PREPARATION OF 2,3-seco-5α-CHOLESTANE-2,3-DIOL AND 4α-METHYL-2,3-seco-5α-CHOLESTANE-2,3-DIOL AND ITS REACTIONS WITH o-NITROPHENYL SELENOCYANATE

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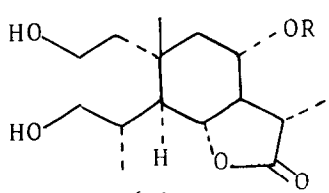
ABSTRACT

The reaction of 2,3-seco-5α-cholestane-2,3-diol and 4α-methyl-2,3-seco-5α-cholestane-2,3-diol with o-nitrophenyl selenocyanate was studied. The diols were synthesized from cholesterol.

In a recent synthesis of melitensin and related elemanolides (1) we have carried out with good yield the transformation of diol (I) to the corresponding diselenide (II) by reaction of diol (I) with o-nitrophenyl selenocyanate (o-NO_2-C_6H_4SeCN) and tri-n-butylphosphine (n-Bu_3P). This result is similar to those reported in the reactions of two similar diols in the synthesis of β-elemenone (2) and β-elemol (3), but they are different from those reported by Grieco et al. in the synthesis of saussurea lactone (4) and (+)-temisine (5), in which only the monoselenides (III) were obtained.



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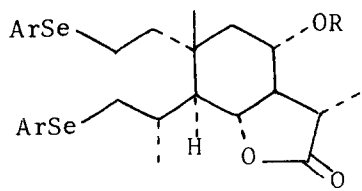

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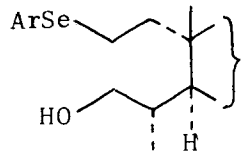

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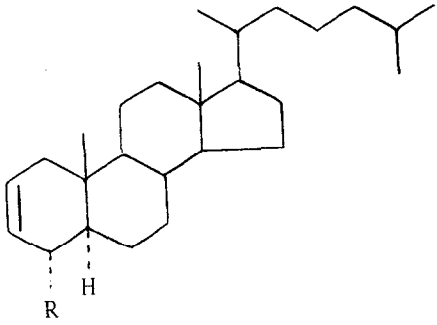

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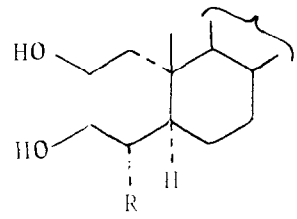
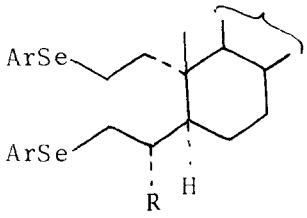


(V) R=H
(VII) R=CH_3



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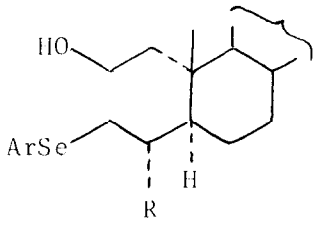
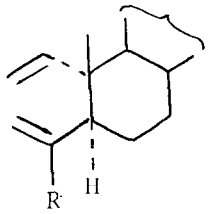
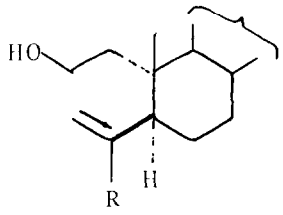


(IX) R=H
(XI) R=CH_3



(XII) R=H
(XIV) R=CH_3



(XIII) R=H
(XV) R=CH_3

In this paper we wish to report the results observed in the reaction of o-$NO_2C_6H_4SeCN$ with two diols with a steroid framework: 2,3-seco-5α-cholestane-2,3-diol (V) and 4α-methyl--2,3-seco-5α-cholestane-2,3-diol (VII).

The diol (V) was prepared by ozonolysis followed by treatment with sodium borohydride ($NaBH_4$) of 5α-cholest-2-ene (IV), which, in turn, was prepared from cholesterol through a known synthetic sequence of several steps (6,7,8). In the same way the diol (VII) was obtained from 4α-methyl--5α-cholest-2-ene (VI), which was prepared from cholesterol through a four step sequence: Oppenauer oxidation (9), methylation at C-4 of the resulting enone (10), hydrogenation of the $\Delta^{4,5}$ double bond (11), epimerization at C-4 (12) and Shapiro reaction (4,13).

