-oxo-N-formyl derivative *IVa* (2·5 g) furnished the thioketal *Va*, m.p. 206—208°C, which after chromatography over silica gel (150 g) in benzene–chloroform–acetone (2 : 2 : 1) and crystallization from ethanol (2·1 g, 72%) melted at 221—224°C, $[\alpha]_D^{20}$ — — 58°C (*c* 0·74). IR spectrum: 1038, 3600 (OH); 1659 cm^{-1} (NCHO). For $C_{30}H_{47}NO_2S_2$ (517·8) calculated: 69·58% C, 9·15% H, 2·71% N, 12·38% S; found: 69·39% C, 8·98% H, 2·80% N 12·55% S.

(22*S*,25*R*)-22,26-Acetylepimino-5-cholesten-3β-ol (*VIb*)

A solution of the thioketal *Vb* (50 g) in ethanol (1000 ml, 99%) was refluxed with Raney nickel (suspension, 100 ml). The same amount of the nickel suspension was added twice more during an overall 3 hours refluxing. After filtration and evaporation of the solvent the residue (32 g) was filtrated free of polar impurities by passing through a column of silica gel (300 g) in benzene–chloroform–acetone (5 : 4 : 1) and the product (24 g, m.p. 240—245°C) chromatographed over silica gel (900 g) in benzene–acetone (5 : 1). Crystallization from aqueous methanol yielded the pure product (14·6 g, 35%), m.p. 247—249°C, $[\alpha]_D^{20}$ — 4° (*c* 0·74). IR spectrum: 1620 ($NCOCH_3$); 3605 (OH); 3014, 3038, 3065, 3085 cm^{-1} (double bond). ^{1}H-NMR spectrum: 0·91 s, 3 H (18-CH_3); 1·03 s, 3 H (19-CH_3; 2·08 s, 3 H (CH_3COO); 4·51 mt, 1 H (—CHO—); 5·34 d, J = 5 Hz, 1 H (olefinic). For $C_{29}H_{47}NO_2$ (441·7) calculated: 78·80% C, 10·70% H, 3·25% N; found: 78·58% C, 10·61% H, 3·48% N.

(22*S*,25*R*)-22,26-Formylepimino-5-cholesten-3β-ol (*VIa*)

The thioketal *Va* (23 g) in ethanol (1000 ml) was treated with Raney Ni (3 × 50 ml suspension) as in the case of *Vb*. The crude product was prepurified by passage through a column of silica gel (200 g) in benzene–acetone (4 : 1) and then chromatographed on silica gel (800 g) in benzene–acetone (9 : 1) to give the compound *VIa* (10·2 g, 54%), m.p. 225—230°C. The analytical sample melted at 229—232°C (ligroin–acetone), $[\alpha]_D^{22}$ + 8° (*c* 0·74). IR spectrum: 1042, 3600 (OH); 1658 cm^{-1} (NCHO). ^{1}H-NMR spectrum: 0·834 d, J = 6 Hz, 3 H (27-CH_3); 0·816 s, 3 H (18-CH_3); 0·94 d, J = 6·6 Hz; 3 H (21-CH_3); 1·02 s, 3 H (19-CH_3); 3·51 br mt, ($C_{(3)}$HOH); 5·36 mt, 1 H, (olefinic); 8·16 mt, 1 H (NCHO). For $C_{28}H_{45}NO_2$ (427·6) calculated: 78·63% C, 10·61% H, 3·28% N; found: 78·45% C, 10·78% H, 3·51% N.

