

1,2-Dithiane-4-carboxylic Acid

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Studies of the stereochemistry of cyclic disulfides presently underway in these laboratories have dictated a need for the compound, 1,2-dithiane-4-carboxylic acid. We wish to report the unequivocal synthesis and preliminary resolution of this compound.

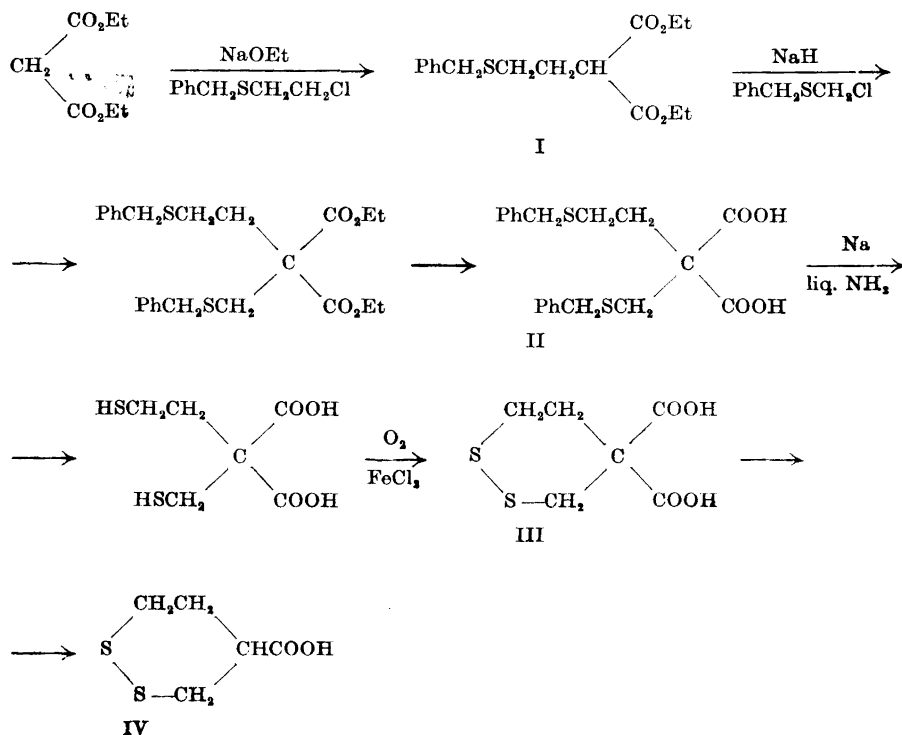
Using the reaction sequence illustrated below, pure 1,2-dithiane-4-carboxylic acid (IV) was obtained in 15 % overall yield from the readily prepared diethyl β -benzylthioethylmalonate (I).

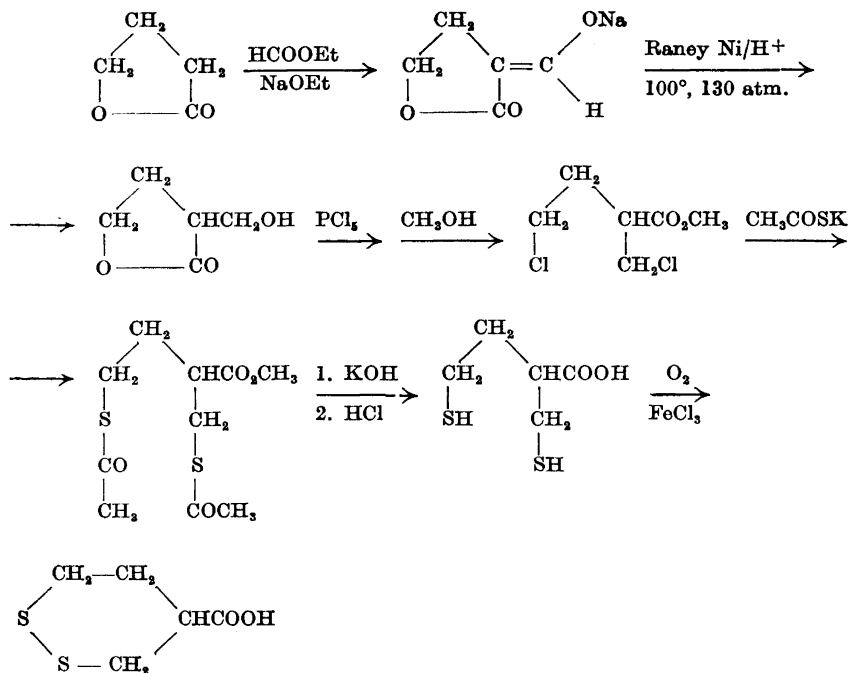
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A small amount of IV was also isolated from among the products resulting when γ -butyrolactone was subjected to the following series of reactions (see p. 841). The presence of active hydrogen in β -position to sulphur, however, is known to favor disproportionation reactions under alkaline conditions¹, and these, together with thio-lactone formation and polymerization reactions permitted very meager success with this synthesis.

