Reaction mechanism studies. 5. The mechanism of the diaxial → diequatorial rearrangement of β-chlorothioethers

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p-Methoxy- and *p*-nitro substituted analogues (**1***b* and **1***c*) of the diaxial β-chlorothioether 2β-chloro-3α-(phenylthio)-5α-cholestane (**1***a*), have been prepared and found to undergo the diaxial → diequatorial rearrangement. The rates of rearrangement of these compounds show the sequence *p*-methoxy > H > *p*-nitro. It is concluded that the transition state for the rearrangement is polarized in the sense of a sulfonium chloride (3). The rearrangement of **1***a* is 1600 times faster in butanol than in decalin (at 110°). There is thus no inherent insensitivity to solvent change in a rearrangement in which there may be a "four-atom arrangement" in the transition state, a conclusion relevant to previous work on the diaxial → diequatorial rearrangement of 1,2-dibromides (1). It was further found that the nitro group slowed the rearrangement (at 110°) more in butanol than in decalin, an observation regarded as consistent with, but not requiring, the incursion of a merged ion-pair, cyclic concerted mechanism.

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The previous paper (2) describes the synthesis of a diaxial β-halothioether (**1***a*) by the action of benzenesulfenyl chloride on 5α-cholest-2-ene, and the thermal rearrangement of this product to its diequatorial isomer (**2***a*). In the present account we outline experiments which provide some definition of the mechanism of this transformation.

From what is known of the relative capacities of chlorine and arylthio groups to function as leaving groups and as participating functions at neighboring centers, it seemed highly likely that ionization of **1***a* would proceed in the sense of a sulfonium chloride (**3**), rather than a chloronium sulfide (**4**). To obtain experimental evidence on the point we prepared the corresponding *p*-methoxy and *p*-nitro derivatives, **1***b* and **1***c*, respectively, and found that both of these materials rearrange on heating.

The structures of these compounds follow from the close similarities between them and the unsubstituted compounds (**1***a* and **2***a*), both in method of synthesis and in properties. The nuclear magnetic resonance (n.m.r.) spectra of all of the sulfenyl chloride adducts (**1***a*–*c*) are very similar except, of course, for those differences expected as a result of the substitution in the aromatic ring; the spectra of the rearrangement products are also correspondingly similar. In addition, the change in molecular rotation accompanying the transformation **1** → **2** was found to be ca. −600° for **1***b* → **2***b*[2] and −830° for **1***c* → **2***c*, as compared with −410° for the reaction of the unsubstituted compound.

Measurement of the rates of rearrangement indicated the reactions to be first order. As may be seen in Table I, in all of the solvents and at all of the temperatures at which the rates were studied, the rate constants followed the sequence *p*-methoxy > the unsubstituted compound > *p*-nitro. This is readily interpreted in terms of charge separation in the transition state in the sense of a sulfonium chloride (**3**), and not that of a chloronium sulfide (**4**).

As mentioned at the beginning of the previous paper (2), the reason for investigating this reaction was to gain information relevant to our general study of the diaxial → diequatorial rearrangement. We had found (1) that the rates of rearrangement of **5***a*, **5***b*, **6***a*, and **6***b* were much more sensitive to a change in solvent than was the rate of rearrangement of the analogous dibromide (**5***c*). Though the exact positions of the rearranging atoms in the transition states of these reactions are not known, it could have been argued that the difference between the dibromide reaction on the one hand and that of the bromohydrin esters on the other, derived from a different geometrical arrangement in the transition

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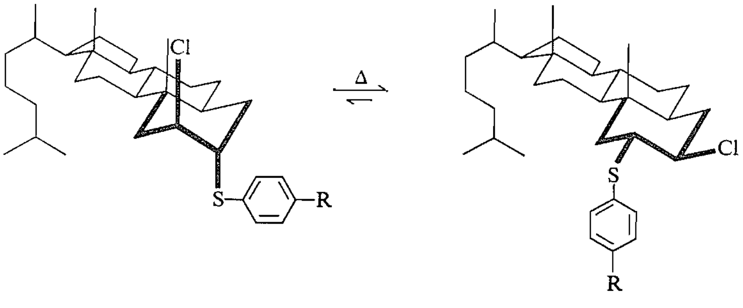
[2] Compound **2***b* was not obtained in a pure, crystalline state, but was characterized as the sulfone. The molecular rotation change quoted is that for the conversion of **1***b* into the equilibrium mixture of **1***b* and **2***b*, which is probably at least 90% **2***b*.



