Substituent Effects on the Chiral Properties of 2,3-Dithiadecalins and 2-Thiahydrindans

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Optically active methyl- and phenyl-substituted 2,3-dithiadecalins have been synthesized and their u.v. and c.d. spectra measured. The external perturbation of a methyl group on a disulphide with a dihedral angle ∠CSS/SSC of *ca.* 60° influences both the 240 and 290 nm bands. The Cotton effect corresponding to the 240 nm transition is especially sensitive to external perturbation. A phenyl group shows such a large influence on the chiral properties that the sign of the Cotton effect at 240 nm expected from the skew conformation of the disulphide group is reversed. A conformationally labile compound has also been investigated, and the effect of substituents on methyl-2-thiahydrindans is described.

A THOROUGH understanding of the relation between the stereochemistry of disulphides and their optical activity would be very useful in conformational studies on numerous biologically important compounds, such as α-lipoic acid, oxytocin, vasopressin, insulin, gliotoxin, *etc.* The dominant influence of the dihedral angle ∠CSS/SSC on the energy of electronic transitions of the disulphide group has been shown by u.v. absorption studies, where the lowest energy absorption band moves to longer wavelength and decreases in magnitude as the angle is reduced from 90 to 0°.[1-9] An empirical correlation of the sign of the longest-wavelength circular dichroism (c.d.) band and the disulphide chirality was provided by the work of Carmack and Neubert,[10] of Dodson and Nelson,[11] and of Claeson.[12] This rule states that in 1,2-dithian ring systems a positive c.d. band corresponding to the lowest energy electronic transition of the disulphide group is associated with a right-handed (*P*) screw sense of the helix containing the atoms C–S–S–C, and a negative c.d. band is associated with a left-handed (*M*) screw sense of the helix.[13] This empirical rule was later elucidated theoretically from a semi-empirical CNDO calculation by Linderberg and Michl and recently by Webb *et al.*[14a,b] and from calculation based on the Bergson model [15] by Woody.[3] The theoretical calculations suggested quadrant behaviour of disulphides, and this has been verified experimentally by Ludescher and Schwyzer.[16]

However, Carmack and Neubert [10] cautioned against indiscriminate use of the rule without knowledge of the effects of perturbations due to asymmetry of the environment. This rule is parallel to the helicity rule [17] developed for skewed dienes. Although the helicity rule has been verified theoretically and experimentally, several recent publications have claimed that a hydroxy-group [18] and/or axial substituents allylic to the diene [18] profoundly affect the c.d. spectrum. This observation prompted us to investigate substituent effects on the rotational strengths of disulphide transitions.

In this work we synthesized model compounds of known absolute configuration and of sufficient simplicity that a maximum number of variables might be fixed. The 2,3-dithiadecalin framework was chosen in order to make use of the wealth of conformational information available for this system. As a perturbing group, we chose the methyl function in various positions and orientations. Furthermore the phenyl function was chosen as a stronger perturbing group than a methyl group.

We also hoped to clarify the influence of a methyl group on the c.d. spectra of the sulphide chromophore in a five-membered ring in order to see whether the sector rule for the episulphide group [19] can be applied to this system.

Synthesis and Absolute Configuration.—The derivatives (1)—(4) were synthesized.

The acid (5) [20] was resolved by use of cinchonidine more readily than was 1-methylcyclohex-4-ene-*cis*-1,2-dicarboxylic acid using quinine.[21] The absolute configuration of compound (−)-(5) was already known to be (1*S*,6*R*),[21] as shown in Scheme 1. Compound (−)-(5) was converted into the bishydroxymethyl derivative (+)-(8b) by reduction of the diester (−)-(7) using $LiAlH_4$.

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[1] G. Bergson, G. Claeson, and L. Schotte, *Acta Chem. Scand.*, 1962, **16**, 1159.

[2] D. B. Boyd, *J. Amer. Chem. Soc.*, 1972, **94**, 8799.

[3] R. W. Woody, *Tetrahedron*, 1973, **29** 1273.

[4] A. F. Beecham J. W. Loder, and G. B. Russell, *Tetrahedron Letters*, 1968, 1785.

[5] A. F. Beecham and A. Mcl. Mathieson, *Tetrahedron Letters*, 1966 3139; J. Friedrichson and A. Mcl. Mathieson *Acta Cryst.*, 1968, **23**, 439.

[6] R. Nagarajan, N. Neuss, and M. M. Marsh, *J. Amer. Chem. Soc.*, 1968, **90**, 6518.

[7] D. B. Cosulich, N. R. Nelson, and J. H. van den Hende, *J. Amer. Chem. Soc.*, 1968, **90**, 6519.

[8] S. Beychok, *Science* 1966, **154**, 1288.

[9] C. Djerassi, A. F. Fredga, and B. Sjoberg, *Acta Chem. Scand.*, 1961, **15**, 417.

[10] M. Carmack and L. A. Neubert, *J. Amer. Chem. Soc.*, 1967, **89**, 7134.

[11] R. M. Dodson and V. C. Nelson, *J. Org. Chem.*, 1968, **33**, 3966.

[12] G. Claeson, *Acta Chem. Scand.*, 1968, **22**, 2429.

[13] R. S. Cahn, C. Ingold, and V. Prelog, *Angew. Chem. Internat. Edn.*, 1966, **5**, 385.

[14] (*a*) J. Linderberg and J. Michl, *J. Amer. Chem. Soc.*, 1970, **92**, 2619; (*b*) J. Webb, R. W. Strickland, and F. S. Richardson, *ibid.*, 1973, **95**, 4775.

[15] G. Bergson, *Arkiv Kemi*, 1958, **12**, 233.

[16] U. Ludescher and R. Schwyzer, *Helv. Chim. Acta*, 1971, **54**, 1637.

[17] A. Moscowitz, E. Charney, U. Weiss, and H. Ziffer, *J. Amer. Chem. Soc.*, 1961, **83**, 4661.

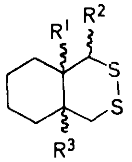
[18] D. M. Jerina, H. Ziffer, and J. W. Daly, *J. Amer. Chem. Soc.*, 1970, **92**, 1056; A. F. Beecham, *Tetrahedron*, 1971, **27**, 5207; W. Hug and G. Wagniere, *ibid.*, 1972, **28**, 1241; A. W. Burgstahler, R. C. Barkhurst, *J. Amer. Chem. Soc.*, 1970, **92**, 7601.

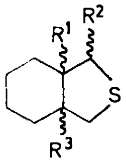
[19] K. Kuriyama, T. Komeno, and K. Takeda, *Tetrahedron*, 1966, **22**, 1039.

[20] I. N. Nazarov and V. F. Kucherov, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1952, 63.

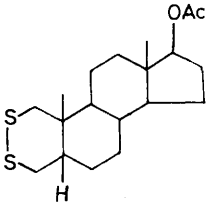
[21] J. Dixon, B. Lythgoe, I. A. Siddiqui, and J. Tideswel, *J. Chem. Soc. (C)*, 1971, 1301.

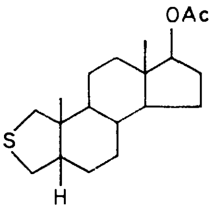
Heating compound (—)-(6) at 180° for 21 h in concentrated HCl gave an equilibrium mixture (*ca.* 1 : 1) of *cis*-dibasic acid and the epimerized *trans*-dibasic acid (+)-(9).[20] The pure *trans*-dibasic acid, obtained by fractional recrystallization, was converted into the (—)-*trans*-bishydroxymethyl compound (—)-(8c) by the use of an excess of $LiAlH_4$ in tetrahydrofuran (Scheme 1).


(1a-g)


(2b-e)

a; R^1 = β-H, R^2 = H; R^3 = α-H
b; R^1 = α-Me, R^2 = H, R^3 = α-H
c; R^1 = α-Me, R^2 = H, R^3 = β-H
d; R^1 = β-H, R^2 = α-Me, R^3 = α-H
e; R^1 = β-H, R^2 = β-Me, R^3 = α-H
f; R^1 = β-H, R^2 = α-Ph, R^3 = α-H
g; R^1 = β-H, R^2 = β-Ph, R^3 = α-H


(3)


(4)

Starting from the optically active (+)-*trans*-cyclohexane-1,2-dicarboxylic acid (+)-(11), whose absolute configuration was known to be (1*S*,2*S*)[22,23] the (+)-acid chloride (+)-(14) was obtained as shown in Scheme 1. The (—)-methyl ketone derivative (—)-(15) was prepared in high yield by treatment with diethyl malonate–Mg followed by hydrolysis and decarboxylation.[24] The reduction of the keto-ester (—)-(15) at 0 to —5° with an excess of $LiAlH_4$ gave two epimeric isomers of the diol (*ca.* 1 : 1) in quantitative yield, which were then separated on an alumina column.

The (+)-benzoyl derivative (+)-(16) was also obtained from (+)-*trans*-cyclohexane-1,2-dicarboxylic acid by the literature procedure;[25] its absolute configuration is known to be (1*S*,2*S*). Reduction of the keto-ester (+)-(16) with $LiAlH_4$ also gave two epimers (*ca.* 3 : 2) of the diol, but the R_F values of the products on t.l.c. were similar. The racemic diols could be isolated in pure form by conversion into the bis-*p*-nitrobenzoyl ester followed by fractional recrystallization and hydrolysis. But with the optically active diols, fractional recrystallization of the ester failed and the epimers were separated by careful p.l.c., the isomer with the smaller R_F value being finally purified by recrystallization.

The reaction of the diols (8b—g) with toluene-*p*-sulphonyl chloride was carried out at low temperature with gradual addition of the sulphonyl chloride in order to minimize cyclization into the corresponding tetrahydrofuran derivatives through the monotosylate.[26] Even so the yields of bistoluene-*p*-sulphonates were not as good as expected, and the main product from the (—)-(1*S*,2*S*,1′*S*)-diol (—)-(8f) was the corresponding tetrahydrofuran derivative (—)-(17f), none of the expected sulphonate being detected.