We have carried out the reactions of diols (V) and (VII) with 2.4 or 4.8 mol of o-$NO_2C_6H_4SeCN$ in tetrahydrofuran (THF) containing the same number of moles of n-Bu_3P. Typical results are summarized in the following table:

Diol	mol of reagents	Yield of diselenide(%)	Yield of monoselenide(%)	Diol recovered(%)
(V)	4.8	88	-	-
(V)	2.4	-	41	29
(VII)	4.8	79	21	-
(VII)	2.4	18	48	10

As the table shows, the reaction of both diols (V) and (VII) with 4.8 mol of the reagents affords the corresponding diselenides with good yields: 2,3-di-o-nitrophenylseleno-2,3-seco-5α-cholestane (VIII) and 4α-methyl-2,3-di-o-nitrophenyl-

seleno-2,3-seco-5α-cholestane (X), the last one accompanied by the monoselenide 4α-methyl-3-o-nitrophenylseleno-2,3-seco--5α-cholestan-2-ol (XI). In like manner, the reactions of the diols (V) and (VII) with 2.4 mol of the reagents give as main products the monoselenide 3-o-nitrophenylseleno-2,3-seco--5α-cholestan-2-ol (IX) and the monoselenide (XI) respectively, unreacted material being recovered in both cases.

We have also studied the olefins obtained by elimination of the o-nitrophenylselenide groups of the di- and monoselenides when they were treated with 50% H_2O_2 in THF. These olefins allowed the correct assignment for the position of the o-nitrophenylselenide group in monoselenides (IX) and (XI).

It is interesting to note that both monoselenides (IX) and (XI) have been formed by substitution of the 3-hydroxyl function, rather than of the 2-hydroxyl function, in contradistinction to the situation with products of the elemanolide series (1,4,5).

EXPERIMENTAL PART

Melting points were determined on a Büchi apparatus and they are uncorrected. The spectra were recorded with the following instruments: IR Perkin-Elmer 281; NMR Perkin-Elmer R12B. Chemical shifts are reported in δ units, parts per million (ppm) downfield from tetramethylsilane. Mass spectra were performed at 70 eV on a Varian 166 machine, using the direct inlet system. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Column chromatography was performed on silica gel 60, TLC on silica gel HF_{254} and PLC on silica gel $PF_{254+366}$, Merck. Organic solutions were dried over anhydrous $MgSO_4$ or Na_2SO_4, and solvents removed in vacuo on a rotary evaporator. Yields refer to products homogeneous on TLC.

2,3-seco-5α-Cholestane-2,3-diol (V). A stirred solution of 5α-cholest-2-ene (IV) (0.529 g, 1.42 mmol) in a mixture of ethanol (29 mL) and methylene chloride (13.9 mL) at 0°C was treated with a precooled (0°C) saturated solution of ozone (ca. 1.69 mmol) in methylene chloride (42.1 mL). After 15 min $NaBH_4$ (64 mg) was added at 0°C and three new equal portions of $NaBH_4$ were added at 15 min intervals at the same temperature. The total amount of $NaBH_4$ was 256 mg (6.76 mmol). The reaction mixture was warmed to room temperature and stirring was continued overnight. The solvent was removed in vacuo and then the residue diluted with water and acidified with 1N HCl to pH 1. The product was isolated with ether and chromatographed on a silica gel column (elution:ether) to give the diol (V) (0.428 g, 73%), mp 158-160°C (ethyl acetate), $\{\alpha\}_D$ 0.6 (c 0.33,Cl_3CH), described (14): mp 154-155°C, $\{\alpha\}_D$ -8 (c,2); IR (KBr) ν_{max} 3300 (OH) and 1025 (C-OH) cm^{-1}; NMR ($DCCl_3$) 0.64 and 0.73 (2s, angular CH_3) and 3.30-3.80 (4H, m, CH_2-OH).

