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# PARTIAL SYNTHESIS OF 20(R),22(R)-$\Delta^5$-CHOLESTENE-3$\beta$,20,22, TRIOL


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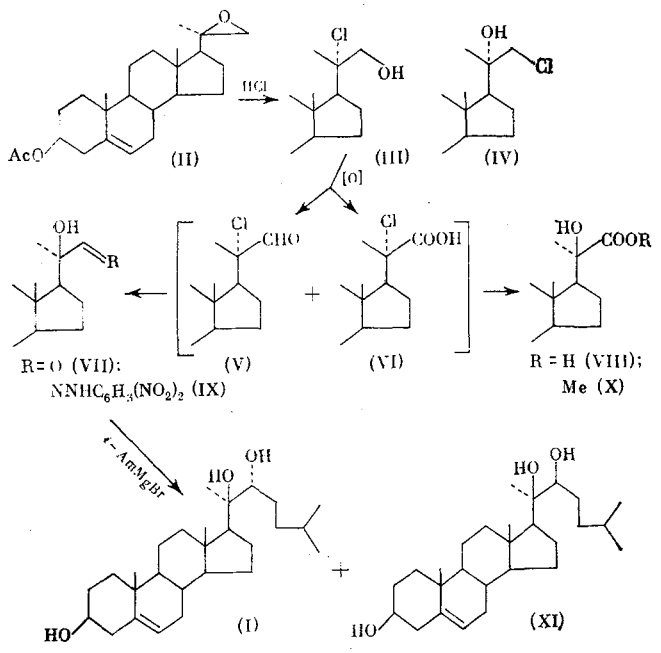
20(R),22(R)-$\Delta^5$-cholestene-3$\beta$,20,22-triol (I) has a side chain analogous to the chains of phytoecdysones of ponasterone types A and B [1, 2] and can be used in the synthesis of the latter. This triol is a catabolite of cholesterol, formed in mammals during the biosynthesis of steroid hormones [3]. It has also been obtained from the extract of Norwegian lilies [4]. Following our plan of investigation of ecdysone-like compounds, we considered preparing the triol (I), starting with the oxirane (II), which is formed from pregnenolone acetate by reaction with dimethylsulfonium methylide as described by Corey and Chaikovskii. However it was shown [5] that when the oxirane ring is opened, an inversion occurs at C-20 leading to the formation of a compound with





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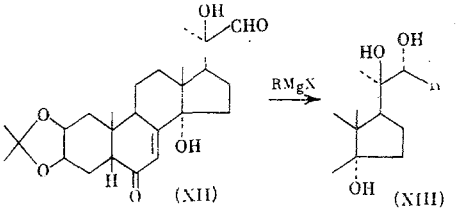
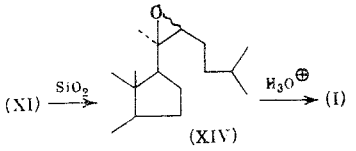
an unnatural C-20 configuration. The required epimer was successfully prepared by a reaction sequence leading to a double Walden inversion at this asymmetric carbon atom. By reaction with gaseous HCl in $CHCl_3$, oxirane (II) was quantitatively converted into the 20(S)-chlorohydrin (III) with no observed formation of the tertiary hydroxyl structure (IV). The structure of (III) was established by Jones oxidation which leads to either the chloroaldehyde (V) or the chloroacid (VI) depending on the amount of oxidant employed. These two compounds are not obtained pure, since in the work-up procedure, on treatment with water, they are converted by $S_N2$ mechanism to the corresponding α-hydroxy derivatives (VII) and (VIII). The latter compounds were characterized as the 2,4-dinitrophenylhydrazone (IX) and methyl ester (X), respectively. Thus, we developed a preparative route for obtaining 10-hydroxy derivatives of bisnorcholene aldehyde, usually obtainable by ozonization of 20-hydroxy-$\Delta^{22}$-steroids [6].