N.m.r. data for the two epimeric isomers (17g and f) are described in the Experimental section and their *trans*-2-oxahydrindan frameworks are essentially rigid. The proton at C-1 gives a doublet and the coupling constants between the protons C-1 and -8 are 9·0 Hz in one isomer and 7·5 Hz in the other. Therefore it is assumed that the isomer with the larger coupling constant is (—)-(17f) and the one with the smaller constant is (—)-(17 g) from the dihedral angles of the protons. Furthermore, this assignment is supported by the experimental fact that the chemical shift of the pseudo-axial proton at C-1 of compound (—)-(17f) is higher than that of the pseudo-equatorial one of compound (—)-(17g), since it has been reported that the axial proton of a methine group adjacent to oxygen is less shielded than an equatorial one in the same position.[27]

The dithiadecalin derivatives could be obtained from these bistoluene-*p*-sulphonates by treatment with sodium disulphide.[28,29] The yield was extremely low, the main products being the corresponding 2-thiahydrindan derivatives, except from the (1*S*,2*S*,1′*S*)-diol (+)-(8d) and the (1*S*,2*S*,1′*R*)-diol (—)-(8g). As the same displacement has been proved to take place with 100% inversion of configuration in the synthesis of 3,6-dimethyl-1,2-dithians,[29] we chose these reaction sequences in spite of the low yield (Scheme 1).

Assignment of the configuration at C-1 of compounds (1d and e) could be made by analysis of their n.m.r. spectra. It has been reported that the protons of an axial methyl group at C-1 of a dithian are less shielded than those of an equatorial methyl group in the same position owing to deshielding by the magnetically anisotropic S–S bond, the shift difference being *ca.* 0·42 p.p.m.[11,29] The resonance absorption by the

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[22] D. E. Applequist and N. D. Werner, *J. Org. Chem.*, 1963, **28**, 48; A. Werner and H. E. Conrad, *Ber.*, 1899, **32**, 3046; U. Nagai, T. Shishido, R. Chiba, and H. Mitsuhashi, *Tetrahedron*, 1965, **21**, 1701.

[23] P. Laur, H. Häuser, J. E. Gurst, and K. Mislow, *J. Org. Chem.*, 1967, **32**, 498.

[24] H. E. Walker and C. R. Hauser, *J. Amer. Chem. Soc.*, 1946, **68**, 1306.

[25] G. Snatzke and P. C. Ho, *Tetrahedron*, 1971, **27**, 3645.

[26] G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, 1953, 389.

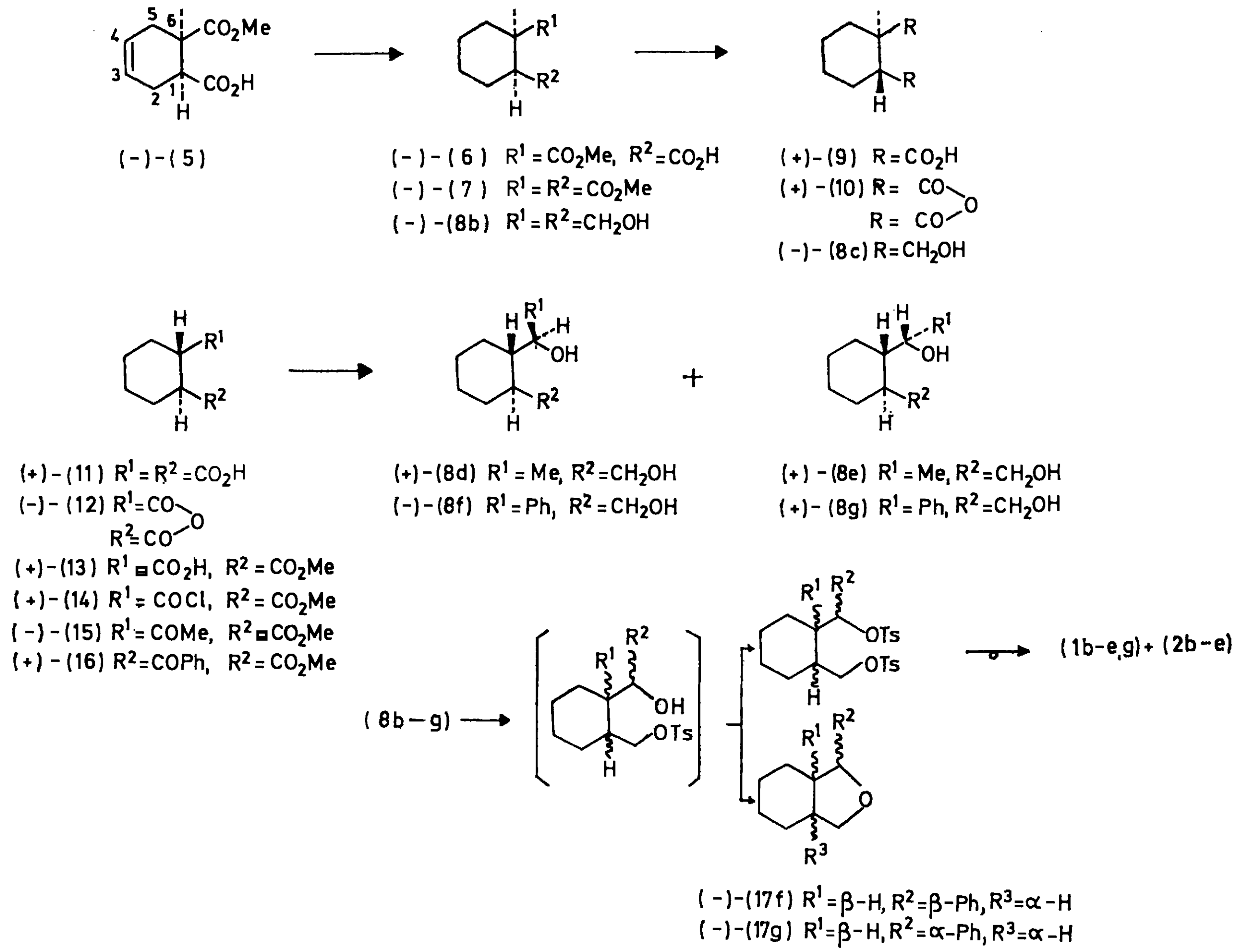
[27] A. B. Foster, T. D. Inch, M. H. Qadir, and J. M. Webber, *Chem. Comm.*, 1968, 1086.

[28] A. Luttringhaus and A. Brechlin, *Chem. Ber.*, 1959, **92**, 2271.

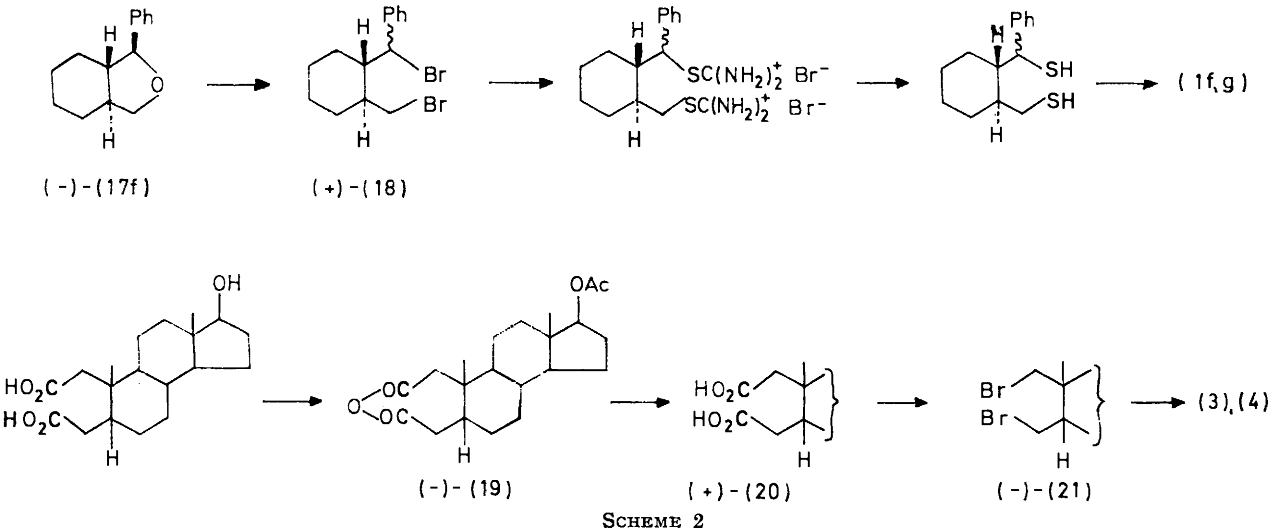
[29] N. Isenberg and H. F. Herbrandson, *Tetrahedron*, 1965, **21**, 1067.

methyl protons of the two epimeric isomers are at τ 8·45 (*J* 7·0 Hz) in one and 8·82 (*J* 7·0 Hz) in the other. As these molecules exist in a single conformation, these results firmly establish that the compound having the lower τ value is the equatorial methyl isomer (—)-(1e) and the one with the higher τ value is the axial methyl isomer (—)-(1d). Configurations of compounds (—)-(2d) and (+)-(2e) were determined on the basis of the same reaction mechanism.

The reaction of the oxide (—)-(17f) with dry hydrogen bromide at 80° gave the *trans*-dibromide (+)-(18), which was then converted into the dithiadecalin deriv-



SCHEME 1



SCHEME 2

active (−)-(1f) through the isothiuronium salt, as shown in Scheme 2. However, an epimeric isomer (+)-(1g) was also isolated, the ratio (1f) : (1g) being 9 : 10.

