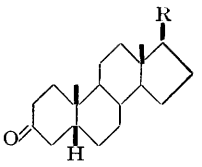
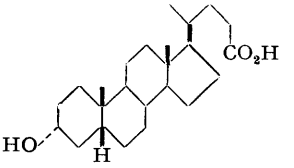
196. *Long-range Effects in Alicyclic Systems. Part I. The Rates of Rearrangement of Some Steroidal Dibromides*

By D. H. R. Barton and A. J. Head.

The rates of mutarotation of some steroidal 5α : 6β-dibromides have been investigated. 5α : 6β : 22ξ : 23ξ-Tetrabromostigmastane reacts at only 75% of the rate observed with 5α : 6β-dibromo-cholestane and -stigmastane. The rate of rearrangement of 5α : 6β-dibromodeoxytigogenin is similar. These anomalies represent long-range effects in systems which are conformationally unambiguous.

The intramolecular interaction of functional groups through a chain of saturated carbon atoms is germane to organic chemistry. Short-range interactions through a few carbon atoms are well understood and have recently been discussed authoritatively by Ingold.[1] Longer-range interactions, involving unit polar charges, are exemplified by the classical work of Gane and Ingold [2] on the dissociation constants of aliphatic dicarboxylic acids. Some interaction, transmitted through three or four saturated carbon atoms, was found by Conant and his collaborators [3] in observations on the rate of displacement of chloride ion from alkyl chlorides by iodide ion. Much more spectacular effects have been claimed by Rothen [4] involving enzyme–substrate interactions through several hundred Å of inert material. Such claims are difficult to justify on a physical basis and have been the subject of criticism.[5] Another remarkable report was made by Marker *et al.*[6] that the point of oxidative cleavage in ring A of coprostanone (I; R = C_8H_{17}) and of pregnane-3 : 20-dione (I; R = COMe) was at $C_{(2)} : C_{(3)}$ whereas that of lithocholic acid (II) was at $C_{(3)} : C_{(4)}$.[7] Arguments recently adduced by Georg [8] show that Marker's 2 : 3-*seco*-dicarboxylic acids

(I) 



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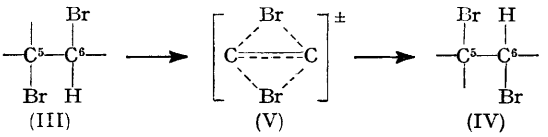
are really 3 : 4-*seco*-compounds and that, in fact, no long-range effects are involved. It is well known that minor changes in steroidal side chains may inhibit digitonide formation. This is not a long-range phenomenon but a function of the crystal lattice. Catalytic-hydrogenation effects, where surface–molecule interactions are concerned, belong to the same category.

The present series of investigations was undertaken because of the paucity of knowledge of long-range effects in molecules of rigid conformation. Studies with aliphatic compounds, such as those cited above, deal with molecules of flexible conformation where the distances between functional groups in solution cannot be defined with precision. With molecules where the stereochemical nature defines the conformation quite exactly (for example, *trans*-A/B steroids and triterpenoids of the β-amyrin or lanosterol type) the possible existence of long-range effects can be explored with a precision governed only by the difficulties of practical measurement. Our first objective has been to establish the existence of long-range effects in such molecules; it is hoped to discuss their origin later.[9]

[1] Ingold, " Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, New York, 1953, Chap. 2.
[2] Gane and Ingold, *J.*, 1928, 1594, 2267; 1929, 1691; 1931, 2153.
[3] Conant *et al.*, *J. Amer. Chem. Soc.*, 1924, **46**, 232; 1925, **47**, 476, 488.
[4] Rothen, *Helv. Chim. Acta*, 1950, **33**, 834; *J. Amer. Chem. Soc.*, 1948, **70**, 2732; and references there cited.
[5] Trurnit, *Science*, 1950, **112**, 329; see also Rothen, *ibid.*, p. 330.
[6] Marker, Wittle, Plambeck, Rohrmann, Krueger, and Ulshafer, *J. Amer. Chem. Soc.*, 1939, **61**, 3317.
[7] Wieland, Dane, and Scholz, *Z. physiol. Chem.*, 1932, **211**, 261.
[8] Georg, *Arch. Sci.*, 1954, **7**, 114.
[9] See Barton, *Experientia*, 1955, Suppl. II, p. 121.