(22*S*,25*R*)-22,26-Epimino-5-cholesten-3β-ol (Dihydroisoverazine, *VII*)

a) A solution of the N-formyl derivative *VIa* (12 g) and potassium hydroxide (60 g) in ethylene glycol (800 ml) was heated at reflux temperature overnight. The cooled solution was poured on

ice, the precipitate filtered, washed with water and dried. The crude product (10 g) was repeatedly crystallized from benzene–ligroin to give *VII* (2·34 g, 21%), m.p. 235—238°C, $[\alpha]_D^{22}$ + 19° (*c* 0·74). Chromatography of the mother liquors over silica gel (400 g) in chloroform–methanol (10 : 1) saturated with gaseous ammonia, and crystallization from benzene–ligroin yielded an additional amount of the product, m.p. 234—238°C (2·03 g, 18%). IR spectrum: 1045, 3600 (OH), 1667, 1672 (double bond), 3200 cm^{-1} (NH assoc.). ^{1}H-NMR spectrum: 0·68 s, 3 H (18 CH_3), 0·865 d, J = 6 Hz, 3 H (27-CH_3); 0·90 d, J = 6 Hz, 3 H (21-CH_3), 0·99 s, 3 H (19 CH_3); 3·50 br mt (3α-H); 5·34 mt, 1 H (olefinic). For $C_{27}H_{45}NO$ (399·6) calculated: 81·13 C, 11·35% H, 3·51% N; found: 80·89% C, 11·30% H, 3·58% N.

b) A solution of the N-acetyl derivative *VIb* (11·3 g) and potassium hydroxide (113 g) in ethylene glycol (750 ml) was refluxed under nitrogen atmosphere for 72 hours. After working up as under *a*) the crude product (10·3 g) was purified by chromatography over silica gel (750 g). Elution with benzene–chloroform–acetone (2 : 2 : 1) gave unreacted *VIb* (8·4 g). Elution with the same solvent mixture, saturated with gaseous ammonia, furnished *VII* (2·4 g, 23%), m.p. 215—217°C. Repeated crystallization from aqueous ethanol gave pure *VII*, m.p. 233—236°C, undepressed on admixture with the product obtained by the procedure *a*). The IR spectra of both compounds were identical.

(22*S*,25*R*)-22,26-Chloroepimino-5-cholesten-3β-ol (*VIII*)

N-chlorosuccinimide (1·3 g) was added with stirring to a solution of *VII* (3·7 g) in dichloromethane (500 ml) under cooling with ice. The solution was allowed to stand at room temperaturefor 1·5 hours, washed with water three times, dried with magnesium sulfate and the filtrate evaporated under reduced pressure. The residue (3·8 g) was sufficiently pure to be used in the following step. The analytical sample was obtained by chromatography over silica gel in light petroleum–acetone (4 : 1) followed by crystallization from light petroleum–ether, m.p. 220—245°C (decomp.), $[\alpha]_D^{20}$ — 32° (*c* 0·74). IR spectrum: 1043, 3600 (OH); 1667 cm^{-1} (double bond). ^{1}HNMR spectrum: 0·69 s, 3 H (18-CH_3); 0·996 s, 3 H (19-CH_3); 0·837 d, J = 6·6 Hz, 3 H (27-CH_3); 1·01 d, J = 6·0 Hz, 3 H (21-CH_3); 3·49 mt, 1 H (3α-H); 5·33 mt, 1 H (olefinic). For $C_{27}H_{44}ClNO$ (434·1) calculated: 74·70% C, 10·22% H, 3·23% N, 8·17% Cl; found: 74·87% C, 10·45% H, 3·62% N, 8·11% Cl.

(25*R*)-22,26-Epimino-5,22(N)-cholestadien-3β-ol (Deoxotomatillidine, Isoverazine, *IX*)

A solution of N-chloroamine *VIII* (0·44 g) in benzene (20 ml) was treated under nitrogen atmosphere with diazabicycloundecene (2 ml) at 35°C overnight. The solution was then washed five times with water, dried with magnesium sulfate and the solvent evaporated under reduced pressure. Chromatography over alumina in benzene–ether and ether gave isoverazine (300 mg, 74%), m.p. 132—136°C after repeated crystallization from aqueous methanol, $[\alpha]_D^{22}$ + 6° (*c* 0·74). Literature[6] reports m.p. 139—141°C, $[\alpha]_D^{20}$ + 4° (methanol). IR spectrum: 1688 (C=N); 3410 cm^{-1} (OH). ^{1}H-NMR spectrum: 0·790 s, 3 H (18-CH_3); 0·99 s, 3 H (19-CH_3); 1·075 d, J = 6·5 Hz (sec-CH_3); 1305 d, J = 7·0 Hz (sec-CH_3); 3·23 br mt (C<u>H</u>—O); 5·28 mt, 1 H (olefinic).