The protons at C-1 of 1-phenyl-2,3-dithiadecalins show signals at τ 6·20 and 6·40 (2 × d, J 10·0 and 3·2 Hz, respectively). We assigned the compound with the larger coupling constant as the 1-equatorial phenyl isomer and the other as the 1-axial phenyl isomer. The assignment of the 1-equatorial phenyl isomer is in agreement with the configuration assigned from 1-phenyl-2-oxahydrindan by following the reaction sequence.

TABLE 1

U.v. and c.d. spectral data for dithiadecalins

Compound	Solvent	U.v. λ/nm (ε)	C.d. λ/nm ([θ] × 10^{-2})	C.d. λ/nm ($10^{40}R$/c.g.s)
(−)-(1a)	i-Oct [a]	288·5 (393), 238 (202)	290 (−164), (241·5 +151), 207 (−797), 200! (−632)	290 (−19·5) 241·5 (+10·8)
(+)-(1b)	Hex [b]	296 (369), 242s (585), 212s (2420), 191! (4130)	300 (+45·4), 246 (−83·7), 216 (+499)	
(+)-(1c)	i-Oct	294 (278), 245s (212), 210s (1990), 191! (2990)	295 (+143), 246 (−165), 211 (+696), 200 (+665)	295 (+17·6) 246 (−10·4)
(−)-(1d)	Hex	289 (373), 240 (136), 205s (3130), 190! (5920)	291 (−178), 243 (+114), 213 (−646), 197 (−496)	291 (−19·6) 243 (+6·82)
(−)-(1e)	Hex	287 (295), 243 (136), 208s (3100), 199s (3720), 191! (3950)	289 (−141), 243 (+112), 212s (−592), 205 (−703), 195! (0)	289 (−14·4) 243 (+6·82)
(−)-(1f)	c-Hex	288s (393), 274s (717), 268s (1100) 260s (1670), 248 (2310), 218s (8850), 207s (13600), 193 (44800)	287 (−169), 272s (−179), 265s (−220), 255s (−319), 250s (−406), 235s (−716), 219 (−898), 207 (−980), 200! (−803)	
(−)-(1g)	c-Hex	305 (120), 294 (301), 283s(400), 268s (701), 262s (982), 250s (1960), 245s (2300), 224s (10300), 196 (3400)	310s (−38·6), 297 (−57·1), 275 (−45·2), 268 (−39·6), 262(−28·5), 228(−653) 197 (−1640)	
(−)-(3)	MeOH	295 (282), 244s (131), 206·5 (2380), 190! (4180)	298 (−131), 247 (+98·4), 213 (−469), 200 (−396)	298 (−15·2), 247 (+5·90)
(+)-(22) [d]	i-Oct	293 (260), 245 (120), 207 (2300)	295 (+147), 245·5 (−143), 212·5 (+835), 200! (+534)	295 (+16·6), 245·5 (−8·65)

[a] Iso-octane. [b] n-Hexane. [c] Cyclohexane. [d] 17β-Acetoxy-2,3-dithia-5α-androstane.[33]
s = Shoulder. ! Lowest recorded value, not a maximum.

Although it is expected that inversion at C-1′ is involved in the preparation of the dibromide and the isothiuronium salt, the products show that Walden inversion is not complete in one or both of these steps.

The configuration at C-1′ of the diols (8d—g) can be determined from these results by following the reaction sequence. The configurations determined are (1S,2S,1′R) for (+)-(8d), (1S,2S,1′S) for (+)-(8e); (1S,2S,1′S) for (−)-(8f), and (1S,2S,1′R) for (+)-(8g).

Also, (−)-17β-acetoxy-2,3-dithia-5β-androstane (−)-(3) and (−)-17β-acetoxy-2-thia-A-nor-5β-androstane (−)-(4) were prepared from 17β-hydroxy-2,3-seco-5β-androstane-2,3-dioic acid,[30] as shown in Scheme 2.

(−)-*trans*-2,3-Dithiadecalin (−)-(1a) was prepared by a known procedure.[10,28,31]

*U.v. and C.d. Spectra of Methyl-*2,3-*dithiadecalins.*—The u.v. and the c.d. spectra of the 2,3-dithiadecalins investigated are shown in Table 1. The derivatives substituted with a methyl group show three absorption bands in the regions 290—300, 240—250, and 205—215 nm. Several investigators have discussed the nature of these transitions.[2,3,14,15,32] Woody[3] has recently assigned the two long wavelength bands to transitions of the p-type lone-pair electron (n_1 and n_4) to the antibonding σ* state by application of the Bergson model.[15] The 205 nm band may be composed of the transition from the σ-type lone pair MO (n_3) to the σ* state and the weak transition of the σ-type lone pair MO (n_2) to the σ* state. Boyd has indicated by extended Hückel calculations that n_1 is the highest filled orbital, but the next highest orbital is the σ-type lone-pair MO, and the third highest band is the σ–σ* band. However, short wavelength transitions have not been well characterized.

Compounds (1d—g) are conformationally rigid. Compound (−)-(3) is also considered to be rigid, since no substantial change could be observed in the temperature dependent n.m.r. and c.d. spectra.

From the c.d. spectra of these model compounds, we can observe the substituent effects of the methyl group, oriented axial or equatorial either α or β to the sulphur atoms, on the Cotton effects of the dithiadecalin chromophore. The chirality of the atoms C–S–S–C agrees well with that obtained by application of the quadrant rule.[14,16] Therefore, it is considered that the influence of the methyl group on the Cotton effect associated with the dithian chromophore is not large enough to change its sign.

We obtained the substituent effects of β-axial, α-axial, and α-equatorial methyl groups by comparison

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[30] E. Caspi, Y. Shimizu, and S. N. Balasubrahmanyan, *Tetrahedron*, 1964, **20**, 1271.

[31] J. P. Casey and R. B. Martin, *J. Amer. Chem. Soc.*, 1972, **94**, 6141.

[32] H. Yamabe, H. Kato, and T. Yonezawa, *Bull. Chem. Soc. Japan*, 1971, **44**, 604.

of the c.d. curves for compounds *ent* *-(+)-(1c), -(—)-(1d), and -(—)-(1e), and compound (—)-(1a).

These results are summarized in Figure 1 for the two long wavelength transitions. For the longest wavelength c.d. band (at *ca.* 290 nm), an α-equatorial methyl group makes a more powerful contribution than a β-axial methyl group, and an α-axial methyl group makes a negligible contribution. For the next longest wavelength c.d. band (at *ca.* 240 nm) the α-axial and equatorial methyl groups make similar, large contributions, while the contribution of a β-equatorial methyl group is negligible. The difference between the c.d. curves of compounds (+)-(1c) and 17β-acetoxy-2,3-dithia-5α-androstane[33] (+)-(22) may be attributed to the effects of the C and D rings of the steroid framework. These are $+1·0 \times 10^{-40}$ and $-1·8 \times 10^{-40}$ c.g.s. in rotational strength *R*.

TABLE 2

U.v. and c.d. spectral data for 2-thiahydrindans

Compound	Solvent	U.v. λ/nm (ε)	C.d. λ/nm ([θ])	C.d. λ/nm ($10^{40}R$/c.g.s.)
(—)-(2b)	i-Oct [a]	238 (44·2), 215s (836), 203·5 (2180)	255 (+176), 238 (—22), 218 (+8840)	
(+)-(2c)	i-Oct	237s (37·4), 216s (684), 203 (1960)	244 (+3940), 211 (+9270), 199 (—4470)	244 (+2·78), 211 (+4·30)
(—)-(2d)	i-Oct	240 (57·2), 215s (2160), 195·5 (7460)	245 (—6090), 215 (+34100), 208! (0)	245 (—4·29), 215 (+12·7)
(+)-(2e)	i-Oct		246 (—1240), 215 (+1290), 207! (0)	246 (—0·87), 215 (+0·48)
(—)-(4)	n-Hex [b]	240s (63·8), 206 (2300), 190! (2490)	246 (—1660), 230s (—840), 223 (+301), 210 (—12800)	246 (—1·17), 210 (—5·26)
(—)-(23) [c]	i-Oct	243s (43), 214s (1080), 204 (2330)	243 (+4420), 209 (+9300)	243 (+3·03), 209 (+4·39)
(2a) [d]	CH_3CN			243 (—3·86), 217 (+3·48)

[a] Iso-octane. [b] n-Hexane. [c] 17β-Acetoxy-2-thia-A-nor-5α-androstane.[34] [d] 2-Thia-*trans*-hydrindan.[23]
s = Shoulder. ! Lowest recorded value, not a maximum.

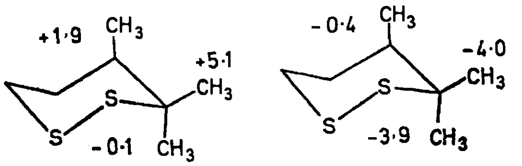

FIGURE 1 Substituent effects of a methyl group in the longer (290—300 nm) (left) and shorter (240—250 nm) (right) wavelength regions. The values given are rotational strengths ($\times 10^{40}$/c.g.s.)

The order of these differences is small compared with the magnitude of the Cotton effects of compound (—)-(1a). Such small differences may be produced by small conformational change of the framework which would be brought about by steric effects such as 1,3-diaxial interactions caused by the substitution of the methyl group. Therefore, we cannot directly attribute the difference only to perturbation by a methyl group, but its magnitude reflects the resultant alkyl substituent effect.

In the shorter wavelength region, compound (—)-(1a) shows only one Cotton effect above 195 nm, and compounds (1c and d) and (3), two Cotton effects of the same sign. The difference in wavelength between the two bands decreases in the order α-axial > β-axial > α-equatorial. The sign is same as that of the longest wavelength transition and the magnitude is very large. We can say that this band is a more reliable indicator of the disulphide configuration.

