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THE 2,4-DIMERCAPTOGLUTARIC ACIDS AND CORRESPONDING DITHIOLANES AND DITHIANES

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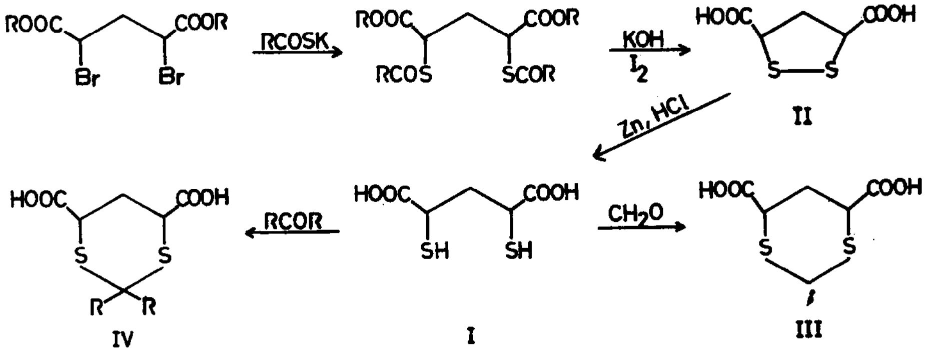
In connection with stereochemical work on cyclic derivatives of α,α'-dimercaptodicarboxylic acids,[1] the diastereomers of 2,4-dimercaptoglutaric acid (I)* were needed. The (±)-isomer has been prepared earlier and optically resolved through the corresponding disulphide.[2] The over-all yield of the acid (I) reported was however low, and as rather large amounts were needed for further synthesis, an improved procedure was desirable.[3]

Thus, a diastereomeric mixture of the dimethyl 2,4-dibromoglutarates was treated with potassium thioacetate in methanol, giving dimethyl 2,4-bis(acetylthio)glutarate. After rapid deacetylation the labile dithiolate dianion was "trapped" as the more stable disulphide (II) by oxidation with iodine. (±)-II crystallized from formic acid, while the syrupy diastereomer was reduced and refined as <u>meso</u>-I.



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* $R = CH_3$ throughout this paper

With hydrogen chloride as catalyst, the acids (I) were each treated with aqueous formaldehyde (37%) and with acetone to yield the 1,3-dithiane-4,6-dicarboxylic acids (III) and their 2,2-dimethyl homologues (IV), respectively.

TABLE 1. Yields and physical properties of I-IV.

	M.p.	Yield (%)	δ (ppm) in acetone-d_6 (31°)	|*J*| (Hz)
meso-I	129-131°	8	3-H_2 2.04m, 2,4-H_2 3.66t^{a}	7.4
(±)-I	134-136°	58	3-H_2 2.30t, 2,4-H_2 3.70t^{a}	7.4
meso-II	151-153°	65	4-H_2 2.83t, 3,5-H_2 4.38t	7.4
(±)-II	193-195°	25	4-H_2 2.75t, 3,5-H_2 4.54t	5.9
meso-III	205-207°	57	5^a-H 2.00, 5^e-H 2.88, 2^e-H 3.88 4,6-H_2 4.00, 2^a-H 4.30 (see Fig. 1)	$2^a,2^e$ 14.3; $2^e,5^e$ 0.8; $4^a,5^a$ 11.9; $4^a,5^e$ 2.5
(±)-III	175-177°	49	5-H_2 2.45t, 2-H_2 4.02s, 4,6-H_2 4.11t	5.4
(+)-III	147-148°	21		
(-)-III	147-148°	35		
meso-IV	187-189°	50	2^e-R^{b} 1.60s, 5^a-H 1.83m, 2^a-R^{b} 1.85s, 5^e-H_2 2.78m, 4,6-H_2 4.15q	$4^a,5^a$ 12.2; $4^a,5^e$ 2.4; $5^a,5^e$ 13.9
(±)-IV	156-158°	25	2-R_2 1.66s, 5-H_2 2.36t, 4,6-H_2 4.24t	5.7

[a] In D_2O. [b] Mutual assignment uncertain.

The (±)-form of III was resolved into its optical antipodes by means of the acid strychnine and neutral quinine salts, giving the acids with $[\alpha]^{25}_{D}$ +159° and -159°, respectively. As (+)-I, assigned the (R,R)-configuration,[4] gave (-)-III, the latter acid must have the same configuration.

