

THE CHIRALITY OF THE DISULPHIDE SYSTEM IN (+)-TROPINE-1,2-DITHIOLANE-3-CARBOXYLATE

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In a disulphide, R-S-S-R', where R and R' impose no constraints, there are two enantiomeric conformations of minimum free energy in which the dihedral angle, RSS/SSR' is close to 90° or close to 270° (1). In general, these are neither resolvable nor detectable unless R and/or R' impart additional asymmetry to the molecule, but, where this asymmetry exists, optical activity in electronic transitions associated with the disulphide group has frequently been observed (2). The -S-S- system is a dissymmetric chromophore whose optical activity is seen in open-chain disulphides when rotamers of opposite -S-S- chirality have unequal energy and hence unequal abundance (2,3).

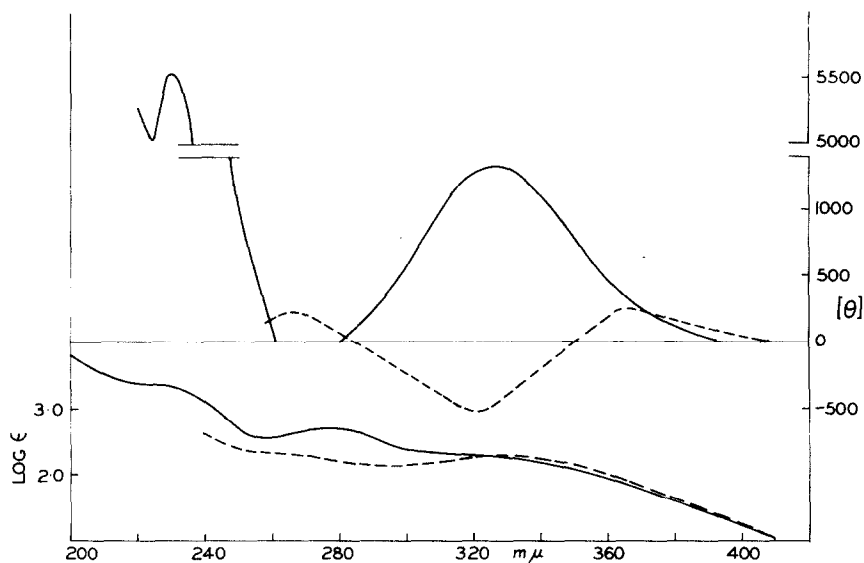
The lowest energy transitions in disulphides occur at progressively longer wavelengths as the -S-S- dihedral angle is reduced from the open chain value ( $\approx 90^\circ$ , ca.250  $m\mu$ (1)) to that in the 1,2-dithiane ring ( $\approx 60^\circ$  (4), ca.286  $m\mu$ (1)) or the 1,2-dithiolane ring ( $\approx 27^\circ$  (5), ca.330  $m\mu$ (1)) and at still longer wavelengths in gliotoxin ( $\approx 14^\circ$  (6), ca.340  $m\mu$ , shoulder (7)) and 1 $\alpha$ ,5 $\alpha$ -epidithioandrostan-3 $\alpha$ ,17 $\beta$ -diol ("almost planar" (8), ca.370  $m\mu$ (8)). In each case optical activity is associated with the lowest energy band (2,6,9). Until recently, the helical sense (lefthanded) and the sign of the first Cotton effect (negative) were known only for gliotoxin and the dangers of generalizing from this result were emphasized (6). However, Carmack (10) has now established, for three 1,2-dithiane compounds of known absolute configuration that in these six-membered ring systems a positive C.D. peak corresponding to the lowest energy U.V. absorption band (281-290  $m\mu$ ) is associated with righthanded helicity in the -S-S- system and a negative C.D. peak with lefthanded helicity.

The lowest energy band, 320  $m\mu$  (shoulder), observed in the U.V. absorption of (+)-tropine-1,2-dithiolane-3-carboxylate (brugine) (11) is typical, both in wavelength and

intensity (1), of the disulphide chromophore in a saturated five-membered ring. Associated with this is a positive C.D. band at 325 m $\mu$ . A more intense, positive C.D. band of higher frequency is coincident with a shoulder at 230 m $\mu$ , in the rising U.V. absorption. It is interesting that no optical activity is detectable in the region of the weak, "perturbed carboxylic" (8) transition at 277 m $\mu$ . The C.D. and U.V. spectra are reproduced in Fig.1, together with corresponding data for (+)-6,8-thioctic acid (9).