U.v. and C.d. Spectra of 1-*Phenyl*-2,3-*dithiadecalins*.—The c.d. and u.v. spectra of 1-phenyl-2,3-dithiadecalins (—)-(1f) and (—)-(1g) are summarized in Table 2.

The minus sign of the Cotton effect for the n_1–σ* transition of the 1-phenyl derivatives is in agreement with the screw sense of the (*M*)-helicity of atoms C–S–S–C. The magnitude of the Cotton effect in the 1-axial phenyl compound (—)-(1f) is similar to that in the 1-axial methyl compound (+)-(1d) and unsubstituted compound (—)-(1a); in the 1-equatorial phenyl derivative (—)-(1g), however, the Cotton effect is very small. The sign and magnitude did not change at —190° in methylcyclohexane–isopentane (1 : 5). Therefore, the 1-equatorial phenyl group contributes positively to the Cotton effect of the (*M*)-helicity of the disulphide chromophore, the same tendency as shown by the 1-equatorial methyl group.

The Cotton effect at *ca.* 270 nm shows the typical vibrational fine structure of the ^1L_b transition of alkyl-substituted benzene[34] in the Platt notation.[35] The fine structure became clearer at —190°. The sign for both compounds (—)-(1f and g) is negative but the value for compound (—)-(1f) is much larger than that for compound (—)-(1g).

Although for compound (—)-(1 g) no c.d. band could apparently be detected at room temperature at around 250 nm, where the electronic absorption band was found as a shoulder, the c.d. spectrum at —190° showed a maximum at 248 nm. Compound (—)-(1f) also shows a shoulder at 252 nm at —190°. Precise assignment of the species giving rise to this band is difficult owing to the high intensity of the u.v. absorption, but it may be assigned to the next longest wave-

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* *ent* = Enantiomer.

[33] M. E. Wolff and G. Zanati, *Experientia*, 1970, **26**, 1115.

[34] L. Verbit and H. C. Price, *J. Amer. Chem. Soc.*, 1972, **94**, 5143.

[35] J. R. Platt, *J. Chem. Phys.*, 1949, **17**, 484.

length transition of the disulphide.* Therefore, it must be considered that the Cotton effect of this transition is reversed in sign to the screw sense of the helicity of the dithian by the influence of strong perturbation by the phenyl group. A similar effect was observed with axial and equatorial methyl groups, although the sign remained unchanged.

The negative Cotton effect at 235 nm of compound (—)-(1f) decreased in magnitude at low temperature, with the same character as the Cotton effect at 228 nm of compound (—)-(1g). As the 1-methyl compounds show a third Cotton effect at *ca.* 210 nm, the phenyl group contributes to shift this band to longer wavelength.

The minimum ($[\theta] = 0$) at 218 nm for compound (—)-(1g) was proved to be a positive Cotton effect by cooling, and compound (—)-(1f) showed a negative Cotton effect at 220 nm. The Cotton effect in the 220 nm region is primarily associated with the ^1L_a transition of the aromatic ring.

The negative Cotton effect at 207 nm of compound (—)-(1f) may be mainly attributed to a fourth disulphide transition at *ca.* 205 nm. But the large negative Cotton effect at 197 nm for compound (—)-(1g) may be assigned to a benzenoid $^1B_{a,b}$ transition.[37] However, in the shorter wavelength region, the c.d. spectrum is too complex to analyse since it is influenced by various kinds of interactions between the two chromophores attached to the same carbon atom.[37]

U.v. and C.d. Spectra of Methyl-2-thiahydrindans.—The u.v. and the c.d. spectra of the 2-thiahydrindans investigated are shown in Table 2. Two Cotton effects are observed, at *ca.* 245 and 215 nm for these cyclic sulphides. The rotational strengths observed are of the order of 10^{-40} c.g.s. Recently, Rosenfeld and Moscowitz have assigned the 245 nm band to the electric-dipole-forbidden–magnetic-dipole-allowed lone pair promotion and the 220 nm band to an electric-dipole-allowed transition.[38]

Compounds (2c—e) and (4) are conformationally rigid. The effect of the methyl substituent on the optical activity of the thiahydrindans was determined as for the dithiadecalins. The α-pseudo-axial, α-pseudo-equatorial, and β-axial methyl effects were determined from the differences in rotational strengths amongst compounds (+)-(2d), (+)-(2e), *ent*-(+)-(2c), and (—)-*trans*-2-thiahydrindan.[23] These results are summarized in Figure 2 for the two longest wavelength transitions. The effects of the C and D rings of the steroid framework were obtained from the differences between the c.d. curves of compounds (+)-(2c) and 17β-acetoxy-2-thia-A-nor-5α-androstane (+)-(23).[23] These are —0·25 and —0·09 × 10^{-40} c.g.s. in rotational strength for the longest and the second longest wavelength bands, respectively.

As these values are sufficiently large compared with the rotational strength produced by (—)-*trans*-2-thiahydrindan,[23] it is reasonable to regard them as due to alkyl side-chain effects on the 2-thiahydrindan chromophore.

Kuriyama *et al.* proposed a sector rule for an episulphide ring from consideration of orbital symmetry.[19] We examined this sector rule for the *trans*-2-thiahydrindans. The rule is illustrated in Figure 3a for the longer wavelength band and in Figure 3b for the shorter wavelength band, where + and — indicate the sign of the Cotton effect due to a perturbing group (alkyl group) in the indicated sector above the plane of the five-membered sulphide ring. The rule leads to the correct prediction of the sign of the c.d. curve in the case of α-alkyl substituents but fails with β-axial substituents.

It has been shown [39,40] that a β-axial substituent of a cyclohexanone in the chair conformation produces a Cotton effect of opposite sign to that predicted from the original octant rule. The similarity of the nature [38] of the sulphide n-π^* transition at *ca.* 245 nm to that of the carbonyl n-π^* transition suggests that a similar β-axial methyl effect is also operative in the sulphide sector rule.

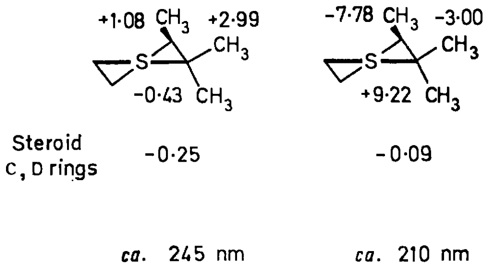

FIGURE 2 Substituent effects of a methyl group in the longer (240—250 nm) (left) and shorter (215—225 nm) (right) wavelength regions. The values given are rotational strengths (× 10^{40}/c.g.s.)

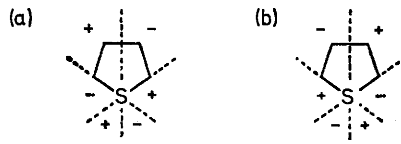

FIGURE 3 Sector rule for five-membered sulphide transitions in the longer (a) and shorter (b) wavelength regions. Signs for the upper sector shown

It is interesting that the alkyl substituent effects in both regions of the c.d. spectra of 2-thiahydrindans are similar in sign and magnitude to those found in the 2,3-dithiadecalins, except for the sign and magnitude of the α-(pseudo)axial methyl effect and the magnitude of the β-axial methyl effect in the shorter wavelength band.

Conformation of 4a-*Methyl*-cis-2,3-*dithiadecalin and* 3a-*Methyl-2-thiahydrindan.*—The existence of conformational isomers of *cis*-2,3-dithiadecalin (+)-(1b) and *cis*-2-thiahydrindan (—)-(2b) is indicated by the

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* This band may be attributed to the coupling transition which occurs between the disulphide group and the benzene ring.[36]

[36] J. C. Craig and W. E. Pereira, *Tetrahedron*, 1970, **26**, 3457.

[37] S. Hagishita and K. Kuriyama, *Tetrahedron*, 1972, **28**, 1435.

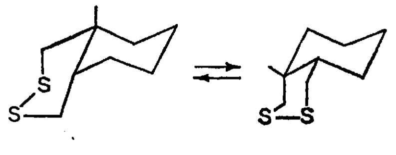
[38] J. S. Rosenfeld and A. Moscowitz, *J. Amer. Chem. Soc.*, 1972, **94**, 4797.

[39] Y. Pao and D. P. Santry, *J. Amer. Chem. Soc.*, 1966, **88**, 4157.

[40] G. Snatzke and G. Eckhardt, *Tetrahedron*, 1968, **24**, 4543.

temperature dependence of the n.m.r. and c.d. spectra of these compounds.

Compound (+)-(1b) would be expected to have a lower barrier to ring inversion between the steroidal (−)-(1b-**s**) and the non-steroidal forms (+)-(1b-**n**) (Figure 4).



(−)-(1b-s) (+)-(1b-n)

FIGURE 4 Conformational isomers of (−)-(1b)

The signals due to the methyl protons of compound (+)-(1b) coalesce at +4°. One peak is observed at room temperature and the maximum separation ($\Delta\nu_{\infty}$) of the two peaks is 8·5 Hz at −45°. From this, we calculate the activation energy ($\Delta G^{\ddagger}$) to be 14·8 kcal mol^{-1}. This is similar to the value obtained for *cis*-2,3-dithiadecalin [41] ($\Delta G^{\ddagger}$ 15·5 kcal mol^{-1}).

Also, the ratio of the areas of the angular methyl signals of the two conformational isomers is 85·5 : 14·5, from which the free energy difference ($-\Delta G^{0}$) between the two forms is estimated to be 880 cal mol^{-1}. The free energy difference is considered to be attributable to the difference between 1,3-diaxial methyl–hydrogen and methyl–sulphur lone pair interactions [42] and is calculated as 0·33 kcal mol^{-1}.