Compounds (VII) and (VIII) have the natural configuration at C-20 which is confirmed by the reaction of the hydroxyaldehyde (VII) with excess isoamylmagnesium bromide. The resulting mixture of the triol (I) and its 22(S)-isomer (XI) is resolved chromatographically on silica gel. The structure of the two isomers follows from the comparison of their physicochemical parameters (melting point, NMR and mass spectra) with data of corresponding structures synthesized earlier [1] by a different route. Both triols, according to thin-layer chromatographic data and NMR spectra (the comparative intensities of the chemical shifts in the 18-$CH_3$ group) are obtained in approximately equal quantities.

In contradiction [7, 8], the 14α-hydroxyaldehyde (XII) in an analogous Grignard reaction gives almost exclusively the corresponding 22(R)-hydroxy derivative (XIII) which is evidently explained by the presence of the 14α-hydroxyl group in (XII) or the corresponding OMgBr group, which effectively screens the α-region of the molecule's D-ring.




During chromatographic separation of the mixture of (I) and (XI), or in the chromatographic purification of (XI), we observed the formation of a weakly polar oily product, which can be assigned the oxirane structure (XIV) on the basis of its conversion to the triol (I) and other data given in the Experimental section. Thus it is possible to convert the 22(S)-isomer (XI) to the 22(R)-isomer (I), the latter having the natural configuration.




## EXPERIMENTAL

IR, UV, and NMR spectra were obtained on UR-10, Specord UV VIS, and Varian XL-100 instruments, respectively. Mass spectra were obtained on an MKh-1309 apparatus at an ionizing voltage of 75 eV.

Chlorhydrin (III). To a solution of 1 g of oxirane (II) in 20 ml $CHCl_3$ was added 5 ml of $CHCl_3$, saturated with gaseous HCl. The mixture was kept at 20° for 2 h and then evaporated under vacuum, yielding 1.08 g (98%) of the oily chlorhydrin (III), which proved to be unstable during attempts at further purification by chromatography on silica gel. IR spectrum (vaseline oil, ν, $cm^{-1}$): 3440 (OH), 1730 and 1262 ($CH_3COO$), 740 (⩾C–Cl).

NMR spectrum ($CDCl_3$, δ, ppm): 0.90 s (18-$CH_3$, 3H); 1.03 s (19-$CH_3$, 3H): 1.58 s (21-$CH_3$, 3H); 2.02 s ($CH_3COO$, 3H); 3.6 m ($CH_2OH$, 2H); 4.6 m (3α-H, 1H); 5.38 d (6-H, 1H). Mass spectrum (20°): molecular ion peak is absent, 378 ($M^+-CH_2OH$, 8%), 377 (8%), 349 ($M^+$–AcOH, 5%), 347 (5%), 341 ($M^+-HCL-CH_2OH$, 100%), 281 ($M^+-CH_2OH-HCl-AcOH$, 44%), 303 ($M^+-CH_3-CH_2OH-AcOH$, 99%), 255 ($M^+$– side chain, 18%).

The chlorhydrin (III) was used without further purification for the following steps.

Oxidation of Chlorhydrin (III). An ice-cooled solution of 1.5 g of chlorhydrin (III) in 7.5 ml of acetone (redistilled over $KMnO_4$, and then over $CrO_3$) was treated with 1.5 ml of the Jones reagent and allowed to stand

for 20 min, at ~20°. After the addition of excess $CH_3OH$, the mixture was poured into water, and the product was extracted with ether. The extract was washed with water and then with aqueous ammonia. Acidification of the alkaline solution yielded 150 mg (10%) of the hydroxyacid (VIII) mp 175-177° (from methanol). IR spectrum (vaseline oil, $\nu$, $cm^{-1}$): 3400-2600 (wide band, COOH), 1735 and 1253 ($CH_3COO$), 1712 (CO). NMR spectrum ($CDCl_3$, $\delta$, ppm): 0.86 s (18-$CH_3$, 3H); 1.02 s (19-$CH_3$, 3H); 1.79 s (21-$CH_3$, 3H); 2.06 s ($CH_3COO$, 3H); 4.61 m (3$\alpha$-H, 1H); 5.38 d (6-H, 1H). Mass spectrum (30°): 392 ($M^+$, 2%), 377 ($M^+-CH_3$, 3%), 374 ($M^+-H_2O$, 12%), 359 ($M^+-CH_3-H_2O$, 3%), 344 ($M^+-CO_2$, 5%), 332 ($M^+$–AcOH, 100%), 314 ($M^+$–AcOH–$H_2O$, 17%) 299 (12%), 283 (32%), 271 (13%), 255 (14%).