A partial resolution of 1,2-dithiane-4-carboxylic acid has been accomplished.

Experimental. β -Benzylthioethyl-benzylthio-methylmalonic acid (II). β -Benzylthioethyl chloride and diethyl α -benzylthioethylmalonate (I) were prepared by the methods of du Vigneaud and Brown². The pure monoalkyl ester (I), b.p. 176–178°/1 mm, was obtained in 56 % yield from diethyl malonate. (No physical constants were reported for compound I in Ref.²) Benzylthiomethyl chloride (b.p. 116.5–117.5°/8 mm) was obtained in 54 % yield using the method of Böhme, Fisher and Frank³ at room temperature.





IV

A solution of 23.5 g (0.0755 mole) of diethyl β -benzylthioethylmalonate (I) in 20 ml of dry toluene was added dropwise and with stirring to 1.9 g (0.0793 mole) of sodium hydride suspended in 40 ml of dry toluene. The evolution of hydrogen had stopped after 5.5 h at 70°, and a solution of 13 g (0.0755 mole) of benzylthiomethyl chloride in 20 ml of toluene was added. The reaction mixture was stirred at 75° for 63 h (shorter reaction times proved to be insufficient). The toluene was removed under reduced pressure, and the crude ester saponified directly by refluxing for 4 h with a solution of 16 g (0.4 mole) of sodium hydroxide in 80 ml of water and 50 ml of ethanol. The alcohol was removed under reduced pressure, and the cooled, heterogeneous residue extracted with three 50 ml portions of ether. The water soluble remainder was acidified to pH 4 with 50 % ice-hydrochloric acid and the resulting yellow oil extracted with two 100 ml portions of benzene. The crude yield of (II) after removal of the benzene under reduced pressure at room temperature was 21 g (71 %). White radial clusters of needles were obtained after digestion in 85 % formic acid and repeated

crystallization from petroleum ether-ether. M. p. 101.8–102.5° with evolution of CO₂ at 122°. Equiv. wt. calc. 195.3; found 201.0.

It is interesting to note that the ether extracts, upon evaporation and recrystallization from alcohol produced 2.8 g (28 % from benzylthiomethyl chloride) of dibenzylthiomethane, m. p. 47.5–48.2°. The structure was established through analyses, melting point and mixed melting point with an authentic specimen⁴. (Found: C 69.27; H 6.20; S 24.59. Calc for C₁₆H₁₆S₂ (260.41): C 69.18; H 6.19; S 24.62.)

