

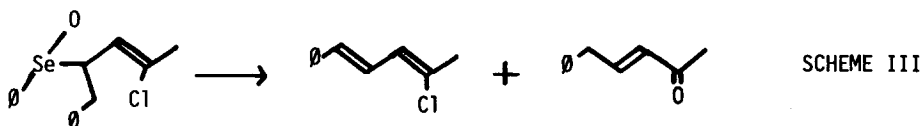
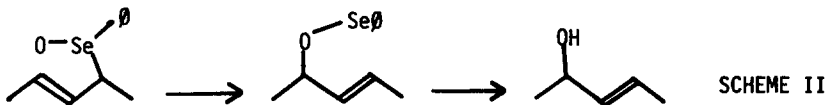
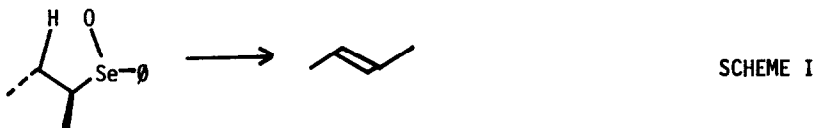
ALTERNATIVE MODES OF DECOMPOSITION OF ALLYLIC SELENOXIDES DIASTEREOISOMERIC AT SELENIUM.

PREPARATION OF $\Delta^{5,7}$ - and 5β -HYDROXY- Δ^6 -STEROIDS.

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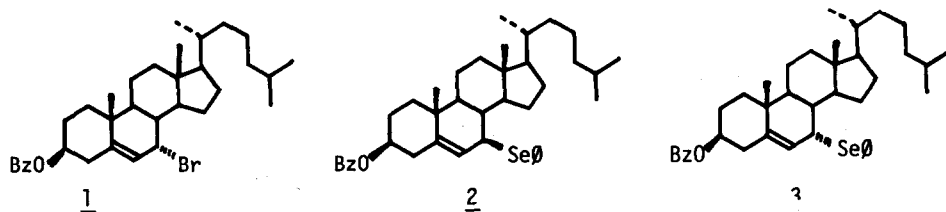
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Selenoxides containing β -hydrogens are well known to decompose readily to yield olefins¹ (Scheme I). Allylic selenoxides normally undergo a 2,3-sigmatropic rearrangement very rapidly at low temperature to yield an allylic alcohol after solvolysis of the intermediate selenate ester² (Scheme II); in some rare cases^{3,4} a competitive syn-elimination may occur. Such an example is shown in Scheme III where the ratio of the products of rearrangement and elimination was 85:15. This departure from the norm was rationalized⁴ in terms of enhanced elimination by the phenyl substituent and retardation of the sigmatropic shift by the γ -substituents. In such sterically



unhindered acyclic systems it might be expected that the rate of elimination would be similar for each chiral selenoxide; likewise, for each selenoxide the rates of rearrangement would be very close. The ratio of the decomposition products would be determined, therefore, simply by the ratio of the rates for the two processes. In highly sterically hindered systems the extreme situation could theoretically arise, namely that one of the pathways for the decomposition of a chiral selenoxide may be so sterically hindered as to prevent its occurrence, leading to decomposition totally by the other available pathway. It is on this possibility that we wish to address ourselves in this communication, and to report the production of a 1,3-diene from one diastereoisomer of an allylic selenoxide, and the rearrangement of the other diastereoisomer to an allylic alcohol.

The reaction of sodium phenyl selenolate with 7 α -bromocholesteryl benzoate⁵ (1) in tetrahydrofuran or benzene gives the 7 β -phenylseleno derivative (2).⁶ The 7 β -configuration is readily