FIG. 1

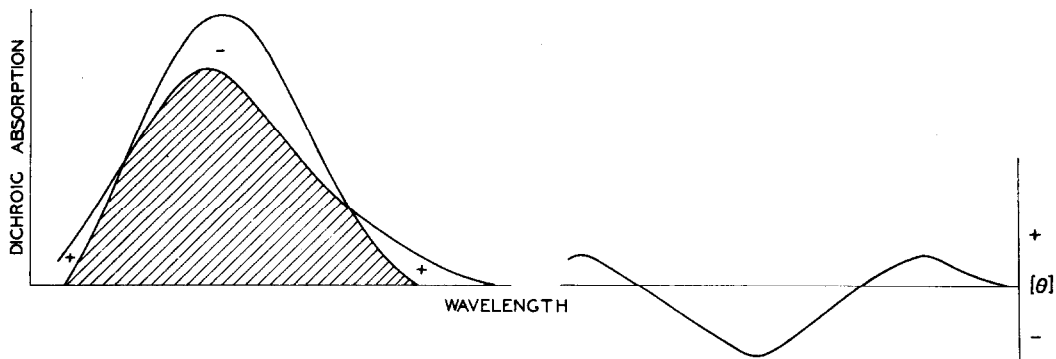
The C.D. and U.V. absorption of brugine in ethanol —, and of (+)-6,8-thioctic acid in dioxane (9) ----. Concentrations for brugine C.D. were 0.024M (400-295 m $\mu$ , 2mm path length) and 0.0024M (310-265 m $\mu$ , 5mm; 260-255, 2mm; 250-220, 1mm). U.V. spectrum, 0.0024M, 1mm.



The -S-S- dihedral angle in a 1,2-dithiolane ring is intermediate between that in 1,2-dithianes and in gliotoxin, in both of which the sign of the lowest frequency C.D. is associated with known helical sense (7,10). From the sign of this band in brugine we, therefore conclude that the skew-sense of the C-S-S-C system is righthanded. Despite the fact that the height of the cis rotational energy barrier must be much reduced from its value in six-membered ring or open-chain disulphides (12), there is no evidence in the C.D. spectrum of the presence of the enantiomeric conformation. The band at 325 m $\mu$  is seen to be symmetrical about the maximum when  $[\theta]$  is plotted against wave-number.

It is interesting to compare the data from brugine with that from the antipodal 6,8-thioctic acids, the only other five-membered ring disulphides whose C.D. spectra have been reported (9). The (+)-antipode exhibits successively positive (367 m $\mu$ ), negative (320 m $\mu$ ) and positive (265 m $\mu$ ) bands of low dichroic intensity compared with the 325 m $\mu$  band of brugine (see Fig.1) while the (-)-antipode shows the same bands with the signs reversed. We suggest that in each of the 6,8-thioctic acid antipodes both screw senses of the -S-S- group are present. If this is so, there are several ways in which the observed C.D. spectra may be accounted for but, in the absence of contrary evidence, we favour those which do not involve a multiplicity of electronic transitions (13) in the C.D. region of lowest energy. One may, for instance, speculate that through peripheral asymmetry associated with C<sub>3</sub> in the dithiolane ring, the vibrational modes, and hence the band contours, of the lowest energy disulphide transition are different for the two helical senses, so that the C.D. band from one is overlapped by the broader, shallower, oppositely-signed band from the other, as in Fig.2.

FIG. 2



Assuming that our arguments are correct, the predominance of one -S-S- helical sense in brugine, as against the presence of both in 6,8-thioctic acid, must result from the different substitution patterns at C<sub>3</sub> in the two molecules. From examination of models, the tropine moiety of brugine, with either possible configuration at C<sub>3</sub>, does not appear to impose any restraints on the conformation of the dithiolane ring, so that these probably have their origin in the esterified carboxyl group. The 277 m $\mu$  absorption band indicates that some form of interaction takes place between this group and the disulphide system, but since the nature of this is unknown (8) its relationship to the molecular geometry is also unknown. The absolute configuration at C<sub>3</sub> cannot, therefore, be determined on the present evidence.

## References

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