In general, however, we shall not be concerned with processes in which the interaction of unit polar charges is involved, and we intend to focus attention more upon conformational aspects of interaction.

The present paper is concerned with rates of rearrangement of steroidal 5α : 6β-dibromides (III) to give 5β : 6α-dibromides (IV) *via* a transition state [10] which may be symbolised [11] as in (V). Grob and Winstein [10,12] showed that this was a first-order



process, conveniently studied polarimetrically. The reaction is reversible. In cholestane derivatives (VI) the position of equilibrium varies to a first approximation with the size of the group X attached at $C_{(3)}$. Illustrative data are summarised in Table 1. For detailed

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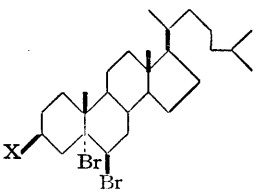
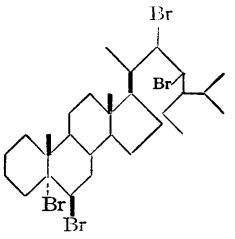




(VII)

kinetic work a series of 5α : 6β-dibromides was chosen where X = H. By a study of the rearranged 5β : 6α-dibromides it was demonstrated in each case that the equilibrium was more than 99% in favour of the 5β : 6α-dibromides.

TABLE 1.

Cholestane derivative; 3β-substituent X	5β : 6α-Dibromide (%) at equilm. at 40·0°	Cholestane derivative; 3β-substituent X	5β : 6α-Dibromide (%) at equilm. at 40·0°
H	>99% *	OH	85·5 *
Cl	13	OBz	80 †
Br	10		

* Grob and Winstein.[10] † Grob and Winstein [10] report 83·7% at about 61·2°.

In agreement with Grob and Winstein [10] the rearrangement of 5α : 6β-dibromocholestane showed good first-order kinetics up to 70% or more of completion of reaction. The data obtained are summarised in Table 2 and indicate rate constants of $1{\cdot}37 \times 10^{-5}$ and of $7{\cdot}00 \times 10^{-5}$ at 25·25° and 40·03° respectively, in fair agreement with those (1·1 and $6{\cdot}4 \times 10^{-5}$ sec.$^{-1}$ respectively) reported by Grob and Winstein [10] in their less detailed examination of the kinetics of the process. In order to show that the reaction was indeed intramolecular the variation of rate constant with concentration was investigated (see Table 3). There was no significant variation in k over a nine-fold variation in concentration. The rate-constant equation for the mutarotation was found to be $k = 10^{10{\cdot}1} \exp(-20{,}400/\boldsymbol{R}T)$ sec.$^{-1}$.

An analogous study was then carried out in the stigmasterol series. Stigmasterol was converted into stigmasta-5 : 22-diene which on bromination gave 5α : 6β : 22ξ : 23ξ-tetrabromostigmastane (VII) which rearranged smoothly in chloroform solution to give the 5β : 6α-coprostigmastane derivative. The kinetics of this process (Table 2) were carefully examined and shown to be of the first order and independent of concentration (see Table 3). At all temperatures the rearrangement of the 5α : 6β : 22ξ : 23ξ-tetrabromostimastane was

[10] Grob and Winstein, *Helv. Chim. Acta*, 1952, **35**, 782.
[11] See Alt and Barton, *J.*, 1954, 4284.
[12] See also Bretschneider, Földi, Galinovsky, and Fodor, *Ber.*, 1941, **74**, 1451.

significantly slower than that of 5α : 6β-dibromocholestane. The rate-constant equation was shown to be $k = 10^{10\cdot0} \exp(-20{,}400/\boldsymbol{R}T)$ sec.$^{-1}$.

TABLE 2.

Temp.	Mean velocity const. 10^5k (sec.$^{-1}$)	No. of runs	Mean error (%) of mean k	Temp.	Mean velocity const. 10^5k (sec.$^{-1}$)	No. of runs	Mean error (%) of mean k
5α : 6β-*Dibromocholestane.*				5α : 6β : 22ξ : 23ξ-*Tetrabromostigmastane.*			
28·0°	1·87	6	0·5	20·0°	0·558	5	0·9
35·0	4·19	9	1·7	35·0	3·00	6	1·5
41·0	7·86	8	0·9	40·0	5·51	7	0·4
				49·0	13·4	4	0·6
5α : 6β-*Dibromostigmastane.*							
29·95	2·3	2	—	5α : 6β-*Dibromodeoxytigogenin.*			
36·0	4·39	3	—	36·0	3·15	7	1·5
45·0	12·3	2	—	41·0	5·47	2	—
				48·0	11·1	2	—

TABLE 3.

