892. *The Generalised Diaxial ⟶ Diequatorial Rearrangement.*

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The acetate, benzoate, and substituted benzoate esters of 2β-halogenocholestane-3α-ol have been shown to rearrange when heated, to give the corresponding 3β-halogenocholestan-2α-yl esters. The rates of these reactions have been determined and the kinetics shown to be of the first order. The equilibrium positions in these systems have been determined and proved to favour greatly the diequatorial compounds. The general scope and mechanism of such rearrangements are discussed.

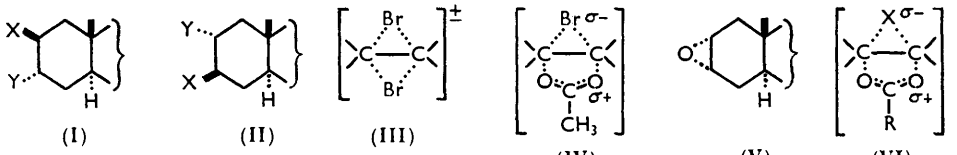
The mutarotation of " ordinary " cholestene dibromide to a more stable isomer [1] has been shown to involve rearrangement of the diaxial 5α : 6β-dibromide to the diequatorial 5β : 6α-isomer.[2] Other examples of the diaxial–diequatorial rearrangement are provided by 2β : 3α-dibromocholestane (I; X = Y = Br) which, when heated,[3] rearranges to 2α : 3β-compound (II; X = Y = Br),[4,5] and by 3α : 4β-dibromocholestane which behaves similarly.[5] That this behaviour of 1 : 2-dibromides is a general reaction has been argued elsewhere,[6] notwithstanding opinions to the contrary.[7] The related thermal rearrangements of 2β-bromo-3α-chloro- (I; X = Br, Y = Cl) and of 3α-bromo-2β-chloro-cholestane (I; X = Cl, Y = Br) afford the isomers (II; X = Br, Y = Cl, and *vice versa*, respectively).[5] Thus the rearrangements proceed in such a way as to retain each halogen substituent on the same side of the molecule. In suitable compounds the dibromide rearrangement can be shown to afford an equilibrium mixture (of the diaxial and diequatorial isomers) which can be approached from either side.[8] All these, and other, facts are in agreement with a mechanism for the reaction [9] which is intramolecular and proceeds through a transition state as in (III).

It seemed to us *ab origine* that diaxial–diequatorial dihalide rearrangements might be merely the prototype of a whole family of rearrangements of the type (I) ⟶ (II). The present paper provides evidence that this is indeed the case.

Since the transition state (III) for the dibromide rearrangement is regarded as having polar character,[9] it seemed probable that if X in (I) could be made relatively electronegative and Y relatively electropositive then rearrangement should occur more readily. Studies were initiated, therefore, with 3α-acetoxy-2β-bromocholestane (I; X = Br, Y = OAc), for in the hypothetical transition state (IV) the charges should be accommodated as

[1] Mauthner and Suida, *Monatsh.*, 1894, **15**, 91; Mauthner, *ibid.*, 1906, **27**, 421.
[2] Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066.
[3] Hattori and Kawasaki, *J. Pharm. Soc. Japan*, 1937, **57**, 115, 588.
[4] Barton and Rosenfelder, *J.*, 1951, 1048.
[5] Alt and Barton, *J.*, 1954, 4284.
[6] Barton, *Bull. Soc. chim. France*, 1956, 973.
[7] Cornubert, *ibid.*, p. 979.
[8] Barton and Head, *J.*, 1956, 932.
[9] Grob and Winstein, *Helv. Chim. Acta*, 1952, **35**, 782; see also Kwart and Weisfeld, *J. Amer. Chem. Soc.*, 1956, **78**, 635.

indicated. Heating the bromo-acetate (I; X = Br, Y = OAc) at 136° transformed it smoothly into an isomer, shown to be (II; X = Br, Y = OAc), on the basis of the following evidence. First, treatment with alkali gave 2α : 3α-epoxycholestane (V), indicating that the product was a *trans*-halogenohydrin [10] substituted at positions 2 and 3. Secondly, hydrogenolysis furnished the known [11] 2α-acetoxycholestane.



(I) (II) (III) (IV) (V) (VI)

Equilibration of the rearranged isomer (II; X = Br, Y = OAc) at 136° showed that the equilibrium mixture (I and II; X = Br, Y = OAc) contained 96 ± 3% of the latter (see Table 1). Similar equilibria were observed with all the other compounds studied (Table 1). Exact specification of the equilibrium points is not possible because of a slow

TABLE 1. *Rates of rearrangement of acyloxyhalogenocholestanes, at* 136° ± 1°.