4α-Methyl-5α-cholest-2-ene (VI): a) Tosylhydrazone of 4α-methyl-5α-cholestan-3-one: A mixture of 4α-methyl-5α-cholestan-3-one (1.040 g, 2.59 mmol) and tosylhydrazine (1.090 g, 5.85 mmol) in anhydrous methanol (63 mL) was refluxed for five hours. The reaction mixture was cooled to room temperature to precipitate a white solid which was filtered, dried in vacuo and identified as the tosylhydrazone of 4α-methyl-5α-cholestan-3-one (1.260 g, 85%), mp 150-155°C (with decomp.); IR (KBr) ν_{max} 3220 (N-H), 1630 (C=N), 1600 (arom.), 1330, 1170 (SO_2) and 810 (arom.) cm^{-1}.

b) 4α-Methyl-5α-cholest-2-ene (VI): In an inert atmosphere, n-butyllithium (17.1 mL of 1.6 M solution in hexane, 27.36 mmol) was added to a stirred mixture of diisopropylamine (2.770 g, 27.42 mmol) and dry THF (10 mL) at -78°C. After adding 11.1 mL of dry THF, a solution of the tosylhydrazone of 4α-methyl-5α-cholestan-3-one (1.260 g, 2.21 mmol) in dry THF (10.5 mL) was added dropwise at -78°C over a pe-

riod of 10 min. After and additional 10 min at -78°C the reaction mixture was warmed to 0°C and stirring was continued for 2 h. The reaction was quenched by addition of NH_4Cl (aq.) and the product was isolated by extraction with ether and purified by chromatography on silica gel (elution:hexane) to give the alkene (VI) (0.700 g, 82%), mp 86-87°C (hexane); $[\alpha]_D$ 0.6 (c 0.90, Cl_3CH); high resolution mass spectrum 384.377 (M^+), $C_{28}H_{48}$ requires 384.375; mass peaks at m/z 384 (M^+, 33.5%), 369(23.7%), 355(13.3%), 343(14.8%), 316(12.0%) and 229(22.9%); IR (KBr) ν_{max} 3010 (=C-H), 1650 (C=C) and 695 (=C-H) cm^{-1}; NMR($DCCl_3$) 0.66 and 0.77 (2s, angular CH_3) and 5.41 (2H, m, -CH=CH-).

4α-Methyl-2,3-seco-5α-cholestane-2,3-diol (VII): The alkene (VI) (0.670 g, 1.74 mmol) was treated with ozone in the same way as the 5α-cholest-2-ene (IV) to afford the diol (VII) (0.533 g, 73%), mp 173-174°C (ethyl acetate); $[\alpha]_D$ 1.8 (c 0.11,Cl_3CH); high resolution mass spectrum 402.387(M^+-H_2O), $C_{28}H_{50}O$ requires 402.386; mass peaks at m/z 402(M^+-H_2O,7.2%), 375(22.6%), 358(16.3%), 357(12.2%) and 247(13.1%); IR (KBr) ν_{max} 3250 (O-H) and 1040 (C-OH) cm^{-1}; NMR ($DCCl_3$) 0.65 and 0.73 (2s, angular CH_3), 3.35 (2H, d, J=7 Hz, CH-$\underline{CH_2}$OH) and 3.40-4.10 (2H, m, overlaping d, $CH_2\underline{CH_2}OH$).

2,3-di-o-Nitrophenylseleno-2,3-seco-5α-cholestane (VIII). In an inert atmosphere, n-Bu_3P (0.894 g, 4.42 mmol) was added to a stirred mixture of the diol (V) (0.376 g, 0.92 mmol) and o-$NO_2C_6H_4SeCN$ (15) (1.005 g, 4.42 mmol) in dry THF (7.8 mL). After 30 min the solvent was removed under reduced pressure and the mixture was chromatographed on a silica gel column (elution: hexane-ether, 99:1) to give the diselenide (VIII) (0.632 g, 88%), m.p. 93-95°C (hexane-ether); IR (KBr) ν_{max} 3080 (arom.), 1590, 1565 (arom.), 1505, 1330 (NO_2) and 725 (arom.) cm^{-1}; NMR (CCl_4) 0.62 and 0.80 (2s, angular CH_3), 2.40-3.30 (4H, m, -CH_2Se-), 7.00-7.70 (6H, m, arom. H) and 8.00-8.40 (2H, m. arom. H).