The ether layer was evaporated, the residue stirred for 2 h in 30 ml of a saturated aqueous $NaHSO_3$ solution, and an equal volume of ether added. The crystalline product which precipitated at the phase boundary was filtered off and washed with ether and with water. It was then treated with 150 ml of ether to which 100 ml of 10% aqueous $Na_2CO_3$ was added. The ether layer was washed with water, dried, and evaporated under vacuum, yielding 0.8 g (81%) of the hydroxyaldehyde (VII) as a colorless oil, which could be kept only in an inert atmosphere. IR spectrum (neat film, $\nu$, $cm^{-1}$): 3450 (OH), 1725 and 1260 ($CH_3COO$), 1740 (CHO). NMR spectrum ($CDCl_3$, $\delta$, ppm): 0.85 s (18-$CH_3$, 3H); 1.03 s (19-$CH_3$, 3H); 1.27 s (21-$CH_3$, 3H); 2.02 s ($CH_3COO$, 3H); 4.6 m (3$\alpha$-H, 1H); 5.39 d (6-H, 1H); 9.62 s (CHO, 1H). Mass spectrum (20°): 388 ($M^+$, 8%), 387 ($M^+$–H, 13%), 373 ($M^+-CH_3$, 10%), 370 ($M^+-H_2O$, 7%), 359 ($M^+$–CHO–H, 16%), 328 ($M^+$–AcOH, 20%), 310 ($M^+$–AcOH–$H_2O$, 100%), 299 ($M^+$–AcOH – side chain 300%). The mp of its 2,4-dinitrophenylhydrazone (IX) was 130-135° (from methanol). Found: N 10.20%. $C_{30}H_{40}NO_7$. Calculated: N 9.85%. IR spectrum (vaseline oil, $\nu$, $cm^{-1}$): 3325 (OH), 3110 (>NH), 1730 and 1265 ($CH_3COO$), 1620 (>C=CH), 1590 (–CH=N–), 1515, 1345, 835 and 750 ($NO_2$). NMR spectrum ($CDCl_3$, $\delta$, ppm): 0.87 s (18-$CH_3$, 3H); 1.03 s (19-CH 3H); 1.7 s (>NH, 1H); 2.01 s (21-$CH_3$, 3H); 2.05 s ($CH_3COO$, 3H); 4.62 m (3$\alpha$-H, 1H); 5.40 d (6-H, 1H); 7.86-8.41 (aggregate of aromatic-H atoms, 3H); 9.1 s (CH=N, 1 H). UV spectrum: $\lambda_{max}$ (in ethanol): 231 ($\varepsilon$ 30,000), 263 ($\varepsilon$ 27,000), 365 nm ($\varepsilon$ 32,000). Mass spectrum (120°): 568 ($M^+$, 2%), 553 ($M^+-CH_3$, 34%), 550 ($M^+-H_2O$, 23%), 538 ($M^+-2CH_3$, 21%), 508 ($M^+$–AcOH, 25%), 490 ($M^+$–AcOH–$H_2O$, 50%), 478 (100%), 463 (23%), 450 (30%), 443 (70%), 418 (50%), 401 (25%), 299 (20%), 298 (53%), 292 (80%).

Methyl ester (X) was obtained from hydroxyacid (VIII) by treatment with an ether solution of diazomethane. Its mp was 120-122° (from methanol. Found: C 71.20; H 9.57%. $C_{24}H_{38}O_5$. Calculated: C 70.90; H 9.42%. IR spectrum (vaseline oil, $\nu$, $cm^{-1}$): 3450 (OH), 1735 and 1262 ($CH_3COO$ and $COOCH_3$) 1630 (>C=CH). NMR spectrum ($CDCl_3$, $\delta$, ppm): 0.84 s (18-$CH_3$, 3H); 1.01 s (19-$CH_3$, 3H); 1.75 s (21-$CH_3$, 3H); 2.02 s ($CH_3COO$, 3H); 3.75 s ($COOCH_3$, 3H); 4.6 m (3$\alpha$-H, 1H); 5.38 d (6-H, 1H). Mass spectrum (40°): the molecular ion peak is absent, 388 ($M^+-H_2O$, 94%), 373 ($M^+-H_2O-CH_3$, 41%), 346 ($M^+$ – AcOH – $H_2O$, 100%), 315 ($M^+$ – AcOH – $OCH_3$, 10%), 297 ($M^+$– AcOH – $COOCH_3$, 45%), 254 (38%).