Diaxial 2β : 3α-disubstituted cholestane		Half-life for rearrangement,	Average	10^4k	Diequatorial isomer (%) at	Rate relative to that of 3α-acetoxy-2β-bromocholestane
2β	3α	$t_{\frac{1}{2}}$ (min.)	$t_{\frac{1}{2}}$	(sec.$^{-1}$)	equilibrium	
Br	OAc	100, 117	108	1·07	96 ± 3	1·00
Br	OBz	77, 85	81	1·43	95 ± 2	1·33
Br	*p*-MeO·C_6H_4·CO_2	35·5, 27·5	32·5	3·55	97 ± 2	3·32
I	OAc	14·4, 15·0	14·7	8·04	96 ± 4	7·52
Cl	OAc	2460, 2500	2480	0·0466	93 ± 2	0·0435
Br	Br	71·5, 83·5	77·5	1·49	93 ± 1	1·39
Br	OAc *	29, 30	29·5	3·92	98 ± 2	—
Br	*p*-NO_2·C_6H_4·CO_2	105, 100	102·5	1·13	97 ± 3	0·29 †

* In phenanthrene solution. † Corrected for solvent effect.

more general decomposition observed with all the compounds. The acetate rearrangement was shown to follow good first-order kinetics proceeding at the rate indicated in Table 1.

Attention was next turned to the rearrangement of 3α-acetoxy-2β-chloro- and -2β-iodocholestane (I; X = Cl or I, Y = OAc, respectively). These compounds isomerised, following first-order kinetics (Table 1), to furnish 2α-acetoxy-3β-chloro- and -3β-iodocholestane (II; X = Cl and I, Y = OAc, respectively). The nature of these substances is based upon the exactly analogous behaviour of the corresponding bromide (see above), upon a comparison of $[M]_D$ data for these and all the other rearranged compounds reported in this paper (see Table 2), and upon the appropriate mixed m. p. relations (see Experimental section). The use of such comparisons has been justified in a similar series of diaxial and diequatorial isomers at the 2 : 3-positions in cholestane.[5] The constitutions of all the other diequatorial rearrangement products described in this paper are justified in a similar way.

It was of interest (see Table 1) that the rate of rearrangement of the chloro-acetate (I; X = Cl, Y = OAc) was about one twenty-fifth of that of the corresponding bromide, whereas the iodo-acetate (I; X = I, Y = OAc) rearranged about seven times as fast. The relative rates do not parallel the electronegativities of the halogens, which is what the order should be if only the capacity to bear negative charge, as in (IV), were important. The rates do follow, however, the relative polarisabilities of the halogens and ease of rupture

[10] Bartlett, *J. Amer. Chem. Soc.*, 1935, **57**, 224.
[11] Fürst and Plattner, *Helv. Chim. Acta*, 1949, **32**, 279.

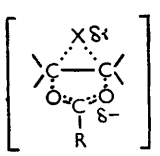
of the carbon–halogen bond. The transition state indicated as in (IV) implies that the reaction is exclusively intramolecular. Although this is not established rigidly by experiment, the conditions under which the reaction occurs are not such as to favour the incursion

TABLE 2. *Molecular rotations of* 2β : 3α- *and* 2α : 3β-*disubstituted cholestanes.*

2β : 3α-Isomer (I)		$[M_D]$ (in $CHCl_3$)	2α : 3β-Isomer (II)		$[M]_D$ (in $CHCl_3$)
2β	3α		2α	3β	
Br	Br	+403°	Br	Br	−159°
Br	OAc	+361	OAc	Br	−119
Cl	OAc	+297	OAc	Cl	−132
I	OAc	+507	OAc	I	−105
Br	Bz	+487	OBz	Br	−246
Br	*p*-MeO·C_6H_4·CO_2	+499	*p*-MeO·C_6H_4·CO_2	Br	−222
Br	*p*-NO_2·C_6H_4·CO_2	+497	*p*-NO_2·C_6H_4·CO_2	Br	−229
Br	*p*-C_6H_4Me·SO_3	+310	—	—	—

of a truly ionic mechanism. Similar considerations apply, of course, for the dibromide rearrangement [9] whose intramolecular nature is generally accepted.