3-*Acetate X* was obtained following the reported[6] acetylation procedure, m.p. 167—169°C, $[\alpha]_{20}^{D}$ + 4°, literature[6] reports m.p. 160—161°C, $[\alpha]_D$ + 3°. IR and ^{1}H-NMR spectra are in agreement with the formula and literature data[6].

(22*R*,25*R*)-26-Acetylamino-5-cholesten-3β,22-diol 3-Acetate (*XIIb*) and (22*S*,25*R*)Isomer *XIIa*

A solution of the 22-oxo derivative[6] *XI* (320 mg) in methanol (30 ml) was treated with sodium borohydride (660 mg) for 3 hours at room temperature. The mixture was diluted with ammonia,

the precipitate taken up in ether, the solution washed with water, dried with magnesium sulfate and the solvent removed under reduced pressure. The product (305 mg) was shown (thin-layer chromatography) to be a mixture of two epimers, the less polar one being preponderant. Chromatography over silica gel (300 g) in chloroform–methanol (99 : 1) furnished the less polar (22*S*)-epimer *XIIa* (160 mg, 50%), m.p. 157—159°C (acetone–ligroin), $[\alpha]_D^{24}$ — 24° (*c* 0·74). IR spectrum: 3610 (OH); 1528, 1668, 3450 ($NHCOCH_3$); 1030, 1259, 1722 cm^{-1} ($OCOCH_3$). ^{1}H-NMR spectrum: 0·67 s, and 1·02 s (2 × 3 H, 18-CH_3, 19-CH_3); 0·89 d, J = 6·5 Hz and 1·09 d, J = = 7·0 Hz (21-CH_3 and 27-CH_3); 1·99 s, and 2·02 s, (2 × $COCH_3$); 1·46 s (OH); 3·10 t, 2 H, J = 7 Hz which collapses into 7 Hz doublet after CD_3COOD addition (—CH_2N—); 3·92 mt, 1 H (C<u>H</u>OH); 4·62 br mt, 1 H (3α-H); 5·36 mt, 1 H (olefinic); 5·84 br mt, 1 H (exchangeable, NH). For $C_{31}H_{51}NO_4$ (501·7) calculated: 74·21% C, 10·25% H, 2·79% N; found: 74·08% C, 9·94% H, 2·83% N. Further elution yielded an intermediate fraction (83 mg) of less and more polar components and the more polar epimer *XIIb* (58 mg, 18%), m.p. 160—163°C (acetone–ligroin), $[\alpha]_D^{22}$ — — 6°C. IR spectrum: 3600 (OH); 1523, 1665, 3450 ($NHCOCH_3$); 1035, 1259, 1721 cm^{-1} ($OCOCH_3$). ^{1}H-NMR spectrum: 0·68 s, 3 H and 0·95 s, 3 H (18-CH_3 and 19-CH_3); 0·85 d, J = 6 Hz, and 0·99 d, J = 6 Hz (27-CH_3 and 21-CH_3); 1·97 s, 2·05 s (2 × $COCH_3$); 3·12 mt, 2 H (CH_2N); 3·60 mt, 1 H (C<u>H</u>OH); 1·41 s (OH); 4·65 br mt, 1 H (3α-H); 5·35 mt, 1 H (olefinic), 5·92 br mt, 1 H (exchangeable, NH). For $C_{31}H_{51}NO_4$ (501·7) found: 73·97% C, 10·01% H, 2·91% N.