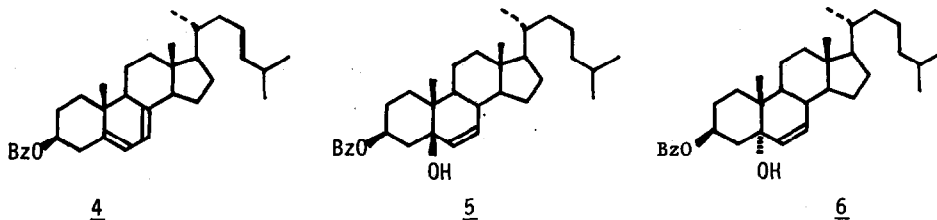


confirmed by the reactions compound (2) undergoes; by the upfield resonance (δ 0.51) in the NMR of the 19-methyl (shielded by the π -cloud of the aromatic ring); and by comparison with the 7 α -compound (3).⁶

In our earlier work we generated sodium phenylselenolate by the rather cumbersome procedure of adding sodium borohydride to a solution of diphenyl diselenide in aqueous tetrahydrofuran (10% water). The undesirable exotherm of this reaction, the voluminous evolution of hydrogen, and the need for a large excess of sodium borohydride led us to examine alternatives suitable for larger scale work. This was achieved by reducing diphenyl diselenide to phenylselenol with hypophosphorous acid⁷, extracting the selenol into benzene and adding one equivalent of sodium hydroxide. The yield is essentially quantitative.

Thus: A solution of diphenyl diselenide (1.56 g) in tetrahydrofuran (10 ml) was added to 50% aq. hypophosphorous acid (4.0 ml) and the mixture boiled under reflux for 20 minutes. After cooling, the mixture was extracted into benzene (25 ml) and the phases separated. To the benzene solution of the selenol 50% aq. NaOH solution (0.65 ml) was added, yielding a white granular precipitate of sodium phenylselenolate. To this suspension was added 7 α -bromocholesteryl benzoate (5.70 g) dissolved in dry tetrahydrofuran (25 ml). An immediate reaction took place. After 15 minutes the mixture was quenched with water, the phases separated, and the organic layer dried and evaporated. The residue was crystallized from acetone to give 7 β -phenylselenocholesteryl benzoate (5.68 g, 88%) m.p. 121-122°. NMR (CDCl₃): δ 0.51s(3H); 0.73s(3H); 3.47 broad doublet (1H); 4.80, broad multiplet (1H); 5.56m(1H); 7.11-7.67m(8H); 7.91-8.02m(2H). R_f : (10% ethyl acetate/hexane) - 0.62. $[\alpha]_D$ (CHCl₃) +178° (c = 0.83).⁸

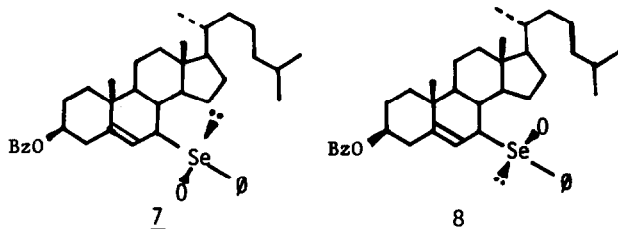
Oxidation of the selenide (2) with 90% hydrogen peroxide at 0 to -5° in tetrahydrofuran yielded after conventional workup a mixture of two products in approximately equal yields of 45%, namely 7-dehydrocholesteryl benzoate (4) identified by comparison with an authentic specimen and



the 3-benzoate of coprost-6-en-3 β ,5-diol (5).^{8,9} The latter crystallized from methanol m.p. 134-135°. NMR (CDCl₃): Singlets at δ 0.72, 0.83, 0.92, 0.94; multiplet (1H) 5.42; singlet (2H) 5.58; multiplet (3H) 7.4; multiplet (2H) 8.0. $[\alpha]_D$ (CHCl₃) -8° (c = 0.87). In contrast oxidation of

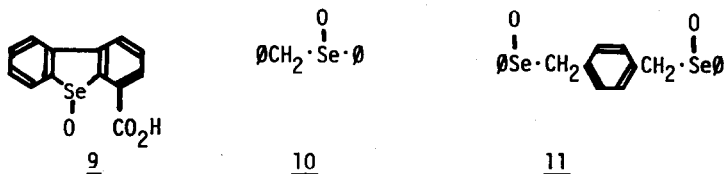
the 7 α -selenide (3) led to the 3-benzoate of cholest-6-en-3 β ,5 α -diol (6)¹⁰ in 94% yield. No 5,7-diene was detected.