Concn. (g./100 ml.) of 5α : 6β-dibromide	Velocity const. 10^5k (sec.$^{-1}$)	Concn. (g./100 ml.) of 5α : 6β-dibromide	Velocity const. 10^5k (sec.$^{-1}$)
5α : 6β-*Dibromocholestane at* 41·0°.		5α : 6β : 22ξ : 23ξ-*Tetrabromostigmastane at* 40·0.	
1·06	7·7	1·08	5·3
2·02	8·2	2·91	5·55
3·79	7·8	3·07	5·45
3·89	7·7	5·16	5·6
3·96	7·75	9·71	5·55
4·03	7·75		
4·92	8·1		
9·30	7·75		
Mean	7·86		

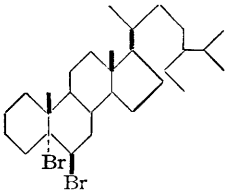
At first we were loth to accept this difference as real and an alternative explanation was sought. The difference could be due to complication of the reaction by rearrangement of the 22 : 23-dibromide grouping. This was shown not to be correct as follows. Stigmasteryl benzoate was converted into its tetrabromide which was selectively debrominated [13] to stigmasteryl benzoate 22 : 23-dibromide. The latter showed no sign of rearrangement in chloroform solution and gave back the original tetrabromide on bromination. The side-chain dibromide grouping cannot, therefore, be undergoing rearrangement during the time required for the study of the mutarotation. The difference could be explained by incomplete transformation of stigmasta-5 : 22-diene into its tetrabromide. This explanation was also rejected since several batches of tetrabromide, whose bromine content was checked by analysis, all gave the same results. Further, Dr. A. W. Burgstahler, whose kind collaboration we acknowledge, repeated the preparation of both 5α : 6β-dibromocholestane and 5α : 6β : 22ξ : 23ξ-tetrabromostigmastane and checked the kinetic data independently. The difference could also possibly be explained if the small quantity of hydrogen bromide produced in a side reaction catalysed [14] the process. We reject this, first, because of the reproducibility of our results and, secondly, because the influence of hydrogen bromide has already been shown to be negligible by Grob and Winstein.[10]

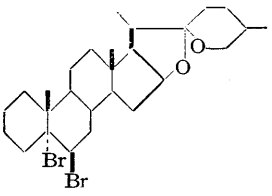
The structural difference between (VI) and (VII) consists of an extra ethyl group and two extra bromine atoms. That it is the two bromine atoms that are of importance in creating a rate-constant difference was made probable by showing that an extra ethyl group had no effect. Thus β-sitosterol was converted into stigmast-5-ene and thence into 5α : 6β-dibromostigmastane (VIII). The latter was smoothly rearranged to 5β : 6α-dibromocoprostigmastane in chloroform solution. The kinetics of this rearrangement were studied (see Table 2), although not in great detail. The reaction was of the first order

[13] Cf. Fernholz and Stavely, *J. Amer. Chem. Soc.*, 1939, **61**, 2956.
[14] Cf. Kwart and Weisfield Abs. Amer. Chem. Soc. Meeting, Cincinatti, 1955, p. 49N.

and *identical in rate* with that of 5α : 6β-dibromocholestane. The rate-constant equation was $k = 10^{10\cdot1} \exp(-20{,}400/\boldsymbol{R}T)$ sec.$^{-1}$.

Finally, the effect of a more radical structural modification of the side chain was investigated. Diosgenin was converted by conventional methods into deoxydiosgenin which afforded 5α : 6β-dibromodeoxytigogenin (IX) on bromination. This was smoothly

(VIII) 



(IX)

rearranged in chloroform solution to give 5β : 6α-dibromodeoxycoprotigogenin. The kinetics of this process were investigated (see Table 2). The reaction was of the first order but significantly slower than that of 5α : 6β-dibromocholestane. The rate-constant equation was found to be given by $k = 10^{10\cdot0} \exp(-20{,}400/\boldsymbol{R}T)$ sec.$^{-1}$. The appropriate model experiments showed that the rate measurements were not being invalidated by the action of traces of hydrogen bromide on the steroidal sapogenin side chain.