Preparation of the Triol (I) and Its 22(S)-Isomer (XI). To a Grignard reagent, formed from 1.5 g of Mg in 8.2 g of isoamyl bromide in 30 ml of absolute ether, at 0°, was added 0.5 g of the hydroxyaldehyde (VII) in 15 ml of absolute tetrahydrofuran. The mixture was boiled for 3 h and then worked up in the usual manner. The product (0.55 g) was repeatedly subjected to thin-layer chromatography on silica gel using $CHCl_3$–methanol (96:4). From the $R_f$ 0.25 zone, 0.2 g (45%) of the triol (I) was washed out. Its mp was 175-178° (from methanol); cf [1]. IR spectrum (vaseline oil, $\nu$, $cm^{-1}$): 3360 (OH) 1640 (>C=CH). NMR spectrum ($CDCl_3$, $\delta$, ppm): 0.92 s 18-$CH_3$, 3H); 1.03 s (19-$CH_3$, 3H); 0.85 and 0.95 (26-$CH_3$ and 27-$CH_3$, 6H); 1.24 s (21-$CH_3$, 3H). Mass spectrum (20°); the molecular ion peak is absent, 400 ($M^+ - H_2O$, 85%), 382 ($M^+ - 2H_2O$, 60%), 367 ($M^+ - 2H_2O - CH_3$, 75%), 329 (52%), 317 (100%), 299 (89%), 281 (37%), 271 (62%), 255 (75%), 253 (45%). From the $R_f$ 0.35 zone 0.22 g of the triol (XI) was washed out. Its mp was 189-190° (from methanol); cf. [1]. IR spectrum (vaseline oil, $\nu$, $cm^{-1}$): 3400 (OH), 1630 (>C=CH). NMR spectrum ($CDCl_3$, $\delta$, ppm): 0.71 s (18-$CH_3$, 3H); 1.03 s (19-$CH_3$, 3H); 0.85 and 0.92 (26-$CH_3$ and 27-$CH_3$, 6H); 1.26 s (21-$CH_3$, 3H).

From the $R_f$ 0.7 zone 33 mg of the epoxide (XIV) was obtained as an oil. IR spectrum (neat film, $\nu$, $cm^{-1}$): 3370 (OH), 1640 (>C = CH), 1240 (oxirane). NMR spectrum ($CDCl_3$, $\delta$, ppm): 0.88 s (18-$CH_3$, 3H); 1.03 s (19-$CH_3$, 3H); 0.92 and 0.94 (26-$CH_3$ and 27-$CH_3$, 6H); 1.34 s (21-$CH_3$, 3H). Mass-spectrum (20°): 400 ($M^+$, 9%), 385 ($M^+ - CH_3$, 8%), 382 ($M^+ - H_2O$, 8%), 367 ($M^+ - H_2O - CH_3$, 100%), 357 ($M^+ - C_3H_7$, 44%), 339 ($M^+ - C_3H_7 - H_2O$, 73%), 299 (85%), 281 (55%), 271 (66%), 255 (22%).

On treatment of (XIV) with aqueous methanol, containing a small amount of $H_2SO_4$ (20°, 12 h), triol (I) was formed. Its mp was 174-177° and was fully identical with the previously described sample.

## CONCLUSION

1. The synthesis of 3β-acetoxy-20-hydroxy-$\Delta^5$-bisnorcholenealdehyde (VII), the starting material for the synthesis of ecdysone-related compounds, was accomplished.

2. Starting with (VII), the isomeric $\Delta^5$-cholestene-3β,20,22-triols (I and XI) were obtained by the Grignard reaction.

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