A generalised transition state for halogenohydrin ester rearrangement, depicted in (VI), suggests that the rate of reaction should be increased by electron-accession from R and decreased by electron-withdrawal into R. Experiments were made with substituted benzoates in order to examine this idea. 2β-Bromocholestan-3α-yl benzoate (I; X = Br, Y = OBz) rearranged to the diequatorial isomer (II) with first-order kinetics (Table 1). The rate of reaction was about 30% greater than that for the acetate in agreement with the greater capacity of the benzoate to accommodate positive charge. The corresponding *p*-methoxy-derivative rearranged with first-order kinetics more than twice as fast (Table 1) as the unsubstituted benzoate in agreement with the electron-donating power of the *para*-methoxyl group. The *p*-nitrobenzoate (I) did not melt at 136°. Its rate of rearrangement was, therefore, determined in phenanthrene solution, the rate of rearrangement of the acetate being measured at the same time. Both reactions followed first-order kinetics but the rate for the acetate was four times as fast as for the pure molten ester. A similar marked solvent-dependence of rate has been observed previously with the cholestene dibromide.[9] Correcting the rearrangement rate of the *p*-nitrobenzoate for this solvent effect gave a rate about one-fifth of that of the unsubstituted benzoate. Electron-recession does, therefore, reduce the rate of the reaction. The relative rates of the benzoate rearrangements imply that an alternative representation of the transition state as in (VII) is improbable. The reason why simple polar considerations can be applied for variation of the electronic character of the benzoate, but not for variation in the nature of the halogen, is presumably that making and breaking of the partial covalent bond with respect to positions 2 and 3 remains the same for all the benzoates but varies for the various halogeno-acetate rearrangements. In principle it should be possible to test this idea by studying a diester rearrangement of the type (I) ⟶ (II) where X = Y = substituted benzoate, one ester having an electropositive substituent and the other an electronegative substituent.



(VII)

For comparison the rearrangement of the dibromide (I; X = Y = Br) was followed kinetically (Table 1). At 136° the reaction followed first-order kinetics at a rate slightly faster than that for the bromo-acetate (I; X = Br, Y = OAc).

The halogenohydrin ester rearrangements described here illustrate a principle which may be of importance in preparative work. It is well known that the oxide from an olefin opens diaxially to place the oxygen atom specifically on one of the two (olefinic) carbons. By the sort of rearrangement described here this oxygen can, in effect, be transferred from the carbon atom favoured by the geometrical requirements of oxide opening to the other carbon atom.

We conclude that the mechanism of these rearrangements is intramolecular through a generalised transition state of type (VI). The driving force for the rearrangement is clearly of conformational origin; *i.e.*, the compressions of the diaxial compound are minimised by isomerisation to the diequatorial isomer.

Experimental

Rotations were determined for chloroform solutions at room temperature. Neutral alumina graded according to the Brockmann scale of activity was used in chromatography. Solutions for chromatography were made up in light petroleum (b. p. 40—60°). Rearrangements were carried out in an atmosphere of oxygen-free nitrogen.

Rearrangement Procedure.—The samples were rearranged in a test-tube heated by vapour of a refluxing liquid. The latter was in a 1 l. flask fitted with condenser, thermometer, and Quickfit B24 neck. The test tube (20 × 2 cm.) was constructed with a Quickfit B24 male joint as the wall at the middle so that it fitted into the flask with the lower 5 cm. of the tube protruding into the bulb of the flask. The sample (30—60 mg.) was weighed into the tube, and a measured volume (2—3 ml.) of chloroform added. A portion of the solution was transferred to a polarimetric tube and the rotation determined. The polarimetric sample was quantitatively washed back into the test-tube with chloroform and the solvent carefully removed at <70° under reduced pressure. The test-tube was then inserted into the heating-flask and the rearrangement begun. The course of the reaction was followed by, at intervals, removing the test-tube, cooling it quickly to room temperature, determining the optical rotation (in $CHCl_3$ solution, as above), and returning the sample to the test-tube as before.

Ethylbenzene, which gave a temperature of 136° ± 1°, was used as the heating liquid in all kinetic experiments and for the determination of the positions of equilibria for the acetate derivatives and for the dibromides. Phenetole (b. p. 169° ± 1°) was used in the determination of the equilibrium positions in the other systems. The equilibrium points were approached from both the more stable (diequatorial) and the less stable (diaxial) isomers in every case.

2β-*Bromocholestan*-3α-*yl Acetate.*—Prepared according to Alt and Barton,[5] this was dimorphous, having m. p. 115—118° and 139—143°, $[\alpha]_D$ +70° (*c* 2·00). Alt and Barton [5] give m. p. 120—122°, $[\alpha]_D$ +71°.