In summary it may be stated that, if the rates of mutarotation of 5α : 6β-dibromocholestane and -stigmastane are represented as 100, the corresponding rates for 5α : 6β : 22ξ : 23ξ-tetrabromostigmastane and 5α : 6β-dibromodeoxytigogenin are 75 and 69 respectively. The difference in reaction rate between 5α : 6β-dibromocholestane and

TABLE 4.

	$[M]_D$		
Parent compound	5α : 6β-Dibromide	5β : 6α-Dibromide	$\Delta[M]_D$
Cholest-5-ene	−215°	+267°	+482°
Stigmast-5-ene	−197	+274	+471
22ξ : 23ξ-Dibromostigmast-5-ene...	−226	+246	+472
Deoxydiosgenin	−586	−158	+428

5α : 6β : 22ξ : 23ξ-tetrabromostigmastane represents a long-range effect in conformationally unambiguous systems transmitted through six saturated carbon atoms or (from accurate scale models) through 9·3 Å.

No correlation was apparent between molecular-rotation anomalies (Table 4) and reaction rates.

EXPERIMENTAL

For general experimental details see Barton *et al.*[15] All rotations refer to $CHCl_3$ solutions : the solvent was purified by washing it twice with concentrated sulphuric acid and then with aqueous sodium carbonate, dried ($CaCl_2$), and stored in the dark; it was checked for the development of acidity before use. The thermostat was controlled to within ±0·03°.

The procedure in a kinetic run was as follows. The dibromide was weighed into a calibrated 10 ml. flask which had been painted black to exclude light, except for a small window at the graduation mark, then dissolved in pure chloroform in a thermostat at the required temperature, and the solution was quickly made up to 10 ml. Samples (approx. 1 ml.), withdrawn at suitable intervals, were rapidly cooled (ice-bath) to room temperature and the rotation was determined. Concentrations of 3—4% w/v were used unless specified otherwise. Allowance was made for the difference between the temperature at which the solutions were made up and that at which the rotations were measured by using the coefficients of expansion of chloroform.[16] Values of k were calculated graphically, for greatest accuracy, on observations up to 50% reaction in the usual way.[10]

Recrystallisations of metastable dibromides were conducted at or below room temperature.

[15] Barnes, Barton, Fawcett, and Thomas, *J.*, 1952, 2339.
[16] "Handbook of Chemistry and Physics," 31st Edn., Chem. Rubber Publ. Co., Cleveland, Ohio, 1949.

These dibromides were conveniently prepared by dissolving the hydrocarbon in chloroform–acetic acid containing approx. 1·2 mols. of sodium acetate at 0° and adding 1·1 mols. of bromine in acetic acid.[17]

Derivatives of Cholestane.—5α : 6β-Dibromocholestane[18] had a constant $[\alpha]_D$ −40·5°. The derived 5β : 6α-dibromocoprostane had a constant $[\alpha]_D$ +50·4° (*c*, 7·62), unchanged at room temperature overnight. 5α : 6β-Dibromocholestanyl benzoate had a constant $[\alpha]_D$ −36·4° (*c*, 3·96); the derived 5β : 6α-dibromide had $[\alpha]_D$ +83·1° (*c*, 4·41). 3β-Chloro-5α : 6β-dibromocholestane[19] {$[\alpha]_D$ −51·5° (*c*, 5·85); 12·2 g.} in chloroform (50 ml.) was refluxed for 6 hr. ($[\alpha]_D$ −38·2°). After removal, by addition of methanol, of two crops of unrearranged dibromide, the mother-liquors were evaporated *in vacuo* at room temperature, to give a residue (3·0 g.; $[\alpha]_D$ +4°). This residue (1·61 g.) in chloroform (16 ml.) was treated with sodium iodide (6·45 g.) in " AnalaR " acetone (390 ml.) at 20° for 65 min. The product, in methylene dichloride (50 ml.), was ozonised at −78° until negative to tetranitromethane (30 min.), then shaken with water at room temperature. The methylene dichloride layer was filtered through alumina. Removal of the solvent *in vacuo* at room temperature and crystallisation at <20° from chloroform–methanol gave 5β : 6α-*dibromo*-3β-*chlorocoprostane* (540 mg.), m. p. 126—127°, $[\alpha]_D$ +49·1° (*c*, 4·76) (Found : C, 57·75; H, 8·05; Cl + Br, 34·3. $C_{27}H_{45}ClBr_2$ requires C, 57·4; H, 8·05; Cl + Br, 34·55%). 3β : 5α : 6β-Tribromocholestane[20] had $[\alpha]_D$ −51·5° (*c*, 3·91).