4α-Methyl-2,3-di-o-nitrophenylseleno-2,3-seco-5α-cholestane (X). The diol (VII) (0.485 g, 1.15 mmol) was treated in the same way as the diol (V). The crude product was chromatographed on a silica gel column. Elution with hexane-ether (98:2) gave diselenide (X) (0.714 g, 79%), mp 125-126°C(hexane-ether); IR (KBr), ν_{max} 3100, 3080 (arom.), 1580, 1565 (arom.), 1510, 1335 (NO_2) and 720 (arom.) cm^{-1}; NMR (CCl_4) 0.65 and 0.90 (2s, angular CH_3), 2.50-3.10 (4H, m, $-CH_2-Se$), 6.90-7.50 (6H, m, arom. H), 7.90 (1H, br.d., J=7.3 Hz arom. H) and 8.13 (1H, br.d., J=7.3 Hz, arom. H). Elution with hexane-ether (8:2), gave monoselenide (XI) (0.149 g, 21%).

3-o-Nitrophenylseleno-2,3-seco-5α-cholestan-2-ol (IX). The diol (V) was treated in a similar way as in the synthesis of the diselenide (VIII). The reagents were used as follows: diol (V) (0.037 g, 0.09 mmol), o-$NO_2C_6H_4SeCN$ (0.050 g, 0.22 mmol) in dry THF (0.77 mL) and n-Bu_3P (0.045 g, 0.22 mmol); the reaction time was 1 h 45 min. PLC of the crude product (hexane-ether, 1:1) gave starting product (V) (0.011 g, 29%) and monoselenide (IX) (0.022 g, 41%), mp 130-132°C (hexane-methylene chloride); IR (NaCl) ν_{max} 3450 (O-H), 3070 (arom.) 1570, 1555 (arom.), 1510, 1330 (NO_2), 1025 (C-OH) and 725 (arom.) cm^{-1}; NMR (CCl_4) 0.64 and 0.74 (2s, angular CH_3), 2.70-3.10 (2H, m, $-CH_2-Se$), 3.63 (2H, t, J=7.3 Hz, $-CH_2-OH$), 7.30-7.80 (3H, m, arom. H) and 8.60-8.30 (1H, br.d., J=7.3 Hz, arom.H).

4α-Methyl-3-o-nitrophenylseleno-2,3-seco-5α-cholestan-2-ol (XI). The diol (VII) (0.050 g, 0.119 mmol) was treated in the same way as the diol (V) in the synthesis of monoselenide (IX), giving, after chromatography on a silica gel column, the diselenide (X) (elution:hexane-ether, 98:2) (0.017 g, 18%) and monoselenide (XI) (elution:hexane-ether, 8:2) (0.035 g, 48%), mp 139-140°(cyclohexane-ethyl acetate); IR (KBr) ν_{max} 3560 (O-H), 3080 (arom.),1585,1560 (arom.), 1500,1320 (NO_2) and 730 (arom.) cm^{-1}; NMR ($DCCl_3$) 0.64 and 0.83 (2s, angular CH_3), 2.90 (2H, d, J=7.3 Hz, $CH-CH_2-Se$), 3.50-3.90 (2H, m, $-CH_2-OH$),

7.30-7.80 (3H, m, arom. H) and 8.52 (1H, br. d., J=8 Hz, arom. H). Unreacted starting material (VII) was recovered (0.005 g, 10%).

2,3-seco-5α-Cholestane-1,3-diene (XII). To a solution of diselenide (VIII) (0.353 g, 0.45 mmol) in THF (4.3 mL), at 0°C, 50% H_2O_2 (0.25 mL, 3.60 mmol) was slowly added. After addition was complete the reaction was warmed to room temperature. After 3 h the reaction was quenched with water (8.6 mL) and the solvent was removed in vacuo. The product was extracted with ether and chromatographed on a silica gel column (elution:hexane) to give the diene (XII) (0.151 g, 89%) as a solid of very low melting point which was not possible to recrystallize; $[\alpha]_D$ 4.4 (c 0.93, Cl_3CH); high resolution mass spectrum 370.361 (M^+), $C_{27}H_{46}$ requires 370.360; mass peaks at m/z 370 (M^+, 20.0%), 355(12.7%), 341(5.2%), 329(6.6%), 257(26.5%) and 215 (21.1%); IR (NaCl) ν_{max} 3080 (=C-H), 1635 (C=C), 1415, 1000 and 905 (-CH=CH_2) cm^{-1}; NMR (CCl_4) 0.65 and 0.83 (2s, angular CH_3), 4.50-5.10 (4H, typical vinyl pattern, -CH=$\underline{CH_2}$), 5.53 (1H, dd, J=10.5 and 16.5 Hz, C_1-H) and 5.73 (1H, ddd, J=5.5, 11.5 and 14 Hz overlaping dd, C_4-H).