1,2-Dithiane-4,4-dicarboxylic acid (III). A solution of 19 g (0.046 mole) of crude II in 30 ml of dry toluene was added dropwise over a period of one hour to 500 ml of liquid ammonia to which a small piece of sodium had been added. The blue colour was maintained by appropriate additions of sodium. After a total of 3 h, and the addition of 8.2 g (0.357 mole) of sodium, the reaction was complete. The excess sodium was neutralized with powdered ammonium chloride, the ammonia allowed to evaporate, and the remaining salts extracted with 1 500 ml of water. The pH was adjusted

to 7.5 with hydrochloric acid, 2 ml of 1% ferric chloride added, and air was bubbled through *via* a sintered glass filter. After 27 h, the solution became clear yellow, and it was acidified to pH 3. An unidentified yellow oil was first removed by extraction with five 100 ml portions of benzene, and then the product (III) was isolated by extraction with three 100 ml portions of ether. The crude yield of 1,2-dithiane-4,4-dicarboxylic acid was 5 g (52%). Recrystallization from alcohol-water produced white crystals which melted with decarboxylation at 152°. Equiv. wt. calc. 104.1; found 107.0.

1,2-Dithiane-4-carboxylic acid (IV). 4 g (0.0192 mole) of crude 1,2-dithiane-4,4-dicarboxylic acid (III) was heated at 150–170° for half an hour. Recrystallization from alcohol-water and subsequently from petroleum ether-benzene produced 1.85 g (59%) of pure 1,2-dithiane-4-carboxylic acid melting at 115.2–116.2°. (Found: C 37.10; H 4.90; S 38.78; equiv. wt. 165.0. Calc. for $C_6H_8S_2O_2$ (164.2); C 36.81; H 4.91; S 39.05; equiv. wt. 164.2.)

Preliminary resolution of 1,2-dithiane-4-carboxylic acid. Quinine and cinchonidine salts were found to be suitable for the resolution of racemic IV. Brucine, α -phenyl-ethylthiuronium chloride and α -(2-naphthyl)-ethylamine proved to be ineffective as resolving agents. The impure dextro enantiomorph, $[\alpha]_D^{25} = +71.5^\circ$ in ethanol solution; m. p. 109–113°, was obtained after four crystallizations of the cinchonidine salt from abs. ethanol. The impure levo antipode, $[\alpha]_D^{25} = -123.5^\circ$; m. p. 106.5–108°, was obtained after four crystallizations of the quinine salt from abs. ethanol. The UV spectra of the two enantiomorphs were essentially identical, with absorption maxima at 211 and 298 μ (in ethanol).

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A Note on the Constitution of Rhodopin

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The carotenoid rhodopin was first isolated in 1936 by Karrer and Solmssen¹ from mixed cultures containing *Rhodovibrio* species and was also shown to be present in *Thiocystis*². The elementary analysis was in good agreement with a molecular formula $C_{40}H_{58}O$, although Karrer *et al.*³ did not exclude the possibility of $C_{40}H_{56}O$. The oxygen function was shown to be a hydroxyl group by quantitative determination of active hydrogen^{2,3}. Because of its resistance to acetylation rhodopin was assumed to have a tertiary hydroxyl group³. Upon catalytic hydrogenation an uptake of 11.93 and 11.71 moles of hydrogen per mole rhodopin was recorded, and Karrer and Solmssen³ assumed that twelve carbon-carbon double bonds were present in rhodopin. Rhodopin occurred in complex mixture with other carotenoids including a carotene which these workers named rhodopurpurin¹, and they suggested that rhodopin might be a derivative of rhodopurpurin¹. They also pointed out the possible identity of lycopene and rhodopurpurin^{2,4}, but no structural formula for rhodopin was suggested.

More recently Goodwin *et al.*^{4,5} have isolated from a number of photosynthetic bacteria (*Athiorhodaceae* and *Thiorhodaceae*) a carotenoid which has the lycopene chromophore and which according to partition tests and chromatographic behaviour was assumed to be a mono-OH-lycopene. Taking into account the source of isolation and the visible spectra and chromatographic behaviour Goodwin and Land concluded that this pigment was identical with rhodopin.

A mono hydroxy derivative of lycopene, lycoxanthin, had previously been isolated by Zechmeister and Cholnoky⁶ from the berries of *Solanum dulcamara*. Lycoxan-

* This suggestion has since been verified by Goodwin and Land⁵ by mixed chromatography and comparison of spectroscopic properties. It should, however, be kept in mind that lycopene from photosynthetic bacteria has so far not been isolated in crystalline state.