2β-*Chlorocholestan*-3α-*yl Acetate.*—Prepared according to Alt and Barton,[5] this had m. p. 131—132°, $[\alpha]_D$ +64° (*c* 2·05) {lit.,[5] m. p. 128—130°, $[\alpha]_D$ +68°}.

2β-*Bromocholestan*-3α-*yl Benzoate.*—2β-Bromocholestan-3α-ol (600 mg.) in dry pyridine (5 ml.) was treated with benzoyl chloride (0·65 ml.) and left overnight at room temperature. It was then poured into water, set aside for 1 hr., and extracted with ether. The extract, after filtering through a column of alumina (Grade III), was evaporated and the residue crystallised four times from acetone, to give 2β-*bromocholestan*-3α-*yl benzoate*, as fine needles, m. p. 98—101°, $[\alpha]_D$ +85° (*c* 1·85) (Found: C, 71·4; H, 8·9; Br, 14·55. $C_{34}H_{51}O_2Br$ requires C, 71·4; H, 9·0; Br, 14·0%).

2β-*Bromocholestan*-3α-*yl* p-*Anisate.*—2β-Bromocholestan-3α-ol (800 mg.) was dissolved in dry pyridine (5 ml.). *p*-Anisoyl chloride (0·9 ml.) was added and the mixture treated as in the benzoylation (above). After three crystallisations from acetone, 2β-*bromocholestan*-3α-*yl* p-*anisate* was obtained as fine needles, m. p. 136—138°, $[\alpha]_D$ +83·1 (*c* 2·00) (Found: C, 70·0; H, 8·6; Br, 13·3. $C_{35}H_{53}O_2Br$ requires C, 69·8; H, 8·9; Br, 13·3%).

2β-*Bromocholestan*-3α-*yl* p-*Nitrobenzoate.*—2β-Bromocholestan-3α-ol (600 mg.) was added to a cold solution of toluene-*p*-sulphonyl chloride [12] (500 mg.) and *p*-nitrobenzoic acid (250 mg.) in pyridine (5 ml.). The mixture was left in an ice-bath for 2 hr., then poured into water and extracted with ether. The material from the extract was chromatographed on Grade III alumina. Elution with benzene gave 2β-*bromocholestan*-3α-*yl* p-*nitrobenzoate* (620 mg.) which, after four crystallisations from chloroform–acetone, had m. p. (fine needles) 198—200°, $[\alpha]_D$ +81° (*c* 2·1) (Found: C, 66·6; H, 8·1; N, 2·2; Br, 13·6. $C_{34}H_{50}O_4NBr$ requires C, 66·2; H, 8·2; N, 2·3; Br, 12·95%).

2β-*Bromocholestan*-3α-*yl Toluene*-p-*sulphonate.*—Toluene-*p*-sulphonyl chloride (500 mg.) was added to 2β-bromocholestan-3α-ol (400 mg.) in dry pyridine (5 ml.), and the mixture left for 4 days at room temperature. The mixture was poured into water and extracted with ether and the extracted material crystallised four times from acetone, to give 2β-*bromocholestan*-3α-*yl*

[12] Brewster and Ciatti, *J. Amer. Chem. Soc.*, 1955, **77**, 6214.

toluene-p-*sulphonate*, m. p. 168—170°, $[\alpha]_D$ +49° (*c* 1·75) (Found: C, 65·6; H, 8·6; Br, 13·35; S, 4·8. $C_{34}H_{53}O_3BrS$ requires C, 65·7; H, 8·6; Br, 12·85; S, 5·2%).

2β-*Iodocholestan*-3α-*ol*.—2α : 3α-Epoxycholestane (630 mg.) in chloroform (30 ml.) was shaken for 3 min. with a 55% aqueous solution of hydriodic acid [2] (12 ml.). The chloroform layer was washed quickly with dilute sodium sulphite solution, and the solvent removed under reduced pressure. The residue was crystallised from ether–methanol and acetone–methanol, to give 2β-*iodocholestan*-3α-*ol*, m. p. 132—133°, $[\alpha]_D$ +53° (*c* 2·0) (Found: C, 62·8; H, 9·4; I, 24·5. $C_{27}H_{47}OI$ requires C, 63·0; H, 9·2; I, 24·65%). 2β-*Iodocholestan*-3α-*yl acetate* was prepared by dissolving the iodohydrin in pyridine, adding excess of acetic anhydride, and allowing the mixture to remain overnight at room temperature. After four crystallisations from acetone–methanol the acetate melted at 131—133° and had $[\alpha]_D$ +91° (*c* 2·25) (Found: C, 62·6; H, 8·8. $C_{29}H_{49}O_2I$ requires C, 62·6; H, 8·9%).

