

Rac.-1,2-Dithiolane-3,5-dicarboxylic Acid

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Already in 1938 Fredga^{1,2} pointed out the importance of the study of aliphatic α,α' -dimercapto dicarboxylic acids and the cyclic disulphides derived from them. Thus both the *racemic* and *meso* form of α,α' -dimercaptoadipic acid were investigated together with the 1,2-dithiane derivatives. Later on α,α' -dimercaptosuccinic acid was reported by Owen and Sultanbawa³, although with no separation of the stereoisomeric forms.

It is the author's intention to continue the investigation of this series with particular reference to the glutaric and pimelic acids. As the monomeric oxidation products from these mercapto acids, the corresponding disulphides, are cyclic, important information might be obtained for the interpretation of redox processes of the mercaptan-disulphide type. As the compounds are water-soluble and the reactions reversible, it should be possible to study more thoroughly the formation and behaviour of the polymeric linear disulphides, which are obtained not only in oxidation processes under certain conditions but also in direct polymerization of the cyclic disulphides. The latter reaction may proceed either through radical formation or by a redox mechanism. — In addition the presence of two asymmetric centres makes it possible to study the influence of steric effects on the ring closure.

The above mentioned investigation is in progress, and this publication concerns the synthesis and preliminary resolution of *rac.*-1,2-dithiolane-3,5-dicarboxylic acid (*rac.*-1,2-dithiacyclopentane-3,5-dicarboxylic acid). Only a few substances with this ring system are known, but already from the existing material, the unsubstituted heterocycle⁴ and its 4,4-dimethyl derivative⁵, it can be seen that, probably due to considerable strain in the molecule, interesting properties characterize this group of compounds. It seems obvious that an examination of the dicarboxylic acid, now accessible, will essentially contribute to the knowledge of this group of heterocycles.

The *rac.*-1,2-dithiolane-3,5-dicarboxylic acid (*rac.*-1,2-dithiacyclopentane-3,5-dicarboxylic acid) has been prepared from the high melting form of α,α' -dibromo glutaric acid and sodium disulphide in water solution. It is very remarkable that the 1,2-dithiolane derivative obtained has a *racemic* structure as the high melting form of α,α' -dibromo glutaric acid is ascribed the *meso*-configuration^{6,7} (the proof is, however, questionable). Two explanations can be offered. Either the hitherto accepted structure for the dibromo acid is erroneous or perhaps the reaction mechanism implies an intermediate formation of a γ -lactone with subsequent attack of the disulphide group within the molecule to form the cyclic disulphide dicarboxylic acid, the last replacement proceeding with inversion. Such a mechanism would involve two inversions at one of the asymmetric centres and one at the other, resulting in a transformation from *meso* to *racemic* structure. It is of course doubtful, whether a ring opening of a γ -lactone can occur as easily as has to be presumed, but it must be remembered that the reaction of alkyl mercaptides with γ -lactones gives rise to a cleavage of the ring with the formation of salts of γ -alkylmercapto butyric acids⁸. It is further of some importance to call attention to the fact that the ring opening step would in this case mean an intramolecular reaction, which must facilitate the disulphide ion attack to form the cyclic dicarboxylic acid. The investigations are being pursued.

Preliminary experiments on resolution with brucine and quinine have given clear evidence of the *racemic* structure of the 1,2-dithiolane-3,5-dicarboxylic acid prepared. The (+)-acid can be obtained from the acid brucine salt, crystallized from dilute alcohol, and the (–)-acid from the neutral brucine salt, best crystallized from the former mother liquor. As could be expected⁹ a rather high rotatory power has been observed (see below), probably due to the combined effects of cyclic structure, the electronic conditions of a disulphide bond and the position of the disulphide group relative to the asymmetric centres. A complete and detailed description will be published later.

