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1,2-Dithiolane-3-carboxylic Acid

II. Synthesis of (*R*)-(—)-1,2-Dithiolane-3-carboxylic Acid

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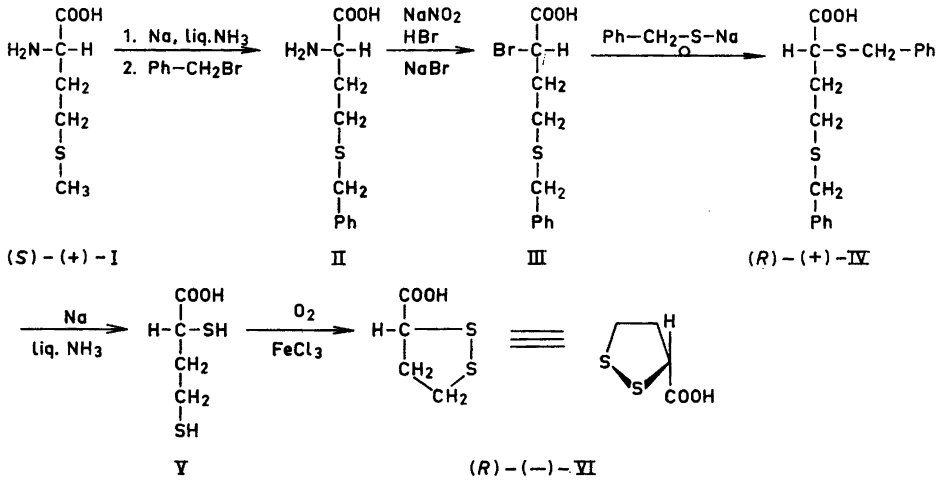
(—)-1,2-Dithiolane-3-carboxylic acid has been synthesized from L-methionine. The different steps in the reaction sequence have been proven to proceed in the expected stereospecific manner. The levorotatory 1,2-dithiolane-3-carboxylic acid must then have the *R*-configuration, which is also confirmed by the result obtained with the quasi-racemate method.[1]

In the first part of this series [1] we have described the synthesis of racemic 1,2-dithiolane-3-carboxylic acid, its resolution into the optically active forms and the determination of their configuration by the quasi-racemate method. One of the enantiomers of 1,2-dithiolane-3-carboxylic acid (VI) has now been synthesized by the stereospecific reaction sequence shown in Scheme 1.



Scheme 1. The symbol ⟶ indicates substitution with inversion of configuration.

The first reaction step in this scheme, the preparation of *S*-benzylhomocysteine (II) from methionine (I), has been described earlier [2-4] and does not involve the optically active center.

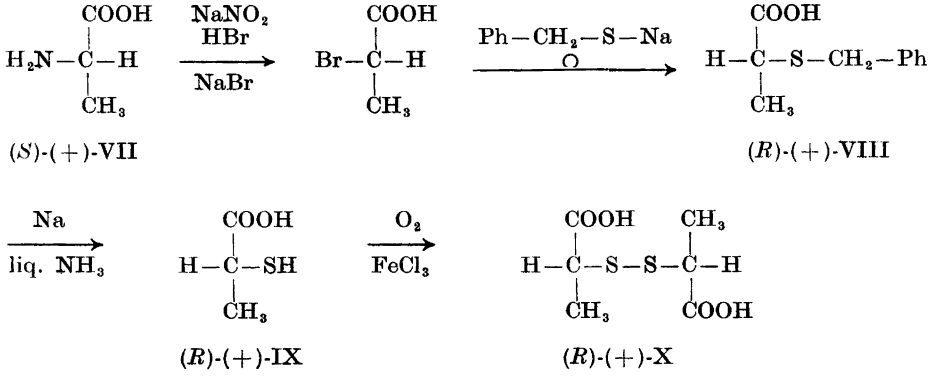
The second step, the deamination of II to 2-bromo-4-benzylthio-butanoic acid (III), should proceed with retention of configuration. It is well known that deamination of free α-amino acids by nitrous acid occurs with retention of configuration, because of participation by the neighbouring carboxyl group.[5-8]

The next step, conversion of III to 2,4-dibenzylthio-butanoic acid (IV), was assumed to proceed mainly by the S_N2 mechanism with a Walden inversion. The crude IV was obtained as a dextrorotatory oil, $[\alpha]_D^{25} = +76°$. (We also isolated a small amount of a levorotatory acid, $[\alpha]_D^{25} = -27.8°$, the structure of which was assigned as 2-hydroxy-4-benzylthio-butanoic acid on the basis of NMR data in conjunction with infrared and elemental analyses).

The (*R*)-(+)-2,4-dibenzylthio-butanoic acid (IV) was debenzylated with sodium in liquid ammonia giving (*R*)-2,4-dimercapto-butanoic acid as its sodium salt. The salt was immediately dissolved in water, the pH was adjusted to 9, and the dimercapto acid oxidized with air and ferric chloride as catalyst and indicator to (*R*)-1,2-dithiolane-3-carboxylic acid, with $[\alpha]_D^{25} = -318°$. Equivalent weight, IR, and UV spectra were in agreement with those for authentic 1,2-dithiolane-3-carboxylic acid.