(22*R*,25*R*)-26-Acetylamino-5-cholesten-3β,22-diol (*XIIIb*)

A solution of the 3-acetate *XIIb* (25 mg) and potassium carbonate (50 mg) in aqueous methanol (3 ml) was refluxed for 6 hours, the solvent evaporated under reduced pressure, the residue dissolved in ether–chloroform, washed with water, dried with magnesium sulfate and the solvent evaporated *in vacuo*. The product (12 mg, 52%) melts at 181—184°C (acetone–ligroin), $[\alpha]_D^{22}$ + 2°. IR spectrum: 1048, 3600 (OH); 1527, 1664, 3445 cm^{-1} ($NHCOCH_3$). For $C_{29}H_{49}NO_3$ (459·7) calculated: 75·80% C, 10·70% H, 3·05% N; found: 75·68% C, 10·42% H, 2·81% N.

(22*S*,25*R*)-26-Acetylamino-5-cholesten-3β,22-diol (*XIIIa*)

In the same manner, the 3-acetate *XIIa* (35 mg) gave the diol *XIIIa* (19 mg, 58%) m.p. 168 to 171°C (acetone–ligroin), $[\alpha]_D^{20}$ — 21°. IR spectrum: 3600 (OH); 1524, 1665, 3450 cm^{-1} ($NHCOCH_3$). For $C_{29}H_{49}NO_3$ (459·7) calculated: 75·80% C, 10·70% H, 3·05% N; found: 75·71% C, 10·57% H, 2·96% N.

(22*R*,25*R*)-26-Acetylamino-3β,22-bistetrahydropyranyloxy-5-cholestene (*XIVb*)

A mixture of (22*R*)-diol *XIIIb* (92 mg), dihydropyran (0·5 ml) and one drop of hydrochloric acid in chloroform (5 ml) was shaken for one hour and then allowed to stand for two hours at room temperature. The mixture was neutralized with ammonia, diluted with ether, the organic layer washed with water and dried. After evaporation of the solvent under reduced pressure, the residue was chromatographed over silica gel (25 g) in light petroleum–ether–acetone (3 : 1 : 1) to yield an amorphous product (90 mg) which, after precipitation from ether–light petroleum at low temperature and recrystallization from heptane, melted at 158—161°C, $[\alpha]_D^{22}$ — 15° (*c* 0·74) as compared with m.p. 159—161°C and $[\alpha]_D$ — 12° reported in our foregoing paper[1]. The IR and NMR spectra and the migratory rate were identical with those of the authentic sample[1]. The mixture m.p. with authentic sample showed no depression; on the other hand, admixture of the (22S)-epimer *XIVa* caused a depression of 8°C. For $C_{39}H_{65}NO_5$ (627·9) calculated: 74·59% C, 10·43% H, 2·23% N; found: 74·76% C, 10·51% H, 2·10% N.

(22*S*,25*R*)-26-Acetylamino-3β,22-bistetrahydropyranyloxy-5-cholestene (*XIVa*)

The same procedure as in the case of *XIVb* was applied to 69 mg of the (22*S*)-diol *XIIIa*. Chromatography on silica gel (20 g) in light petroleum–ether–acetone (3 : 1 : 1) gave an amorphous (22*S*)-derivative *XIVa* (55 mg). Reprecipitation from ether–light petroleum at low temperature gave the product m.p. 144—148°C, $[\alpha]_D^{22}$ — 22° (*c* 0·74). The values reported[1] are: m.p. 145 to 148°C, $[\alpha]_D^{22}$ — 23°. The compounds showed an identical migratory rate with the authentic sample[1] and exhibited no m.p. depression on admixture with it. The IR and NMR spectra were identical. For $C_{39}H_{65}NO_5$ (627·9) calculated: 74·59% C, 10·43% H, 2·23% N; found: 74·70% C, 10·58% H, 2·17% N.

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