EXPERIMENTAL. *Rac.*-1,2-Dithiolane-3,5-dicarboxylic acid. 25.7 g (0.09 moles) of α,α' -dibromo glutaric acid (m.p. 169–170°) was rapidly neutralized with a water solution of 25.8 g (0.09 moles) of sodium carbonate de-

cahydrate. A solution of sodium disulphide in excess (0.11 moles), prepared about 48 hours before use from $\text{Na}_2\text{S} \cdot 9 \text{H}_2\text{O}$ and sulphur in water as solvent, was added cautiously with cooling. The total volume was 200 ml, and the solution was allowed to stand for 8 hours with occasional shaking. Some sulphur, having separated, was filtered off and the still alkaline solution acidified with dilute sulphuric acid. After the removal of precipitated amounts of non-crystalline material, mainly sulphur, the aqueous part was extracted 10 times with 50 ml portions of ether. The ether was allowed to evaporate spontaneously, leaving a semi-solid, colourless mass. By treatment with a small volume of hot water, this product mostly dissolved, and after rapid filtration the solution was placed in a refrigerator over night. The dicarboxylic acid crystallized as beautifully formed prisms. Repeated recrystallizations yielded 1.9 g (11 %) of a pure substance with the melting point 197–199°. The melting point depends on the rate of heating; the value given was found by plunging the capillary tube into the preheated (about 190°) apparatus. (Found: Equiv.wt. 97.8; S 33.33; Mol.wt. 191, 186, 188. Calc. for $\text{C}_6\text{H}_8\text{O}_4\text{S}_2$ (194.2). Equiv. wt. 97.1; S 33.02; Mol. wt. 194.2).

Preliminary experiments on resolution. (+)-1,2-Dithiolane-3,5-dicarboxylic acid. 0.39 g (0.002 moles) of the racemic acid and 0.94 g (0.002 moles) of brucine were dissolved in a hot mixture of water (10 ml) and ethanol (6 ml). Crystallization over night at room temperature yielded 0.60 g (45 %) of salt. The acid was set free from its salt by acidifying with dilute sulphuric acid and extraction with ether in the usual manner. The rotatory power was measured in alcohol. M.p. 176–180°.

$$[\alpha]_{\text{D}}^{25} = +414^\circ$$

(-)-1,2-Dithiolane-3,5-dicarboxylic acid. 0.47 g (0.001 mole) of brucine was added to the mother liquor from above together with 5 ml of ethanol. Crystallization as before yielded 0.60 g of salt. The measurement of the rotatory power was performed as described above. M.p. 177–181°; $[\alpha]_{\text{D}}^{25} = -564^\circ$, Equiv. wt. Calc. 97.1. Found 97.3.

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Some Sulphur Compounds Related to Pimelic Acid

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In the preceding paper¹ attention is drawn to the study of α, α' -dimercapto dicarboxylic acids and the important results, that might be obtained by investigations already shortly outlined. No such derivatives related to pimelic acid have until now been published, and only those of adipic acid have been more thoroughly investigated^{2,3}.

The corresponding dibromo acids are usually employed as starting materials, but for α, α' -dibromo pimelic acid the isolation of one of the stereoisomeric forms still remains. Fehnel and Oppenlander⁴ report and discuss the preparation of the high melting form in connection with an examination of some symmetrical 2,6-disubstituted tetrahydrothiapyrans. In a reaction with sodium sulphide they obtained *cis*-(*meso*)-2,6-tetrahydrothiapyrandicarboxylic acid, and they thus concluded that the high melting isomer of α, α' -dibromo pimelic acid possesses the *meso* configuration. Already before these results were published, the same compounds had been prepared in a slightly different way by the present author. As his observations are in good agreement with those of Fehnel and Oppenlander, it seems unnecessary to publish the experimental details.

The present publication deals with some further sulphur derivatives obtained from the high melting dibromo acid, while attempts to isolate the other stereoisomer are in progress.

For the preparation of mercapto-substituted carboxylic acids two methods are