As methionine is easily demethylated by sodium in liquid ammonia,[2-4] it may seem unnecessary to replace its *S*-methyl group by benzyl, only to again remove it after the deamination. Attempts to bypass the first step and treat methionine according to the same reaction sequence as *S*-benzylhomocysteine (Scheme 1), were unsuccessful. After deamination and reaction with benzylmercaptide we obtained the expected 2-benzylthio-4-methylthio-butanoic acid. Several reductions with sodium in liquid ammonia failed, however. The benzyl group is easily removed, but the demethylation process is so slow that desulphurization takes place at the same time. Inhomogeneous products were formed which we did not purify.

To confirm our assumptions concerning the reaction mechanisms in Scheme 1, L-alanine (VII) was subjected to similar reaction conditions (Scheme 2).



Scheme 2.

Fredga [9] has resolved thiolactic acid (IX), and established its absolute configuration as *R* for the dextrorotatory enantiomer. Bernton [10] has shown that the dextrorotatory thiolactic acid on oxidation yields a dextrorotatory dithiodilactic acid (X), $[\alpha]_D^{25} = +417°$.

The *S*-benzyl-thiolactic acid (VIII), which we obtained as colourless crystals, was dextrorotatory, $[\alpha]_D^{25} = +251°$. The acid was debenzylated with sodium in liquid ammonia, and oxidized in aqueous solution with air and ferric chloride yielding dextrorotatory dithiodilactic acid, $[\alpha]_D^{25} = +267°$.

It was concluded that the reaction steps in Scheme 1 and 2 involving the optically active centres followed the expected stereochemical course.

To sum up, the synthesis of 1,2-dithiolane-3-carboxylic acid from L-methionine shows that levorotatory 1,2-dithiolane-3-carboxylic acid (VI) has the *R*-configuration, which is also confirmed by the result obtained by the quasi-racemate method.[1] In addition we obtain for (+)-*S*-benzyl-thiolactic acid and (+)-2,4-dibenzylthio-butanoic acid the configuration *R*.

EXPERIMENTAL

The melting points were determined with a Kofler hot-stage microscope. The infrared spectra were recorded on a Perkin-Elmer Model 421 spectrophotometer. The ultraviolet spectra were measured with a Beckman Model DK-2A spectrophotometer, and the NMR spectra were obtained with a Varian Model A-60 spectrometer using tetramethylsilane as an internal reference. The optical rotations were taken on a Perkin-Elmer Model 141 polarimeter.

Optically pure (+)-S-*benzyl-L-homocysteine (II)* was prepared from L-methionine by the method described in Refs. 2–4. $[\alpha]_D^{25} = 24.5°$ (c=1, 1 N HCl) (lit.[3] $[\alpha]_D^{25} = +24.5°$; c=1, 1 N HCl).

(R)-(+)-*2,4-Dibenzylthio-butanoic acid (IV).* In a 2000 ml three-necked flask fitted with two dropping funnels, gas outlet tube and teflon stirrer, were placed 11.3 g (0.05 mole) of *S*-benzyl-L-homocysteine and 350 g (2.95 moles) of potassium bromide dissolved in 750 ml of water. One of the dropping funnels was filled with 4.15 g (0.06 mole) of sodium nitrite dissolved in 20 ml of water, and the other with 7.7 ml (0.11 mole) of 66 % hydrobromic acid and 32 ml of water. The flask was cooled in an ice bath, and 20 ml of the dilute hydrobromic acid was added in one portion. Then the sodium nitrite solution and the rest of the hydrobromic acid were added dropwise, simultaneously with vigorous stirring. The nitrogen evolved was collected over water in a graduated vessel. After 2 h, all of the solution had been added, and the reaction was allowed to proceed with the ice bath removed. After one hour no more nitrogen was evolved, and the solution was extracted with ether (2×200 ml). The ether solution was dried over sodium sulphate, evaporated on a rotary evaporator, and the crude 4-benzylthio-2-bromobutanoic acid, a yellow oil, was dissolved in 25 ml of methanol. The methanol solution was added with stirring to a solution of 18.6 g (0.15 mole) of benzylmercaptan and 6.0 g (0.15 mole) of sodium hydroxide in 75 ml of methanol and 38 ml of water. The mixture was allowed to react for 24 h at room temperature. The pH of the solution was then adjusted to 9, and excess benzylmercaptan was extracted with ether. Then the pH of the solution was lowered to 1, and the crude 2,4-dibenzylthio-butanoic acid was extracted with benzene (4×100 ml). The benzene solution was treated with Norite, dried over magnesium sulphate, and evaporated, yielding 6.7 g (40 %) of 2,4-dibenzylthio-butanoic acid, a pale yellow oil, $[\alpha]_D^{25} = +76.4°$ (c=2.0, 96% ethanol). The IR spectrum (liquid film) is identical with that of racemic 2,4-dibenzylthio-butanoic acid.[1] (Found: Equiv. wt. 330.7. Calc. for $C_{18}H_{20}O_2S_2$: Equiv. wt. 332.5).