Isolation of the Rearranged Halogeno-esters.—Chromatography of the products of thermal rearrangement on Grade I alumina (elution with 1 : 4 benzene–light petroleum) was followed by crystallisation from acetone–methanol. In this way were obtained: 3β-*Bromocholestan*-2α-*yl acetate*, m. p. 118—119°, $[\alpha]_D$ −22° (*c* 2·00) (Found: C, 68·6; H, 9·7; Br, 16·2. $C_{29}H_{49}O_2Br$ requires C, 68·35; H, 9·7; Br, 15·7%). 3β-*Bromocholestan*-2α-*yl benzoate*, m. p. 112—114°, $[\alpha]_D$ −43° (*c* 1·40) (Found: C, 71·4; H, 9·1; Br, 14·1. $C_{34}H_{51}O_2Br$ requires C, 71·4; H, 9·0; Br, 13·95%). 3β-*Bromocholestan*-2α-*yl* p-*anisate*, m. p. 114—115°, $[\alpha]_D$ −37° (*c* 2·25) (Found: C, 69·7; H, 9·0. $C_{35}H_{53}O_3Br$ requires C, 69·8; H, 8·9%). 3β-*Iodocholestan*-2α-*yl acetate*, m. p. 88—92°, $[\alpha]_D$ −19° (*c* 1·6) (Found: C, 62·9; H, 9·1; I, 23·1. $C_{29}H_{49}O_2I$ requires C, 62·6; H, 8·9; I, 22·8%). 3β-*Chlorocholestan*-2α-*yl acetate*, m. p. 138°, $[\alpha]_D$ −28° (*c* 1·95) (Found: C, 75·1; H, 10·3; Cl, 7·4. $C_{29}H_{49}O_2Cl$ requires C, 74·9; H, 10·6; Cl, 7·6%).

3β-*Bromocholestan*-2α-*yl* p-*Nitrobenzoate*.—2β-Bromocholestan-3α-yl *p*-nitrobenzoate (see above) (160 mg.) and phenanthrene (480 mg.) were heated (in four lots) until rearrangement was complete ($[\alpha]_D$). The product was chromatographed on Grade I alumina. After exhaustive elution with light petroleum and light petroleum–benzene (4 : 1) to remove the phenanthrene, elution with benzene gave 3β-*bromocholestan*-2α-*yl* p-*nitrobenzoate* which, after four crystallisations from acetone–methanol, had m. p. 158—159°, $[\alpha]_D$ −37° (*c* 1·85) (Found: C, 66·2; H, 8·1; N, 2·25; Br, 12·4. $C_{34}H_{50}O_4NBr$ requires C, 66·2; H, 8·2; N, 2·3; Br, 12·95%).

Hydrogenolysis of 3β-*Bromocholestan*-2α-*yl Acetate*.—This acetate (101 mg.) was hydrogenated for 8 hr. with prehydrogenated 10% palladium–charcoal (100 mg.) in ethanol (5 ml.) containing anhydrous sodium acetate (1 g.). The product, after three crystallisations from chloroform–methanol, was by m. p., mixed m. p., $[\alpha]_D$, and infrared spectrum identical with authentic cholestan-2α-yl acetate prepared by the method of Fürst and Plattner.[11]

Treatment of 3β-*Bromocholestan*-2α-*yl Acetate with Alkali* (*with* V. V. Kane).—3β-Bromocholestan-2α-yl acetate (75 mg.) was refluxed for 1½ hr. with 5% methanolic potassium hydroxide (10 ml.). Crystallisation of the product from ether–methanol gave 2α : 3α-epoxycholestane, identified by m. p., mixed m. p., and $[\alpha]_D$.

Tests for Isomorphism.—The following compounds were used: (1) 3β-bromocholestan-2α-yl acetate, (2) 3β-chlorocholestan-2α-yl acetate, (3) 3β-iodocholestan-2α-yl acetate, and (4) 2β-bromocholestan-3α-yl acetate. Nos. 1—3 are diequatorial, no. 4 is diaxial. The m. p. of a specimen of the lower-melting component of the mixture was always taken at the same time as that of the mixture. Mixed m. p.s were as follows: Diequatorial pairs (no depressions): (1) + (2) 122—133°; (1) + (3) 84—105°; (2) + (3) 84—110°. Diaxial–diequatorial pairs (depressed): (1) + (4) 95—120°; (2) + (4) 107—112°; (3) + (4) 77—120°.

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