The temperature dependent c.d. spectra are shown in Table 3. The longest and the second longest wavelength bands decrease in magnitude with increase in temperature and have opposite signs to those for compound (+)-(3). Therefore, the non-steroidal form is more stable than the steroidal one, and gives rise to the biggest signal for the protons of the methyl group. The proton signal of the methyl group of the non-steroidal form is downfield compared with the signal of the steroidal methyl group. It is interesting that the protons of the methyl group substituted axially at C-4a of the 2,3-dithiadecalin are more highly shielded than those of the equatorial methyl group. This is contrary to the fact that the chemical shifts of axial protons, and of axial ester methyl protons in the β-position [12] in other dithian derivatives, are found at a lower field than those of the corresponding equatorial protons.

The C and D rings of the steroid framework are situated too far from the dithian chromophore to influence the c.d. spectrum. It can be assumed that the steroidal form shows a similar c.d. curve to that of compound (−)-(3). From this assumption, we can draw the c.d. curve of the non-steroidal form using the c.d. spectrum at −68° of compound (+)-(1b). The estimated values are $[\theta]_{298}$ +12,200, R +11·8 × 10^{-40} c.g.s. and $[\theta]_{245}$ −18,000, R −10·1 × 10^{-40} c.g.s. At least the sign and the order can be considered reliable.

The signals of the methylene protons α to the sulphur atom in compound (+)-(2b) become broad at −45°, but the spectrum could not be measured at temperatures lower than this. This indicates that there exist at least two distinct species.

The c.d. spectrum of this compound shows two Cotton effects at +25° in methylcyclohexane–isopentane (1 : 5) (Table 3). On lowering the temperature the negative Cotton effect disappeared and the longer

TABLE 3

Temperature dependent c.d. spectra in methylcyclohexane–isopentane (1 : 5) solution

Compound	(+)-(1b)			(−)-(1g)		(−)-(1f)		(−)-(2b)		
Temp. (°C)	λ/nm	[θ]	$10^{40}R$/c.g.s.	λ/nm	[θ]	λ/nm	[θ]	λ/nm	[θ]	$10^{40}R$/c.g.s.
+25	301	+5250	+6·02	294	−5900	290	−14600	255	+169	+0·82
	247·5	−9740	−6·17	274	−4800	267s	−18100	239	−74	−0·15
				268	−3700	250s	−32700			
				262	−2500	233	−63900			
				227	−66700	219	−78900			
				205!	−41300	215!	−74000			
−20	300	+6650	+7·66					250	+365	+2·13
	246·5	−11600	−6·98							
−68	299·5	+8250	+9·00	294	−6600	291	−16700	247	+656	+4·33
	245·5	−14000	−8·07	274	−6000	265s	−25000			
				268	−5100	250s	−38000			
				262	−3700	233	−65300			
				245s	−6900	219	−73500			
				227	−54200	215!	−71000			
				215	+36600					
				208!	0					
−190	299·5	+7680	+7·92	295	−6700	292	−15700	242·5	+1760	+12·2
	244	−13000	−7·24	274	−6700	272s	−17900			
				267	−5700	252	−33600			
				259	−4400	235	−44600			
				248	−7700	220·5	−65800			
				239	−4100	215!	−52500			
				226	−59400					
				212	+17500					
				207	0					

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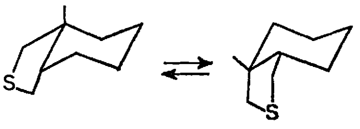
[41] A. Lüttringhaus, S. Kabuss, W. Maier, and H. Friebolin, *Z. Naturforsch.*, 1961, **16b**, 761.

[42] E. L. Eliel and R. O. Hutchins, *J. Amer. Chem. Soc.*, 1969, **91**, 2703.

wavelength transition underwent a blue shift and its magnitude increased. This is consistent with an equilibrium between two conformers (Figure 5), and shows that conformer (2b-**b**) is more stable than (2b-**a**). The free energy difference ($-\Delta G^\circ$) and the rotational strengths for the two conformers were calculated by analysis of the temperature dependent c.d. spectra as 0·6 kcal mol^{-1} and $+1{\cdot}34 \times 10^{-40}$ c.g.s. for (+)-(2b-**a**) and $-3{\cdot}52 \times 10^{-40}$ c.g.s. for (−)-(2b-**b**), respectively.[43]



(2b-b) **(2b-a)**

FIGURE 5 Conformational isomers of (—)-(2b)

EXPERIMENTAL

I.r. spectra were taken using a JASCO model DS 402G double-monochromatic spectrophotometer. Optical rotations were measured on a Perkin-Elmer polarimeter model 141 using a 1 dm cell. C.d. spectra were taken with a JASCO model ORD/UV-6. N.m.r. spectra were measured with a Varian A-60 spectrometer using tetramethylsilane as internal standard. U.v. spectra were measured with a Hitachi model EPS-3T spectrometer. Mass spectra were measured on a Hitachi RUM-6 single-focusing mass spectrometer.

Resolution of c-6-*Methoxycarbonyl*-t-6-*methylcyclohex*-3-*ene*-r-*carboxylic Acid* (5).[20]—A mixture of a solution of the half-ester [20] (5) (118 g) in acetone (700 ml) and cinchonidine (179 g) was heated under reflux for 10 min and left at room temperature overnight. The solid was collected by filtration, washed with acetone, and dried. The salt (91·5 g) was recrystallized from acetone three times, $[\alpha]_D^{20}$ −90·4 ± 1·1° (EtOH; *c* 1·246).

The cinchonidine salt was suspended in ether (300 ml) and then shaken with 2N-HCl (300 ml) for 30 min. The organic phase was separated and the aqueous phase was extracted with ether. The combined ether solutions were washed with water and dried (Na_2SO_4). After evaporation of the solvent, the crystalline residue was recrystallized from benzene–light petroleum (b.p. 50—65°) to give cubes of *acid* (−)-(5) (21·5 g), m.p. 98—99°, $[\alpha]_D^{24}$ −10·4 ± 0·4° (acetone; *c* 1·270) (Found: C, 60·95 H, 7·15. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%).

(−)-(1S,2R)-c-2-*Methoxycarbonyl*-t-2-*methylcyclohexane*-r-*carboxylic Acid* (−)-(6).—A mixture of a solution of the (−)-olefin (−)-(5) (20·7 g) in MeOH (100 ml) and 5% Pd–C (500 mg) was shaken under H_2; 2·34 l of hydrogen was absorbed. After removal of the catalyst by filtration and the solvent by distillation, the residue was crystallized from light petroleum to give *prisms* 19·6 g, 93·7%), $[\alpha]_D^{24}$ −10·2 ± 0·5° (MeOH; *c* 1·230), m.p. 68—71°, $\nu_{max.}$ (Nujol) 1700 and 1728 cm^{-1} (Found: C, 60·75; H, 8·15. $C_{10}H_{16}O_4$ requires C, 60·0; H, 8·05%).

(−)-*Dimethyl* (1R,2S)-1-*Methylcyclohexane*-cis-1,2-*dicarboxylate* (−)-(7).—The half-ester (−)-(6) (5·29 g) was added in small portions to an excess of diazomethane in ether. After 1 h the excess of diazomethane and ether were distilled off under reduced pressure The residue (4·8 g) was distilled at 93° and 1·8 mmHg, n_D^{22} 1·4597, $[\alpha]_D^{22}$ −8·5 ± 0·9° (MeOH; *c* 0·588), $\nu_{max.}$ (film) 1735 cm^{-1}, τ (CCl_4) 8·76 (s) and 4·37 (s) (Found: C, 62·2; H, 8·55. $C_{11}H_{18}O_4$ requires C, 61·65; H, 8·45%).

(+)-(1R,2S)-1-*Methyl*-cis-1,2-*bishydroxymethylcyclohexane* (+)-(8b).—A solution of the diester (−)-(7) (12·4 g) in dry tetrahydrofuran (40 ml) was added to a suspension of an excess of $LiAlH_4$ in tetrahydrofuran at 0—5° with stirring under nitrogen. The mixture was then heated under reflux for 3 h. The excess of $LiAlH_4$ was decomposed, the organic phase was separated, and the aqueous phase was extracted with ether. The combined organic solutions were washed with water and dried (Na_2SO_4). After evaporation of the solvent, the *residue* (9·7 g) was distilled at 130—132° and 2·5 mmHg, $[\alpha]_D^{24}$ +23·4 ± 0·4° (MeOH; *c* 1·347), $\nu_{max.}$ (film) 3300, 1448, and 1037 cm^{-1} (Found: C, 67·8; H, 11·45. $C_9H_{18}O_2$ requires C, 68·3; H, 11·45%).

(−)-(1R,2R)-1-*Methylcyclohexane*-trans-1,2-*dicarboxylic Acid* (−)-(9).—A mixture of the *cis*-half-ester (−)-(6) (3·43 g) and concentrated HCl (30 ml) was heated in a sealed glass tube at 180° for 21 h. The crystals which formed were collected by filtration, washed with water, and dried (3·0 g). Recrystallization from acetone–water (1 : 7) gave the *trans*-isomer. Acetone was distilled from the mother liquor and the residue was recrystallized three times from acetone–water to give further trans-*isomer* (1·32 g) as needles, m.p. 224°, $[\alpha]_D^{24}$ −7·2 ± 0·6° (MeOH; *c* 0·862), $\nu_{max.}$ (Nujol) 1703 cm^{-1} (Found: C, 58·25; H, 7·5. $C_9H_{14}O_4$ requires C, 58·25; H, 7·6%).

(+)-(1R,2R)-1-*Methylcyclohexane*-trans-1,2-*dicarboxylic Anhydride* (+)-(10).—A mixture of acetyl chloride (15 ml) and the dicarboxylic acid (−)-(9) (1·91 g) was heated under reflux for 1 h. After removal of the acetyl chloride by distillation, the residue was distilled at 97—98° and 0·2 mmHg. The *distillate* (1·3 g) solidified immediately; $[\alpha]_D^{23}$ +69·0 ± 3·3° ($CHCl_3$; *c* 0·335), $\nu_{max.}$ (Nujol) 1860, 1800, and 1705 cm^{-1} (Found: C, 64·05; H, 7·3. $C_9H_{12}O_3$ requires C, 64·25; H, 7·2%).