1 **2**

a) R = H
b) R = CH_3O
c) R = NO_2

state. Thus perhaps C-2, C-3, and the two bromine atoms of the dibromide form a four-center arrangement in the transition state, whereas C-2, C-3, the bromine, the two oxygens, and the sulfur (or carbon) of the esters become ordered in a six-membered ring pattern. It is further at least conceivable that such six-atom transition states would (by some unspecified process) be more susceptible to interaction with solvent, and hence lead to a greater sensitivity of the rate of reaction to change in solvent. In the system under discussion in the present study, C-2, C-3, and the chlorine and sulfur atoms are the only atoms directly involved in bond breaking and forming processes. Therefore, if the geometrical effect of the type just indicated were significant, it would be expected that the rate of rearrangement of the β-chlorothioethers would be as insensitive to change in solvent as that of the dibromide (**5**_c_). We have previously shown that on changing the solvent from nitromethane to decalin (at 99°), the rate of rearrangement of the dibromide **5**_c_ decreased 22-fold, whereas those of the bromohydrin esters (**5**_a_, **5**_b_, **6**_a_, and **6**_b_) decreased 100- to nearly 300-fold. The β-chlorothioethers (**1**) in this study were not sufficiently soluble in nitromethane for the rate to be measured in that solvent. However, the rate was measured in a mixture of nitromethane and chloroform (60:40) and also in butanol (both at 60°) and the rates were found to be very similar in these solvents (see Table I). As may be further seen in Table I, the rate of rearrangement of **1**_a_ is reduced about 1600-fold on changing from butanol to decalin (at 110°). It is therefore concluded that the "four-atom arrangement" in the transition state has no intrinsic features rendering it significantly less responsive to a change in the reaction medium, and that the smaller change in sensitivity to solvent change shown by the dibromide rearrangement compared with that of the bromohydrin esters, does not have its origin in differences in geometrical arrangement of the atoms in the transition state.

The question of whether or not the diaxial → diequatorial rearrangement proceeds under any circumstances via a merged ion-pair, cyclic concerted mechanism was taken up in Part 3 of this series (1). After a discussion of some length it was concluded that the data available at that time were consistent with the incursion of a "merged" mechanism, but that it was also at least conceivable that the reaction was proceeding in all cases via an ion-pair mechanism in which the ratio of ion-pairs returning to starting material to ion-pairs giving product was varying with changes in medium and substrate. In the course of the present study we wondered if the β-chlorothioether system might not be used to obtain evidence on the question.

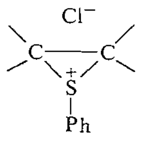
In particular we were interested to see if the presence of a *p*-nitro group, especially in a solvent of very low ionizing power such as decalin, might lead to a manifestly "merged-mechanism" process. We found that the introduction of a nitro group had a smaller effect on the rate of rearrangement in decalin solution than in butanol. Thus the ratio k_{NO_2}/k_H is 0.11 in decalin and 0.053 in butanol (at 110°). This change in the k_{NO_2}/k_H ratio, though small, is qualitatively what would be expected from a "merged" reaction. In such a process complete ionization to an ion-pair would not occur in less polar media. Thus when the reaction is carried out in decalin, the magnitude of the charge on the sulfur atom in the transition state would be

TABLE I

Rate constants for the diaxial → diequatorial rearrangement of the 2β-chloro-3α-(phenylthio)-cholestanes (1)

	Solvent	Temperature (°C)	k_{equil}* (s^{-1})	k/k_{1_a}†
2β-Chloro-3α-(phenylthio)-5α-cholestane (**1***a*)	Nitromethane–chloroform (3:2)	60	1.51×10^{-4}	(1.00)
2β-Chloro-3α-(phenylthio)-5α-cholestane (**1***a*)	1-Butanol	50	4.7×10^{-5}	(1.00)
2β-Chloro-3α-(phenylthio)-5α-cholestane (**1***a*)	1-Butanol	60	1.55×10^{-4}	(1.00)
2β-Chloro-3α-(phenylthio)-5α-cholestane (**1***a*)	1-Butanol	80	9.2×10^{-4}	(1.00)
2β-Chloro-3α-(phenylthio)-5α-cholestane (**1***a*)	1-Butanol	110	1.36×10^{-2} (estimated)‡	(1.00)
2β-Chloro-3α-(phenylthio)-5α-cholestane (**1***a*)	Decalin	110	8.5×10^{-6}	(1.00)
2β-Chloro-3α-(*p*-methoxyphenylthio)-5α-cholestane (**1***b*)	Nitromethane–chloroform (3:2)	60	4.5×10^{-4}	3.0
2β-Chloro-3α-(*p*-nitrophenylthio)-5α-cholestane (**1***c*)	Nitromethane–chloroform (3:2)	60	5.1×10^{-6}	0.034
2β-Chloro-3α-(*p*-nitrophenylthio)-5α-cholestane (**1***c*)	1-Butanol	110	7.3×10^{-4}	0.053
2β-Chloro-3α-(*p*-nitrophenylthio)-5α-cholestane(**1***c*)	Decalin	110	9.3×10^{-7}	0.11

*k_{equil} is the first order rate constant for the rate of formation of the equilibrium mixture of **1** and **2**.
†The ratio of k_{equil} for the compound to k_{equil} for **1***a* under the same conditions.
‡Estimated by extrapolation of the plot of log k_{equil} for the other three temperatures vs. $1/T$.