The mutual assignment of (±)- and *meso*-acids was confirmed by their PMR spectra (Table 1.). Unlike the *meso*-acids, (±)-III and (±)-IV showed equivalent atoms or groups in positions 2 and 5, indicating rapid equilibrium between chairforms of equal energy or possibly a twist form. Further support was gained from the vicinal coupling constants. These show also that both carboxyl groups in meso-III occupy equatorial positions of a chairform, as expected from their bulkiness. In the spectrum of *meso*-III (Fig. 1), the protons in position 2 appear as an AB quartet and those in positions 4-6 as an A_2MX pattern. As seen from the further broadening and splitting of the B and M parts, weak coupling occurs through five saturated bonds along two routes viz. between the antiparallelly oriented protons in posi-

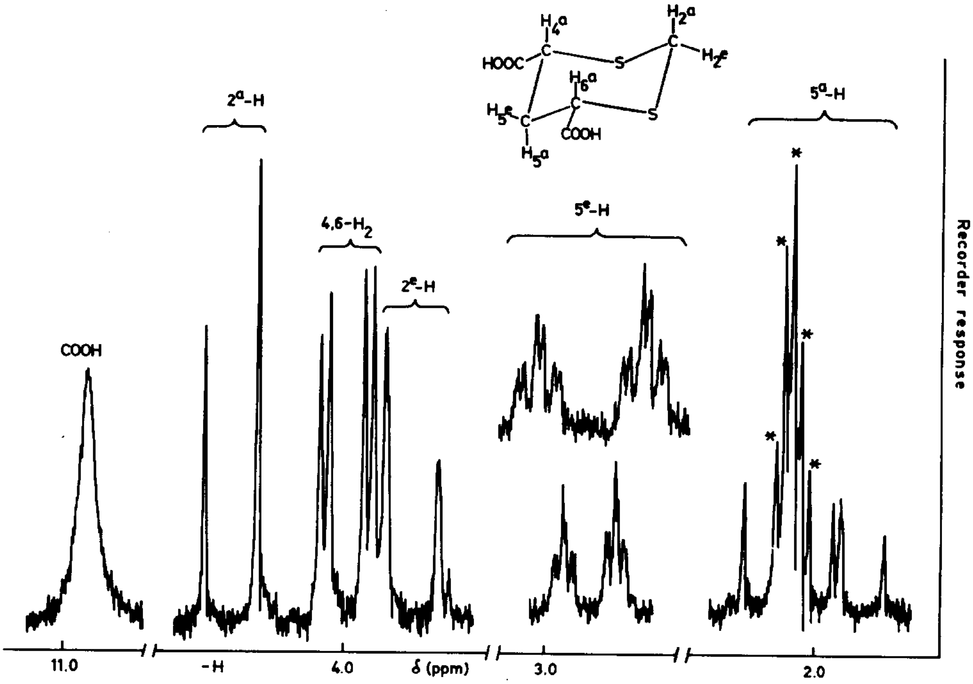

Fig. 1. PMR spectrum of meso-1,3-dithiane-4,6-dicarboxylic acid (meso-III) at 100 MHz in acetone-$\underline{d}_6$. Starred peaks refer to the solvent.

tions 2^e and 5^e. This was confirmed by spin decoupling of the 2^e proton and by observations for other 1,3-dithianes with chair conformation.[5] The same type of coupling is also found in 2,4,6,8-tetrathiaadamantanes.[6] The spectrum has been tested by using the spectral data given in Table 1 as computer input data to simulate the PMR spectrum. The resulting plot was in excellent agreement with the observed spectrum.

The interest in the stereochemistry of cyclic disulphides has been steadily increasing since the discovery of their biological significance. For those with chiral carbon atoms of known absolute configuration, the CD and ORD curves has been used to decide the screw sense of the disulphide group. According to the proposed rule,[7] based on 1,2-dithianes, a positive CD peak corresponding to the lowest UV absorption band of the disulphide group, is associated with righthanded helicity of the disulphide system and vice versa. Inasmuch as this rule may be extended to 1,2-dithiolanes,[8] the interesting absorption band occurs at 330 nm.[9] This is in good agreement with UV data for (±)-II.[10] As (-)-II show a negative CD peak at 333 nm, application of the rule predicts a predominance of the ring with a disulphide group of lefthanded helicity i. e. an M-form according to the convention of Ingold, Cahn and Prelog.[11] As (-)-II has the (R,R)-configuration, the carboxyl groups should have pseudo-axial positions in the dominating conformation. These results are with exception of α-lipoic acid in good agreement with CD investigations of 1,2-dithiolane-3-carboxylic acid and some of its esters.[7] It should however be pointed out that more information about conformations of substituted 1,2-dithiolanes is needed. Until then the helicity rule applied on these substances must be used with caution.

CD data for (-)-II

(nm)	398	333	307	286	267	249	227	222	216
	0	-4610	0	+5930	0	-29000	0	+2630	0

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