(−)-(1R,2R)-1-*Methyl*-trans-1,2-*bishydroxymethylcyclohexane* (−)-(8c).—A solution of the anhydride (+)-(10) (0·873 g) in dry tetrahydrofuran (10 ml) was added dropwise to a suspension of an excess of $LiAlH_4$ in dry tetrahydrofuran (25 ml) at 0—5° with stirring under nitrogen. The mixture was then heated under reflux for 1 day. Excess of $LiAlH_4$ was decomposed, the organic phase was separated, and the aqueous phase was extracted with ether. The combined organic solutions were washed with water and dried (Na_2SO_4). After evaporation of the solvent, the residue was distilled at 105° and 0·1 mmHg. The *distillate* (716 mg) solidified immediately, $[\alpha]_D^{23}$ −1·2 ± 0·5°, $[\alpha]_{365}^{23}$ −8·3 ± 0·6° (MeOH; *c* 0·829), $\nu_{max.}$ (Nujol) 3260, 1050, and 1015 cm^{-1} (Found: C, 67·5; H, 11·3. $C_9H_{18}O_2$ requires C, 68·3; H, 11·45%).

(+)-(1S,2S)-trans-2-*Methoxycarbonylcyclohexanecarbonyl Chloride* (+)-(14).—(−)-(1*S*,2*S*)-Cyclohexane-*trans*-1,2-dicarboxylic anhydride, prepared from the (+)-dicarboxylic acid {8·63 g; $[\alpha]_D^{24}$ +19·4° (acetone)} [21,22,24] was added to a solution of absolute MeOH (25 ml) in dry pyridine (60 ml). The mixture was stoppered, left at room temperature overnight, and then poured onto ice-cold dilute HCl. The organic product was extracted with ether and the extract was washed with water and dried (Na_2SO_4). The solvent was removed by distillation, but the

[43] K. M. Wellman and C. Djerassi, *J. Amer. Chem. Soc.*, 1965, **87**, 60.

product could not be crystallized. The i.r. spectrum showed the product to be the half-ester and therefore we used the crude sample for the next step [racemic, m.p. 94—96° (from benzene–n-hexane)] (Found: C, 58·3; H, 7·65. Calc. for $C_9H_{14}O_4$: C, 58·0; H, 7·6%).

Oxalyl chloride (16·5 g) was added to the product. After evolution of gas ceased, the mixture was left at room temperature for a further 2 h. The excess of oxalyl chloride was removed by distillation under reduced pressure and the *residue* (9·3 g) was distilled at 92—93° and 2 mmHg, $[\alpha]_D^{23}$ +1·1 ± 0·3°, $[\alpha]_{365}^{23}$ −48·8 ± 0·4° (dioxan; *c* 1·164), $\nu_{max.}$ ($CHCl_3$) 1790 and 1735 cm^{-1} (Found: C, 53·7; H, 6·5; Cl, 16·4. $C_9H_{13}ClO_3$ requires C, 52·8; H, 6·4; Cl, 17·3%).

(−)-*Methyl* (1S,2S)-2-*Acetylcyclohexanecarboxylate* (−)-(15).—A mixture of absolute EtOH (2 ml) and CCl_4 (0·3 ml) was added to Mg (1·24 g). The reaction, which started almost immediately, was allowed to proceed for a few min then ether (20 ml) was added cautiously. To the resulting mixture, a solution of diethyl malonate (8·2 g) and EtOH (2·8 ml) in ether (20 ml) was added at such a rate that rapid refluxing was maintained. The mixture was heated under reflux until the Mg had dissolved. A solution of the acid chloride (+)-(14) (9·3 g) in ether (20 ml) was added with vigorous stirring, and the mixture was heated under reflux for 1·5 h, cooled, and acidified with HCl. The organic phase was separated and the aqueous phase was extracted with ether. The combined ether phases were washed with water and the solvent was stripped off.

To the crude diethyl malonate was added a solution of glacial AcOH (14 ml), water (9 ml), and concentrated H_2SO_4 (1·4 ml), and the mixture was heated under reflux for 4 h. The mixture was then cooled and water (50 ml) was added. The organic product was extracted with ether, The extract was washed with water, dried (Na_2SO_4), and distilled under reduced pressure. The oily residue was heated under reflux with concentrated H_2SO_4 (3 ml) and absolute MeOH (100 ml) for 7·5 h. Half the solvent was distilled off and water (50 ml) was added. The mixture was warmed at 70° for 1 h. The product was extracted with ether and the extract was washed with water, dried (Na_2SO_4), and distilled. The *residue* (7·4 g) was distilled at 114° and 11 mmHg, $[\alpha]_D^{23}$ −15·8 ± 0·2° (neat), $\nu_{max.}$ (CCl_4) 1730 and 1716 cm^{-1}, $\lambda_{max.}$ (MeOH) 275 (ε 43·4) and 214 nm (366), c.d. (iso-octane) $[\theta]_{309}^{sh}$ +1020, $[\alpha]_{299}^{sh}$ +2590, $[\theta]_{290}$ +3480, $[\alpha]_{284}$ +3420, and $[\theta]_{214}$ +3140 (Found: C, 65·7; H, 8·9. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·75%).

(+)-(1S,2S,1′S)-trans-1-(α-*Hydroxyethyl*)-2-*hydroxymethylcyclohexane* (+)-(8e) *and the* (+)-(1S,2S,1′R)-*Isomer* (+)-(8d).—A solution of the keto-ester (−)-(15) (7·1 g) in dry ether (20 ml) was added to a suspension of $LiAlH_4$, (3·0 g) in dry ether (130 ml) at −5 to 0° with stirring under nitrogen. The mixture was stirred at 0° for 2 h and then at room temperature for 1 h. Excess of $LiAlH_4$ was decomposed, the organic phase was separated, and the aqueous phase was extracted with ether. The combined ether solutions were washed with water and dried (Na_2SO_4). The solvent was removed by distillation under reduced pressure and the residue (6·3 g) was chromatographed on alumina (200 g; Woelm grade 2). Elution with benzene–chloroform (4 : 1) gave the (1*S*,2*S*,1′*S*)-diol (+)-(8e) (2·71 g) and with benzene–chloroform (1 : 1) the (1*S*,2*S*,1′*R*)-diol (+)-(8d) (1·70 g). The (1*S*,2*S*,1′*S*)-*diol* was distilled at 125° and 2 mmHg, $[\alpha]_D^{24}$ +14·7 ± 0·3° (MeOH; *c* 1·545), $\nu_{max.}$ (CCl_4) 3629, 3542, and 3484 cm^{-1} (Found: C, 68·15; H, 11·5. $C_9H_{18}O_2$ requires C, 68·3; H, 11·45%).

Methyl (+)-(1S,2S)-trans-2-*Benzoylcyclohexanecarboxylate* (+)-(16).[25]—Powdered anhydrous $AlCl_3$ (12·0 g) was added in one portion to a solution of (−)-(1*S*,2*S*)-cyclohexane-*trans*-1,2-dicarboxylic anhydride (6·22 g) in thiophen-free benzene (70 ml) at room temperature. The mixture was stirred for 1 h, then heated under reflux for 2 h. While cooling the mixture on an ice-bath, ice–water was cautiously added, followed by 6N-HCl (100 ml). The organic phase was separated, washed with dilute HCl and water, and dried ($MgSO_4$). The solvent was removed by distillation under reduced pressure. A solution of concentrated H_2SO_4 (5 ml) in absolute MeOH (100 ml) was added to the residue and the solution was heated under reflux for 10 h. The solution was concentrated by distillation under reduced pressure, then water and acetone were added until the mixture became clear. The solution was warmed at 70° for 1 h, then concentrated by distillation under reduced pressure. The organic product was extracted with ether. The extract was washed with water, dried (Na_2SO_4), and evaporated under reduced pressure and the residue was crystallized from light petroleum (b.p. 50—60°) to give *prisms* (5·89 g), m.p. 55—57° (racemic viscous oil, b.p. 160—163° at 3 mmHg), $[\alpha]_D^{24}$ +11·1 ± 0·3° (iso-octane; *c* 1·851), $\nu_{max.}$ (CCl_4) 1688 and 1736 cm^{-1}, $\lambda_{max.}$ (iso-octane; *c* 0·146) 323 (ε 72·5), 288 (607), 279 (844), 248 (838), 240 (12,900), 199 (28,800), and 198 nm (29,100), c.d. (iso-octane; *c* 0·146), $[\theta]_{370}$ +125, $[\theta]_{363}$ −69·3, $[\theta]_{352}$ +729, $[\theta]_{337}$ +1750, $[\theta]_{325}$ +2030, $[\theta]_{313}$ +1540, $[\theta]_{277}$ +2510, $[\theta]_{236}$ −25,700, and $[\theta]_{200!}$ 0 (Found: C, 73·0; H, 7·3. $C_{15}H_{18}O_3$ requires C, 73·15; H, 7·35%).