The explanation for the production of the two products (4) and (5) from the oxidation of the β -selenide (2) rests in the chirality at selenium of the intermediate selenoxides. Clearly two selenoxides with opposite chirality at selenium would be expected to be formed in the oxidation of the selenide. With the R-selenoxide (7) neither rearrangement to (5) nor elimination to (4) is sterically hindered. However, it is known that 2,3 sigmatropic shifts of selenoxides are very fast even at low temperature^{2,4}, whereas 1,2 elimination is relatively slow^{1a}. The R-selenoxide is therefore expected to rearrange rather than to eliminate.



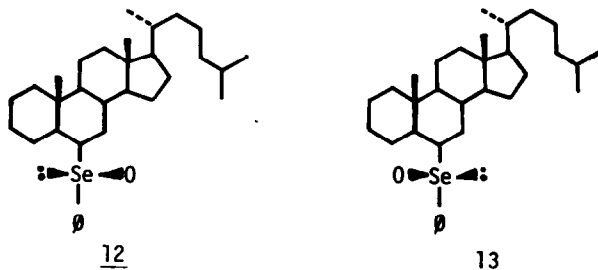
On the other hand the S-compound (8) is relatively unhindered to 1,2-elimination, whilst, to rearrange to the 5 β -hydroxy Δ^6 -system (5), the phenyl group would suffer strong steric interaction with the steroid nucleus. The S-selenoxide thus is expected to undergo 1,2-elimination to yield (4).

Such an explanation, of course, presupposes the configurational stability of selenoxides (7) and (8). Previous work on selenoxides (9)¹¹, (10)¹², and (11)¹³ have indicated their con-



figurational instability in aqueous media.

However, Jones et al.^{1a} have shown that the 6 β -selenoxides (12) and (13), much more closely related to (7) and (8) in this present work, are configurationally stable in the temperature range -70° to 25° in the presence or absence of water. There seems little reason to believe that



the selenoxides (7) and (8) would not possess similar stability. Further, it was shown that selenoxides (12) and (13) were subject to different steric requirements in their decomposition via

a syn-elimination. Thus, compound (12) decomposed more rapidly than compound (13) in which steric interaction with the angular methyl hindered elimination and the formation of cholest-6-ene.

Although selenoxides (7) and (8) were too labile to be isolated, their separate existence was demonstrated and further support for their configurational stability was obtained from the oxidation of the selenide (2) at -70° with ozone in anhydrous methylene chloride. On raising the temperature slowly, appearance of (5) was observed by tlc at ca. -25° whilst appearance of (4) was observed only at ca. -5 to 0° . As far as could be judged by quantitative tlc, the production of (5) was complete before (4) began to be formed. If the selenoxides were not chirally stable it would be expected that interconversion of (8) to (7) would occur leading predominantly to the product (5). This was not observed; the ratio of products in the hydrogen peroxide oxidation was essentially the same as that observed in the ozone oxidation.

References and Footnotes

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6. The 7 β -selenide is stable at room temperature in the solid state for a number of months. On prolonged standing it agglomerated to a tacky solid which on recrystallization from acetone yielded a new compound identified as the 7 α -phenylseleno derivative. M.p. 143-145 $^{\circ}$. NMR (CDCl₃): Singlets at δ 0.68, 0.81, 0.90, 1.00; 7.13-7.63 complex (8H); 7.85-8.03 complex (2H). R_f : (10% ethyl acetate/hexane) -0.62. $[\alpha]_D$ (CHCl₃) -256° (c = 0.86).⁶
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8. Combustion analysis data of all new compounds corroborated the structural assignments.
9. Hydrolysis of this benzoate yielded coprost-6-en-3 β ,5-diol, m.p. (ex acetone) 136-137 $^{\circ}$. NMR (CDCl₃): singlets at δ 0.68, 0.82, 0.92; 4.10m(1H); 5.43s(2H). $[\alpha]_D$ (CHCl₃) -36° (c = 1.02).
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