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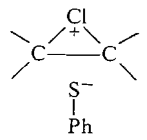

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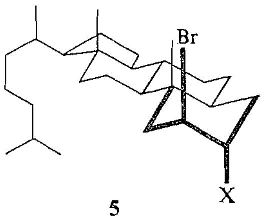

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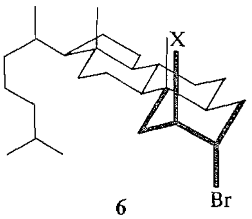

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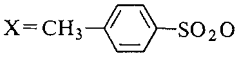
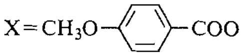
a) 

b) 

c) X=Br

less than in butanol. Accordingly in decalin the presence of the nitro group would have a smaller effect on the reaction rate than in butanol. It must be pointed out, however, that the above experimental result is in effect a small change in the Hammett ρ value accompanying a change in solvent. In view of the difficulties generally associated with determining the origin of small variations in ρ, there seems little point in elaborating the discussion any further than merely pointing out that the results qualitatively agree with what would be expected of a "merged-mechanism", but can probably be accounted for in other ways as well.

Experimental

The general techniques, apparatus, and terminology are the same as in the previous paper (2).

The solvents used in the kinetic measurements were purified as follows. 1-Butanol (British Drug Houses "Analar" grade was shaken with 10% sulfuric acid, 5% sodium bisulfite, and 5% sodium hydroxide solutions, respectively. It was then washed with two portions of water and dried over anhydrous sodium carbonate; final drying was effected by refluxing over calcium hydride followed by distillation under reduced pressure. Fisher "spectranalyzed" grade chloroform was washed five times with water, dried over anhydrous magnesium sulfate, and refluxed over calcium hydride and distilled. Fisher reagent grade nitromethane was distilled from calcium hydride. Decalin was purified as described previously (1).

2β-Chloro-3α-(p-nitrophenylthio)-5α-cholestane (1c)

Freshly crystallized *p*-nitrothiophenol (462 mg, 2.98 mmole) was chlorinated in methylene chloride at 0°. The solvent and excess chlorine were evaporated quickly. The resulting sulfenyl chloride was dissolved in methylene chloride and added to 5α-cholest-2-ene (1.0 g, 2.7 mmole) in methylene chloride little by little with shaking. The mixture was washed quickly three times with water. The solvent was removed after drying over anhydrous magnesium sulfate. The crude product was crystallized from ether–methanol; yield 1.01 g (67%), m.p. 55–60°. Recrystallization from methylene chloride – petroleum ether yielded pure product, m.p. 129°, $[\alpha]_D$ +28.5°. The nuclear magnetic resonance (n.m.r.) spectrum showed bands at 3.95 and 4.35 p.p.m., each with "half-width" of 8 c.p.s. and each corresponding in area to one hydrogen.

Anal. Calcd. for $C_{33}H_{50}NO_2SCl$: C, 70.73; H, 9.00; N, 2.50; S, 5.73; Cl, 6.33. Found: C, 70.88; H, 8.82; N, 2.67; S, 5.95; Cl, 6.45.

2β-Chloro-3α-(p-methoxyphenylthio)-5α-cholestane (1b)

A saturated solution of chlorine in carbon tetrachloride at 0° was added slowly and with shaking to a well-cooled solution of *p*-methoxythiophenol in carbon tetrachloride until a permanent deep red color was obtained. The excess chlorine and solvent were removed quickly by evaporation under reduced pressure. The residue was distilled under reduced pressure; b.p. 118° at 5 mm.

A solution of 5α-cholest-2-ene (500 mg, 1.35 mmole) in methylene chloride was cooled to −5° and the similarly cooled solution of the sulfenyl chloride in the same solvent, was added gradually with shaking until the mixture acquired permanent yellow color. The mixture was washed twice with water. The solvent was removed after drying over anhydrous magnesium sulfate. The residue was crystallized from methylene chloride – petroleum ether; yield 448 mg (60%), m.p. 109–113°. After further crystallization from ether–methanol, the compound melted at 113–115°; $[\alpha]_D$ +16.0°. The n.m.r. spectrum showed bands at 3.53 and 4.33 p.p.m., each with "half-widths" of 10 c.p.s., and each corresponding in area to one hydrogen.

Anal. Calcd. for $C_{34}H_{53}SOCl$: C, 74.89; H, 9.98; S, 5.88; Cl, 6.50. Found: C, 75.34; H, 9.54; S, 6.16; Cl, 6.53.