(+)-(1S,2S,1′R)-trans-1-(α-*Hydroxybenzyl*)-2-*hydroxymethylcyclohexane* (+)-(8g) *and the* (−)-(1S,2S,1′S)-*Isomer* (−)-(8f).—A solution of the keto-ester (+)-(16) (5·78 g) in dry ether (20 ml) was added to a suspension of $LiAlH_4$ (2·7 g) in dry ether (100 ml) at 0 to −8° with stirring under nitrogen. The mixture was stirred at 0° for 2 h, then at room temperature for 1 h. The excess of $LiAlH_4$ was decomposed, the organic phase was separated, and the aqueous phase was extracted with ether. The combined ether solutions were washed with water and dried (Na_2SO_4). The residue (5·5 g) was chromatographed on a thick silica gel plate [Merck GF_{254}; 100 cm × 20 cm; benzene–ethyl acetate (5 : 1)]. Solvent development was repeated 6 times. The *fraction* (1·1 g) having the larger R_F value [(+)-(8g)] was distilled at 162—164° and 0·7 mmHg, $[\alpha]_D^{24}$ +35·6 ± 1·5° (MeOH; *c* 1·243), $\nu_{max.}$ ($CHCl_3$) 3620, 3485, 1605, 1494, 1448, and 1055 cm^{-1}, $\lambda_{max.}$ (MeOH), 268·5 (ε 129), 265 (164), 261·5 (184), 259 (216), 253·5 (189), 249 (153), 243 (119), 219sh (3960), 214sh (6500), 209 (8140), and 206 nm (8200), c.d. (MeOH; *c* 0·1020) $[\theta]_{268\cdot5}$ −1670, $[\theta]_{262}$ −1740, $[\theta]_{256}$ −1080, $[\theta]_{250}$ −510, $[\theta]_{215}$ +9400, and $[\theta]_{200!}$ +2100 (Found: C, 76·15; H, 9·05. $C_{14}H_{20}O_2$ requires C, 76·3; H, 9·15%).

The fraction having the smaller R_F value [(−)-(8f)] was still composed of two isomers, and pure *material* (775 mg) was obtained by two crystallizations from benzene, m.p. 103—105° (racemic m.p. 106—107°), $[\alpha]_D^{24}$ −10·5 ± 0·9° (MeOH; *c* 0·592), $\nu_{max.}$ ($CHCl_3$) 3610, 3420, 1495, 1453, 1407, and 1043 cm^{-1}, $\lambda_{max.}$ (MeOH), 264 (ε 143), 258 (188), 253 (149), 249 (111), 242sh (72), 237 (43), 218sh (4020), 214sh (5880), 209 (8050), and 206 nm (8050), c.d. (MeOH; *c* 0·592), $[\theta]_{268}$ +677, $[\theta]_{262}$ +706, $[\theta]_{255}$ +455, $[\theta]_{250}$ +241, and $[\theta]_{244}^{sh}$ +119 (Found: C, 76·15; H, 9·2%).

With the (±)-compound, the isomer of larger R_F could be separated by fractional recrystallization of its bis-*p*-nitrobenzoate from acetone, m.p. 192—193°, followed by hydrolysis, while the other epimer was purified by crystallization of the diol recovered from the mother liquor. With the optically active compound this technique was unsuccessful.

Preparation of Dithiadecalins and Thiahydrindans (1) *and* (2).—Compounds (+)-(8b), (−)-(8c), (+)-(8e), (+)-(8d), (+)-(8g), and (+)-(8f) were each obtained in the same manner. As an example, we describe the procedure for (+)-(1*S*,2*S*,1′*R*)-1-(α-hydroxyethyl)-2-hydroxymethylcyclohexane (+)-(8d).

Recrystallized toluene-*p*-sulphonyl chloride (2·36 g) was added to a solution of the diol (+)-(8d) (797 mg) in dry pyridine (5 ml) at −5 to −10° over 30 min. The mixture was left at 0° for 2 h, then ice–water was added. After stirring for 1 h, crystals were collected, washed with water, dried *in vacuo*, and recrystallized; yield 1·77 g (75%), m.p. 92—93 °(from MeOH).

The ditosylate was added to a solution of sulphur (323 mg) and anhydrous Na_2S (738 mg) in dry dimethylformamide (15 ml). The brown-purple mixture was warmed at 75° (bath temperature) with stirring for 20 h, then poured onto ice–water (50 ml). The organic product was extracted with ether; the extract was washed with water, dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (20 g; Merck grade 1) in n-pentane. The first fraction (60 ml) gave sulphur; the second (60 ml) (−)-(1*S*,4a,*S*,8a*S*)-1-methyl-2,3-dithia-*trans*-decalin (−)-(1d) (123 mg), and the third (300 ml) (−)-(1*S*,3a*S*,7a*S*)-1-methyl-2-thia-*trans*-hydrindan (−)-(2d) (455 mg). The *dithiadecalin* (−)-(1d) was purified by short path distillation at 80° (bath temperature) and 0·4 mmHg, $[\alpha]_D^{24}$ −403·7 ± 2·8° (iso-octane; *c* 0·2948), τ (CCl_4) 8·82 (d, *J* 7·0 Hz) (Found: C, 57·55; H, 8·4; S, 33·8. $C_9H_{16}S_2$ requires C, 57·4; H, 8·55; S, 34·05%).

The *thiahydrindan* (−)-(2d) was distilled at 98° and 11 mmHg, $[\alpha]_D^{24}$ −166·1 ± 1·4° (iso-octane; *c* 0·4262), τ (CCl_4) 8·88 (d, *J* 6·5 Hz) (Found: C, 68·9; H, 10·3; S, 20·25. $C_9H_{16}S$ requires C, 69·15; H, 10·3; S, 20·5%).

(+)-(4aS,8aS)-4a-*Methyl*-2,3-*dithia*-cis-*decalin* (+)-(1b).—The *dithiadecalin* (2%) was purified by short path distillation at 120° (bath temperature) and 1·5 mmHg, $[\alpha]_D^{24}$ +36·1 ± 3·6° (n-hexane; *c* 0·122), $\nu_{max.}$ (CCl_4) 1449 and 923 cm^{-1}, τ (CCl_4) 7·05 (dd, *J* 13·5 and 11·0 Hz), 7·07 (dd, *J* 13·0 and 1·0 Hz), 7·73 (d, *J* 13·0 Hz), 7·92 (dd, *J* 13·5 and 2·0 Hz), 8·2—8·8 (m), and 8·85 (s) (Found: C, 57·25; H, 8·45; S, 34·05. $C_9H_{16}S_2$ requires C, 57·4; H, 8·55; S, 34·05%).

(−)-(3aR,7aS)-3a-*Methyl*-2-*thia*-cis-*hydrindan* (−)-(2b).—The *thiahydrindan* (27%) was distilled at 108—110° and 23 mmHg, $[\alpha]_D^{24}$ −19·6 ± 2·2° (iso-octane; *c* 0·276), $\nu_{max.}$ (CCl_4) 1465 and 1450 cm^{-1}, τ (CCl_4) 6·8—7·7 (m), 8·2—8·7 (m), and 8·92 (s) (Found: C, 69·1; H, 10·35; S, 20·25. $C_9H_{16}S$ requires C, 69·15; H, 10·3; S, 20·5%).

(+)-(4aR,8aR)-4a-*Methyl*-2,3-*dithia*-trans-*decalin* (+)-(1c).—The *dithiadecalin* (2%) was purified by short path distillation at 110° and 0·1 mmHg, $[\alpha]_D^{24}$ +163 ± 21°, $[\alpha]_{365}^{24}$ +1337 ± 20° (iso-octane; *c* 0·0264), $\nu_{max.}$ (CCl_4) 1448 and 1443 cm^{-1}, τ (CCl_4) 7·05 (dd, *J* 10·5 and 13·0 Hz), 7·07 (dd, *J* 1·5 and 13·0 Hz), 7·73 (dd, *J* 1·0 and 13·0 Hz), 7·92 (dd, *J* 1·0 and 13·0 Hz), and 8·85 (d, *J* 1·0 Hz) (Found: C, 57·1; H, 8·5; S, 34·05. $C_9H_{16}S_2$ requires C, 57·4; H, 8·55; S, 34·05%).

(+)-(3aR,7aR)-3a-*Methyl*-2-*thia*-trans-*hydrindan* (+)-(2c).—The *thiahydrindan* (43%) was distilled at 115—117° and 30 mmHg, $\nu_{max.}$ (CCl_4) 1448 cm^{-1}, τ (CCl_4) 7·0—7·8 (m), 8·0—9·0 (m), and 9·12 (s) (Found: C, 69·1; H, 10·2; S, 20·45. $C_9H_{16}S$ requires C, 69·15; H, 10·3; S, 20·5%).

(−)-(1R,4aS,8aS)-1-*Methyl*-2,3-*dithia*-trans-*decalin* (−)-(1e).—The *dithiadecalin* (52%) was purified by short path distillation at 80° (bath temperature) and 0·4 mmHg, $[\alpha]_D^{24}$ −186·0 ± 3·0° (n-heptane; *c* 0·157), τ (CCl_4) 8·45 (d, *J* 7·0 Hz) (Found: C, 57·75; H, 8·6; S, 33·2. $C_9H_{16}S_2$ requires C, 57·4; H, 8·55; S, 34·05%).

(+)-(1R,3aS,7aS)-1-*Methyl*-2-*thia*-trans-*hydrindan* (+)-(2e).—The *thiahydrindan* (1%) was purified by short path distillation at 90° (bath temperature) and 14 mmHg, $[\alpha]_D^{24}$ +85·7° (cyclohexane; *c* 0·5081), τ (CCl_4) 7·13 (dd, *J* 6·5 and 12·0 Hz), 7·30 (d, *J* 6·5 Hz), 7·55 (dd, *J* 9·5 and 9·5 Hz), and 8·73 (d, *J* 6·5 Hz) (Found: C, 69·05; H, 10·25; S, 20·6. $C_9H_{16}S$ requires C, 69·15; H, 10·3; S, 20·5%).