Equilibrium measurements made with these compounds at 40·0° in chloroform solution are summarised in Table 5.

TABLE 5.

Cholestane derivative; 3β-	Initial composition 5α : 6β-Dibromide	Initial composition 5β : 6α-Dibromide	Total concn. (g./100 ml.)	$[\alpha]_D$ Initial	$[\alpha]_D$ Final	Time of equiln. (hr.)	5β : 6α-Dibromide (%) at equilm.
Chloride	100	0	5·51	−51·5°	−37·9°	162	13
	100	0	4·87	−50·7	−36·2	263	14
	89·9	10·1	6·09	−40·6	−37·3	144	13
	81·9	18·1	6·19	−33·0	−37·8	144	13
Bromide	100	0	4·46	−51·4	−41·9	257 *	10 †
Benzoyloxy...	100	0	5·35	−36·4	+57·4	163	79
	0	100	5·71	+81·2	+58·6	163	80
	14·8	85·2	5·58	+62·9	+60·2	220	81
	23·7	76·3	6·15	+54·1	+60·3	213	81

* Preceded by storage for 21 days at room temperature.

† Based on $[\alpha]_D$ +41·9° for the 5β : 6α-isomer; the latter rotation was calculated from the observed molecular-rotation difference on isomerisation of 5α : 6β-dibromo-3β-chlorocholestane.

Derivatives of Stigmastane.—Stigmasterol was converted into 3β-chlorostigmasta-5 : 22-diene.[21,22] Reduction of this chloride with an equal weight of sodium in refluxing *n*-pentyl alcohol as for the preparation for cholest-5-ene gave *stigmasta*-5 : 22-*diene*, needles (from ethyl acetate), m. p. 115—116°, $[\alpha]_D$ −69° (*c*, 2·86) (Found : C, 87·9; H, 12·3. $C_{29}H_{48}$ requires C, 87·8; H, 12·2%). Treatment with bromine (2·2 mols.) as detailed above gave 5α : 6β : 22ξ : 23ξ-*tetrabromostigmastane*, m. p. 196—198° (from chloroform–ethyl acetate–methanol), $[\alpha]_D$ −31·6° (*c*, 3·60) (Found : C, 48·7; H, 6·5; Br, 45·2. $C_{29}H_{48}Br_4$ requires C, 48·65; H, 6·8; Br, 44·6%). The m. p. recorded is that observed after drying at room temperature; if examined immediately after crystallisation a metastable (solvated) form of much lower m. p. is discernible.

Refluxing a solution of this tetrabromide in chloroform for 4 hr. gave 5β : 6α : 22ξ : 23ξ-*tetrabromocoprostigmastane*, stout needles (from ethyl acetate–methanol), m. p. 202—203° (decomp.), $[\alpha]_D$ +35·0° (*c*, 4·70), unchanged after 8 days in the dark at room temperature (Found : C, 48·7; H, 6·5; Br, 44·8%).

Stigmasterol benzoate was brominated with 2·2 mols. of bromine in the usual way, to give 5α : 6β : 22ξ : 23ξ-*tetrabromostigmastan*-3β-*yl benzoate* (from chloroform–ethyl acetate–methanol), m. p. 148—150° (depends markedly on rate of heating), $[\alpha]_D$ −31·2° (*c*, 2·21) (Found : C, 51·9; H, 6·45; Br, 38·0. $C_{36}H_{52}O_2Br_4$ requires C, 51·7; H, 6·25; Br, 38·2%). The tetrabromide

[17] Cf. Windaus, *Ber.*, 1906, **39**, 518.
[18] Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 1066.
[19] Marker, Whitmore, Kamm, Oakwood, and Blatterman, *ibid.*, 1936, **58**, 338.
[20] Beynon, Heilbron, and Spring, *J.*, 1936, 907, and references there cited.
[21] Windaus and Hauth, *Ber.*, 1906, **39**, 4378.
[22] Shoppee, *J.*, 1946, 1147.