3β-Chloro-2α-(p-nitrophenylthio)-5α-cholestane (2c)

2β-Chloro-3α-(*p*-nitrophenylthio)-5α-cholestane was heated for about 2 h (*ca.* 8 half-lives) in 1-butanol at 110°. The solvent was removed under reduced pressure. The residue was dissolved in benzene and filtered through silica gel; yield 170 mg (85%). Recrystallization from acetone yielded a product melting at 131°; $[\alpha]_D$ −120°. The only absorption in the n.m.r. spectrum between 2.5 and 7.3 p.p.m. was a broad band from 3.2–4.2 p.p.m. having an area consistent with the presence of two hydrogen atoms.

Anal. Calcd. for $C_{33}H_{50}NO_2SCl$: C, 70.73; H, 9.00; N, 2.50; S, 5.73; Cl, 6.33. Found: C, 71.07; H, 8.89; N, 2.64; S, 5.91; Cl, 6.68.

3β-Chloro-2α-(p-methoxyphenylthio)-5α-cholestane (2b)

2β-Chloro-3α-(*p*-methoxyphenylthio)-5α-cholestane (300 mg, 0.55 mmoles) was heated in nitromethane–chloroform (3:2) for 4 h at 60°. The solvent was evaporated to dryness. Thin-layer chromatography showed only one major spot. The n.m.r. spectrum indicated diaxial methine protons showing a broad band from 2.8 to 3.9 p.p.m. partly obscured by the methoxyl peak at 3.75 p.p.m. The compound was not obtained in the crystalline state and for the purposes of characterization was oxidized by heating with hydrogen peroxide in acetic acid as described in the previous paper, whereupon the sulfone was obtained in 77% yield. Crystallization from ether–methanol yielded a compound melting at 181°; $[\alpha]_D$ −30.5°. The n.m.r. spectrum showed the broad absorption band from 3.1–4.1 p.p.m., again partly obscured by the methoxyl peak at 3.83 p.p.m.

Anal. Calcd. for $C_{34}H_{53}SO_3Cl$: C, 70.73; H, 9.25; S, 5.55; Cl, 6.14. Found: C, 70.78; H, 9.16; S, 5.45; Cl, 6.05.

Rate Measurements and Determination of the Composition of the Pyrolytic Equilibrium Mixtures

The rate measurements were carried out in sealed Pyrex ampoules in the manner previously described (1, 3) except that the samples were heated in an ethylene glycol bath maintained at the specified temperature ±0.1°. The extent of reaction was determined polarimetrically, the rotation being measured in the solvent of the reaction together with an equal volume of chloroform.

The equilibrium values for the *p*-nitro and unsubstituted materials in nitromethane–chloroform (3:2) were determined by pyrolyzing two or three samples each of the diaxial and diequatorial compounds for a period corresponding to 8 half-lives and averaging their optical rotations. For the equilibrium **1***a* ⇄ **2***a*, the $[\alpha]_D$ values starting from **1***a* were −57, −51, and −60°, and those from **2***a*, −57, −58, and −58°; the average (−57°) corresponds to an equilibrium mixture containing 98 ± 2% **2***a*. For the equilibrium **1***c* ⇄ **2***c*, the $[\alpha]_D$ values from **1***c* were −99 and −106, and from **2***c*, −112, −108, and −114°; the average (−110°) corresponds to an equilibrium mixture with 93 ± 5% **2***c*. In the *p*-methoxy series the diequatorial isomer (**2***b*) was not obtained pure. To obtain a reasonable approximation of the equilibrium rotation, six samples of the diaxial isomer (**1***b*) were pyrolyzed as above. The $[\alpha]_D$ values so obtained were −36, −30, −32, −38, −35, and −33°; the average, −34°. In butanol the pyrolyses were accompanied by a larger measure of decomposition. The samples were accordingly heated for relatively short times and the equilibrium rotation found by plotting the $[\alpha]_D$ values vs. time and visually estimating the convergence point of the curves. In this way the following values were obtained: **1***a* ⇄ **2***a*, −44 ± 3° (corresponding to 87 ± 4% **2***a*), and **1***c* ⇄ **2***c*, −97 ± 15° (corresponding to 87 ± 10% **2***c*). As in our previous study of the halohydrin esters (1), the direct determination of the equilibrium rotation in decalin was found to be impracticable, owing to decomposition accompanying the long reaction times. As before (1), it was assumed that no important error would be introduced by taking the same equilibrium composition as in another solvent; in this case the data from nitromethane–chloroform were used.

Acknowledgments

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3. J. F. KING, R. G. PEWS, and R. A. SIMMONS. Can. J. Chem. **41**, 2187 (1963).