

RESOLUTION AND CONFIGURATION OF 1,2-DITHIOLANE-3-CARBOXYLIC ACID

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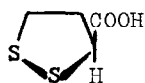
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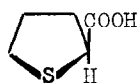
1,2-Dithiolane-3-carboxylic acid (I), the lowest homologue of lipoic acid (6,8-thioctic acid), was synthesized for the first time in 1955 (1). Recently optically active 1,2-dithiolane-3-carboxylic acid has been found in nature. Its tropine ester, brugine, has been isolated from the bark of a tropical mangrove (2). We wish here to report the resolution of 1,2-dithiolane-3-carboxylic acid into optical antipodes, and the determination of the absolute configuration at the C_3 atom.

The dextrorotatory antipode was obtained through several recrystallizations of its cinchonidine salt from ethanol, and the levorotatory antipode was isolated from the first mother liquor. The optical rotation at the sodium D line was $[\alpha]_D^{25} = +337^\circ$ and $[\alpha]_D^{25} = -313^\circ$ respectively.

The absolute configuration was unambiguously determined in two independent ways. By the Fredga quasi-racemate method (3) the configuration at C_3 of 1,2-dithiolane-3-carboxylic acid was correlated to the configuration of thiophane-2-carboxylic acid (II). As seen from Fig. 1 and 2, the acids with opposite signs of rotation give a typical quasi-racemate, while the acids with equal signs of rotation give a diagram of the simple eutectic type. Thus, (+)-I has the same configuration as (+)-II. As the absolute configuration of II has already been determined (4), the configuration of 1,2-dithiolane-3-carboxylic acid (I) is also settled and is given below:



(S)-(+)-I



(S)-(+)-II

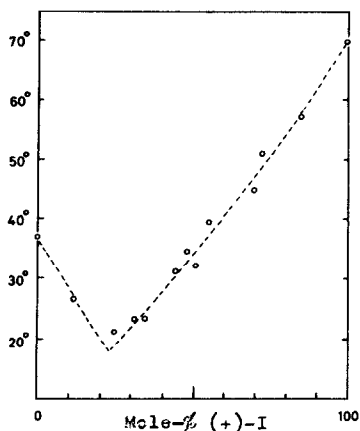


FIG. 1

Melting point diagram
between (+)-I and (+)-II

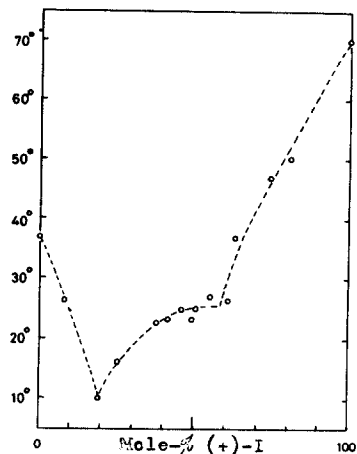
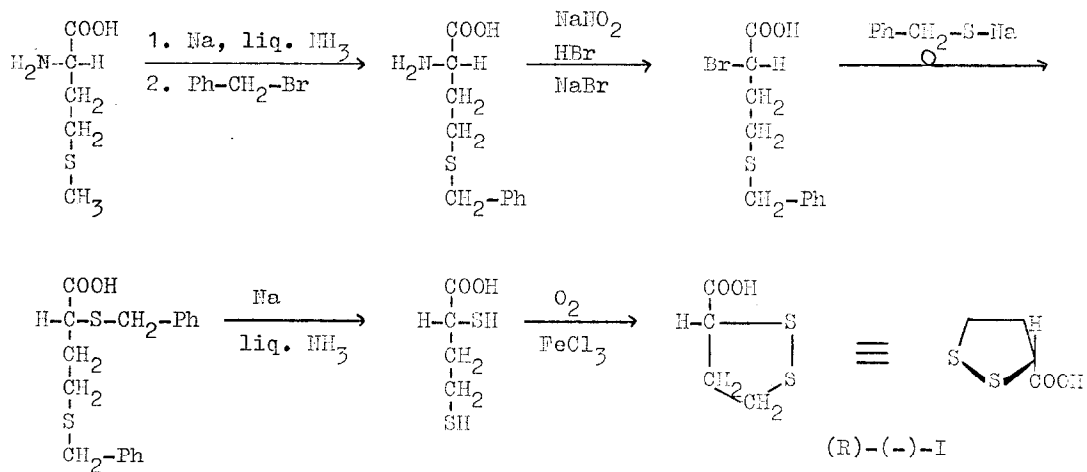


FIG. 2

Melting point diagram
between (+)-I and (-)-II

The configuration of 1,2-dithiolane-3-carboxylic acid was also established by a stereospecific synthesis from L-methionine according to Scheme 1.



SCHEME 1

The symbol $\xrightarrow{\text{O}}$ indicates substitution with inversion of configuration.

The CD spectrum of (+)-I shows a positive band at 327 μ , a negative band at 273 μ , and a more intense band at about 225 μ (4) corresponding to the UV absorption bands (5). The lowest energy transition at 327 μ is characteristic of the disulphide chromophore in a saturated five membered cyclic disulphide (5). The CD spectrum of (+)-tropine 1,2-dithiolane-3-carboxylate (brugine) has recently been published by Beecham, Loder and Russell (6). The shape of its CD curve is very similar to that of (+)-1,2-dithiolane-3-carboxylic acid, both compounds exhibiting a positive band at about 325 μ .

Through studies of 1,2-dithiane compounds, the chirality of the disulphide system has now been correlated to the sign of the CD peak corresponding to the lowest energy UV absorption band (7,8). Beecham et al. (6) also concluded that the skew-sense of the C-S-S-C system in brugine is right handed.

Despite our knowledge of the absolute configuration at C₃ in 1,2-dithiolane-3-carboxylic acid we cannot with certainty predict if the ester group in brugine is pseudo axial or pseudo equatorial, and thus, the absolute configuration at C₃ in brugine cannot be determined.

It should also be noticed that 1,2-dithiolane-3-carboxylic acid and lipoic acid with the same configuration at C₃ have opposite signs of the CD band at about 325 μ .

In order to solve the question about the absolute configuration of brugine, we have begun experiments in order to synthesize brugine from tropine and the optically active 1,2-dithiolane-3-carboxylic acid.

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