(−)-(1S,4aS,8aS)-1-*Phenyl*-2,3-*dithia*-trans-*decalin* (−)-(1g).—Tosylation of the diol (+)-(8g) was difficult, so the reaction mixture was stirred for a further 2 h at room temperature. (−)-(1*R*,3a*S*,7a*S*)-1-Phenyl-2-oxahydrindan (−)-(17g) was obtained in 50% yield. It was purified by distillation at 163° and 19 mmHg, $[\alpha]_D^{24}$ −79·4 ± 0·9° (cyclohexane; *c* 0·899), τ (CCl_4) 2·7, 3·1 (m), 5·01 (d, *J* 7·5 Hz), 5·84 (dd, *J* 6·0 and 7·5 Hz), and 6·61 (dd, *J* 7·5 and 9·0 Hz), $\nu_{max.}$ (CCl_4) 1493, 1448, 1018, and 698 cm^{-1}, $\lambda_{max.}$ (cyclohexane) 268sh (ε 124), 265 (165), 259 (214), 254 (181), 248 (149), 242 (169), 235sh (206), 215·5 (6800), 211 (7930), 207 (7860), and 193! nm (12,000), c.d. (cyclohexane; *c* 1·043) $[\theta]_{269}$ −1060, $[\theta]_{262}$ −1130, $[\theta]_{255\cdot5}$ −749, $[\theta]_{250}$ −360, $[\theta]_{243}^{sh}$ −149, $[\theta]_{220}$ +347, $[\theta]_{215}$ +2480, $[\theta]_{210}^{sh}$ −3530, and $[\theta]_{200!}$ −9930.

The *dithiadecalin* (−)-(1g) was recrystallized from light petroleum (b.p. 50—80°) to give needles (7·0%) m.p. 154—155° (racemic m.p. 136°), $[\alpha]_D^{24}$ −266 ± 11° (cyclohexane; *c* 0·029), *m*/*e* 250 (M^+), τ ($CDCl_3$) 2·74 (s), 6·20 (d, *J* 10·0 Hz), 7·15 (dd, *J* 9·5 and 13·0 Hz), 7·42 (dd, *J* 3·0 and 12·0 Hz), and 8·0—9·2 (m) (Found: C, 66·95; H, 7·35; S, 25·5. $C_{14}H_{18}S_2$ requires C, 67·15; H, 7·25; S, 25·6%).

(−)-17β-*Acetoxy*-2,3-*seco*-5β-*androstane*-2,3-*dioic Anhydride* (−)-(19).—A mixture of 17β-hydroxy-2,3-seco-5β-androstane-2,3-dioic acid [30] (209 mg), dry pyridine (5 ml), and Ac_2O (0·5 ml) was left at room temperature overnight. The solution was poured into ice-water (30 ml) and the *crystals* (175 mg) were collected by filtration, washed with water, dried *in vacuo*, and recrystallized from acetone–n-hexane, m.p. 231—235°, $[\alpha]_D^{25}$ −8·0 ± 2·6°, $[\alpha]_{365}^{25}$ −19·1 ± 3·2° ($CHCl_3$; *c* 0·188), $\nu_{max.}$ ($CHCl_3$) 1800, 1760, and 1740 cm^{-1} (Found: C, 69·35; H, 8·6. $C_{21}H_{30}O_5$ requires C, 69·85; H, 8·35%).

(+)-17β-*Acetoxy*-2,3-*seco*-5β-*androstane*-2,3-*dioic Acid* (+)-(20).—The anhydride (−)-(19) (1·531 g) was dissolved in acetone (50 ml) and aqueous Na_2CO_3 (1·6 g) was added. The mixture was shaken at 60° for 10 min, then water (80 ml) was added. Insoluble material was removed by filtration. The filtrate was acidified with dilute HCl. Solid was collected by filtration, washed with water, dried *in vacuo*, and recrystallized from ethyl acetate–benzene to give a *powder* (1·41 g), m.p. 218—222°, $[\alpha]_D^{25}$ +33·5 ± 3·0° (MeOH; *c* 0·251), $\nu_{max.}$ (Nujol) 1743 and 1708 cm^{-1} (Found: C, 65·6; H, 8·4. $C_{21}H_{36}O_6$ requires C, 66·3; H, 8·5%).

(−)-17β-*Acetoxy*-1,4-*dibromo*-2,3-*dinor*-1,4-*seco*-5β-*androstane* (−)-(21).—A suspension of the seco-acid (+)-(20)

(1·81 g) in dry CCl_4 (100 ml) was heated under reflux with stirring. Red mercury(II) oxide (1·55 g) was added to the suspension. The mixture was shielded from light and a solution of bromine (1·53 g) in dry CCl_4 (10 ml) was added dropwise to the suspension over 1 h. The mixture was further heated under reflux for 1·5 h, then allowed to cool. The precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel (40 g; Merck grade 1) in benzene (1 l). The product was recrystallized from light petroleum (b.p. 50—80°) to give a *powder* (533 mg), m.p. 113—115°, $[\alpha]_D^{24}$ −62·9 ± 0·9° ($CHCl_3$; *c* 1·218), $\nu_{max.}$ ($CHCl_3$) 1735 and 1250 cm^{-1} (Found: C, 50·05; H, 6·75; Br, 35·95. $C_{19}H_{30}Br_2O_2$ requires C, 50·7; H, 6·7; Br, 35·5%).

(−)-17β-*Acetoxy*-2,3-*dithia*-5β-*androstane* (−)-(3) *and* (−)-17β-*Acetoxy*-A-*nor*-2-*thia*-5β-*androstane* (−)-(4).—The dibromide (−)-(21) was treated with dry Na_2S and sulphur by the same procedure as described for the tosylates. The *dithia-derivative* (−)-(3) (30·3%) was recrystallized from n-hexane, m.p. 160—162°, $[\alpha]_D^{24}$ −15·7 ± 1·4° (MeOH; *c* 0·2901), $\nu_{max.}$ ($CHCl_3$) 1729, 1255, 1045, and 1025 cm^{-1}, τ ($CDCl_3$) 5·36 (t, *J* 7·0 Hz), 6·39 (dd, *J* 12·0 and 14·0 Hz), 7·16 (s), 7·77 (dd, *J* 14·0 and 3·0 Hz), 7·97 (s), 8·1—8·3 (m), 8·94 (s), and 9·22 (s) (Found: C, 64·2; H, 8·4; S, 17·75. $C_{19}H_{30}O_2S_2$ requires C, 64·35; H, 8·55; S, 18·1%).

The *monothia-derivative* (−)-(4) (45%) was recrystallized from light petroleum (b.p. 60—70°) to give plates, m.p. 116—117° $[\alpha]_{365}^{24}$ −15·7 ± 1·7° (n-hexane; *c* 0·24175), $\nu_{max.}$ ($CHCl_3$) 1728, 1258, 1040, and 1025 cm^{-1}, τ ($CDCl_3$) 5·42 (t, *J* 7·5 Hz), 7·18 (m), 7·98 (s), 8·2—8·8 (m), 8·92 (s), and 9·20 (s) (Found: C, 70·75; H, 9·3; S, 9·9. $C_{19}H_{30}O_2S_2$ requires C, 70·75; H, 9·4; S, 9·95%).

(−)-(1S,3aS,7aS)-1-*Phenyl*-2-*oxa*-trans-*hydrindan* (−)-(17f).—By the above method of tosylation, the hydrindan (−)-(17f) was obtained as the sole product (88%). The product was chromatographed on alumina in benzene, then distilled at 162° and 19 mmHg and again at 107° and 0·5 mmHg, $[\alpha]_D^{24}$ −56·4 ± 0·7° (cyclohexane; *c* 1·102), τ (CCl_4) 2·82 (s), 5·70 (d, *J* 9·0 Hz), 5·95 (dd, *J* 7·7 and 7·5 Hz), 6·47 (dd, *J* 7·0 and 9·0 Hz), and 7·8—9·0 (m), c.d. (cyclohexane; *c* 1·102) $[\theta]_{269}$ +790 $[\theta]_{263}$ +910, $[\theta]_{256\cdot5}$ +640, $[\theta]_{250\cdot5}$ +370, $[\theta]_{245}$ +160, and $[\theta]_{2001}$ +8000.

(+)-(1R,4aS,8aS)-1-*Phenyl*-2,3-*dithiadecalin* (−)-(1f).—Dry hydrogen bromide was passed into the hydrindan (−)-(17) (0·50 g) at 80—90°. After 30 min a lower, aqueous layer began to separate. After a further 5 h the reaction was discontinued and the brown oil was dissolved in $CHCl_3$, washed with water, aqueous $NaHCO_3$, and water, and dried (Na_2SO_4). After removal of the solvent, the residue (0·70 g) was distilled at 146° and 0·3 mmHg, $[\alpha]_D^{23}$ +60·8 ± 0·9° (cyclohexane; *c* 0·823).

A solution of the dibromide (0·69 g) in MeOH (50 ml) was added to a refluxing MeOH solution of thiourea (0·42 g) over a period of 30 min with stirring. The solution was then further heated under gentle reflux for 6·5 h. The solvent was removed under reduced pressure and the residue was dissolved in ethanol–ether. Crystalline thiourea was removed by filtration but the salt could not be crystallized.

The crude salt in 2N-NaOH (20 ml) solution was heated under reflux for 1·5 h with stirring, cooled, acidified with dilute HCl, and then extracted with ether. The ether solution was washed with water and dried (Na_2SO_4). The solvent was removed by distillation and the residue was chromatographed on a thick silica gel plate (Merck GF_{254}) in pentane–benzene (2 : 1). The product of largest R_F value was recrystallized from pentane and was (−)-(1*S*,4a*S*,8a*S*)-1-phenyl-2,3-dithiadecalin (8·7 mg), identical with the sample obtained above. The product of next largest R_F value (10·2 mg) was subjected to silica gel t.l.c. (Merck GF_{254}) in pentane and purified by short-path distillation at 150° (bath temperature) and 0·3 mmHg. G.l.c. analysis showed that it was pure, *m/e* 250 (M^+), $[\alpha]_D^{24}$ −628 ± 30° (cyclohexane; *c* 0·0239). [The racemic compound was prepared by the same procedure, τ ($CDCl_3$) 2·35 (m), 2·70 (m), 6·40 (d, *J* 3·5 Hz), 7·0—7·6 (m), and 7·8—9·2 (m).]

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