was converted into the 22 : 23-dibromide as follows.[23] The tetrabromide (1·2 g.) in benzene (10 ml.) was treated with sodium iodide (800 mg.) in ethanol (7 ml.) and set aside at room temperature for 20 hr. Crystallisation of the product from benzene–ethanol afforded 22ξ : 23ξ-*dibromostigmast-5-en-3β-yl benzoate*, m. p. 182—185° (decomp.) (depends on rate of heating), $[\alpha]_D$ −6·2° (*c*, 2·73; unchanged for 5 days) (Found : C, 64·0; H, 7·75; Br, 24·0. $C_{36}H_{52}O_2Br_2$ requires C, 63·9; H, 7·75; Br, 23·6%). Treatment with 1·1 mols. of bromine in the usual way gave back the previously described 5α : 6β : 22ξ : 23ξ-tetrabromostigmastan-3β-yl benzoate, identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ −30° (*c*, 3·70)}.

β-*Sitosterol Derivatives.*—β-Sitosterol was converted into stigmast-5-ene, m. p. 76—77° (from ethyl acetate–methanol), $[\alpha]_D$ −53° (*c*, 4·20) (Found : C, 87·75; H, 12·5. Calc. for $C_{29}H_{50}$: C, 87·35; H, 12·65%), as described earlier. Treatment with bromine afforded 5α : 6β-*dibromostigmastane* (from ethyl acetate–methanol), m. p. 103—104°, $[\alpha]_D$ −35·3° (*c*, 5·27) (Found : C, 62·3; H, 9·05; Br, 28·9. $C_{29}H_{50}Br_2$ requires C, 62·35; H, 9·0; Br, 28·6%). When this dibromide was refluxed in chloroform solution for 6 hr. it gave 5β : 6α-*dibromostigmastane*, m. p. 123—125° (from ethyl acetate–methanol), $[\alpha]_D$ +49·1° (*c*, 5·54) (Found : C, 62·7; H, 8·85; Br, 28·4%).

Derivatives of Diosgenin.—Dried purified diosgenin (1·76 g.) in dry alcohol-free chloroform (50 ml.) at −60° was treated with phosphorus pentachloride (1·08 g., 1·2 mols.) with good stirring. The stirring was continued and the mixture allowed to come to room temperature (1 hr.). Crystallisation from ethyl acetate–methanol gave the chloride (55%), m. p. 204—209°, $[\alpha]_D$ −111° (*c*, 3·80). Reduction of the chloride with sodium–pentyl alcohol or, more conveniently, with sodium–propan-1-ol, afforded deoxydiosgenin (80%), m. p. 190—198° $[\alpha]_D$ −144° (*c*, 5·07).[24] The homogeneity of this material was established by extensive chromatographic fractionation. Treatment with bromine in the usual way showed (by titration) an uptake of only one mol.; crystallisation from chloroform–methanol gave 5α : 6β-*dibromodeoxytigogenin*, m. p. 167—169° (decomp.) (but rather variable), $[\alpha]_D$ −105° (*c*, 3·37) (Found : C, 58·45; H, 7·35; Br, 28·75. $C_{27}H_{42}O_2Br_2$ requires C, 58·05; H, 7·6; Br, 28·6%). Rearrangement was conveniently effected by leaving the dibromide in chloroform solution at 36° for 21 hr. Crystallisation of the product from ethyl acetate–methanol afforded the highly crystalline 5β : 6α-*dibromocoprodeoxytigogenin*, m. p. 168—172°, $[\alpha]_D$ −28·3° (*c*, 4·29; unchanged after 8 days at room temperature in the dark) (Found : C, 58·25; H, 7·65; Br, 28·5%). The constitution of this compound was confirmed as follows. Debromination by stirring with zinc dust in chloroform–acetic acid gave deoxydiosgenin, identified by m. p., mixed m. p., and rotation {$[\alpha]_D$ −143° (*c*, 3·10)}. The dibromide (43·9 mg.) in "AnalaR" acetone (20 ml.) was treated with a 0·134M-solution (20 ml.) of sodium iodide in the same solvent at 0°. After 2 hr. at this temperature no debromination had occurred, whereas the corresponding 5α : 6β-dibromide was debrominated to the extent of 90% under the same conditions.

The following experiment was carried out to show that the spiro-ketal side chain was not damaged by traces of hydrogen bromide which might possibly be formed in a side reaction during mutarotation. Diosgenin acetate (241 mg.) in chloroform–acetic acid (99 : 1; 1 ml.) containing hydrogen bromide (solution 0·0099N) was left for 21 hr. at room temperature; the rotation did not change.

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