4α-Methyl-2,3-seco-5α-cholestane-1,3-diene (XIV). The diselenide (X) (0.714 g, 0.90 mmol) was treated in the same way as the diselenide (VIII) in the synthesis of the diene (XII) to give the diene (XIV) (0.226 g, 65%) as a solid of very low melting point which was not possible to recrystallize; $[\alpha]_D$ -2.48 (c 0.86, Cl_3CH); high resolution mass spectrum 384.374 (M^+), $C_{28}H_{48}$ requires 384.375; mass peaks at m/z 384 (M^+, 27.6%), 369(12.9%), 343(3.3%), 271(14.7%), 247(8.4%) and 229(10.3%); IR (NaCl) ν_{max} 3080 (=C-H), 1640 (C=C), 1410, 1000, 905 and 890 (CH=CH_2, C=CH_2) cm^{-1}; NMR (CCl_4) 0.65 and 0.90 (2s, angular CH_3), 1.65 (s, C_4-CH_3), 4.40-5.10 (4H, typical vinyl pattern, -CH=$\underline{CH_2}$ and C=$\underline{CH_2}$) and 5.55 (1H, dd, J=10.6 and 16.6Hz, C_1-H).

2,3-seco-5α-cholest-3-en-2-ol (XIII). The monoselenide (IX) (0.022 g, 0.037 mmol) was treated in the same way as the diselenide (VIII). The product was isolated by ethyl acetate extraction and chromatography on a silica gel column (elution: hexane-ether, 1:1) giving the vinyl alcohol (XIII) (0.014 g, 97%) as a colorless oil; $[\alpha]_D$ 12.6 (c 0.50, Cl_3CH); high resolution mass spectrum 388.371 (M^+), $C_{27}H_{48}O$ requires 388.370; mass peaks at m/z 388 (M^+, 5.2%), 370 (0.8%), 344 (21.2%), 321(15.3%) and 247 (5.5%); IR (NaCl) ν_{max} 3300 (O-H), 3070 (=C-H), 1635 (C=C), 1010 (C-OH), 995 and 905 ($CH=CH_2$) cm^{-1}; NMR (CCl_4) 0.66 and 0.79 (2s, angular CH_3), 3.59 (2H, br.t., J=7.3 Hz, $-C\underline{H}_2-OH$), 4.85-5.03 (2H, typical vinyl pattern, $-CH=C\underline{H}_2$) and 5.60-6.10 (1H, m, C_4-H).

4α-Methyl-2,3-seco-5α-cholest-3-en-2-ol(XV). The monoselenide (XI) (0.128 g, 0.21 mmol) was treated in the same way as the diselenide (VIII). Chromatography of the crude product on a silica gel column (elution: hexane-ether 9:1) gave the vinyl alcohol (XV) (0.063 g, 74%) as an oil; $[\alpha]_D$ 28.1(c 0.37, Cl_3CH); high resolution mass spectrum 402.383 (M^+), $C_{28}H_{50}O$ requires 402.386; mass peaks at m/z 402 (M^+, 12.8%), 384 (3.2%), 321(10.0%), 247 (10.4%) and 207(8.8%); IR (NaCl) ν_{max} 3300 (O-H), 3070 (=C-H), 1630 (C=C), 1015 (C-OH) and 885 ($C=CH_2$) cm^{-1}; NMR (CCl_4) 0.68 and 0.88 (2s, angular CH_3), 1.78 (s, $C_4-C\underline{H}_3$), 3.40-3.80 (2H, m, $C\underline{H}_2-OH$), 4.68 and 4.85 (2H, two br.s., $C=CH_2$).

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