In another batch, in which the excess of potassium bromide and benzylmercaptan was kept much smaller, about 20 % of *2-hydroxy-4-benzylthio-butanoic acid* separated as white crystals from the crude, oily dibenzylthio-butanoic acid. The crystals were filtered

and recrystallized from benzene-cyclohexane, m.p. 72–80°, $[\alpha]_D^{25} = -27.8°$ ($c = 0.7$, 96 % ethanol). (Found: C 58.18; H 6.40; S 14.16; Equiv. wt. 227.4. Calc. for $C_{11}H_{14}O_3S$: C 58.37; H 6.24; S 14.17; Equiv. wt. 226.3).

Its NMR spectrum in chloroform-*d* consists of a multiplet at δ 1.98 (3-CH_2), a triplet at δ 2.61 (4-CH_2), a singlet at δ 3.72 (φ-CH_2), a multiplet at δ 4.17 (2-CH), and a singlet at δ 7.27 (C_6H_5) in the intensity ratios 2:2:2:1:5. Integration showed two hydrogens (OH, COOH) between δ 5.5 and 7.

(R)-(−)-*1,2-Dithiolane-3-carboxylic acid (VI).* To 400 ml of liquid ammonia in a three-necked flask equipped with a mechanical stirrer, was added 3.32 g (0.01 mole) of crude (*R*)-(+)-2,4-dibenzylthio-butanoic acid. Sodium 1.5 g (0.065 mole), was added slowly in small pieces, until the blue colour remained for 10 min, and then 1.9 g (0.036 mole) of ammonium chloride was added. The ammonia was allowed to evaporate, and the residue was dissolved in 500 ml of water. The solution was cooled in an ice bath, and the pH was adjusted to 9. A few drops of ferric chloride solution was added, and air was led through the solution until the dark blue colour had disappeared. The pH of the solution was then lowered to 1 by cautious addition of 5 M hydrochloric acid. The acid solution was extracted with benzene (5 × 50 ml). The benzene solution was treated with Fuller's earth to remove polymers, and dried over magnesium sulphate. The volume of the solution was lowered to 25 ml on a rotary evaporator, and the 1,2-dithiolane-3-carboxylic acid crystallized by addition of an equal volume of cyclohexane and thereafter cooling. The yield of (*R*)-(−)-1,2-dithiolane-3-carboxylic acid was 1.03 g (69 %), with m.p. 67–70°, $[\alpha]_D^{25} = -318°$ ($c = 3.2$, 96 % ethanol). Optically pure levorotatory 1,2-dithiolane-3-carboxylic acid melts at 70–72° and has an optical rotatory power of −337° (Ref. 1). The UV spectrum of our product has λ_{max} at 277 mμ and 327 mμ, which is in agreement with the spectrum of an authentic sample. The IR spectrum is identical with that of levorotatory 1,2-dithiolane-3-carboxylic acid obtained by resolution of racemic acid.[1] (Found: Equiv. wt. 149.0. Calc. for $C_4H_6O_2S_2$: Equiv. wt. 150.2).

(±)-*4-Methylthio-2-benzylthio-butanoic acid* was prepared from (±)-methionine by the method given above for 2,4-dibenzylthio-butanoic acid (IV). The acid was obtained as a pale yellow oil in a yield of 43 %. Its infrared spectrum was very similar to that of IV. (Found: C 56.17; H 6.20; S 25.14; Equiv. wt. 253.7. Calc. for $C_{12}H_{16}O_2S_2$: C 56.20; H 6.29; S 25.01; Equiv. wt. 256.4).

(R)-(+)-S-*Benzyl-thiolactic acid (VIII) from* L-*alanine.* The same synthetic procedure as described above for (*R*)-(+)-2,4-dibenzylthio-butanoic acid was followed.

L-Alanine, 8.9 g (0.1 mole), was dissolved in an aqueous solution of 115 g (0.97 mole) of potassium bromide in 300 ml of water. A solution of 7.5 g (0.11 mole) of sodium nitrite and 14.6 ml (0.2 mole) of 66 % hydrobromic acid were slowly added simultaneously with stirring and cooling. The crude α-bromopropionic acid was extracted with ether. The ether solution was briefly dried over sodium sulphate, and the ether evaporated. The residue was dissolved in 25 ml of methanol and added to a solution of 24.8 g (0.2 mole) of benzylmercaptan and 8.0 g (0.2 mole) of sodium hydroxide in 60 % methanol. The mixture was allowed to react for 24 h at room temperature. The pH was then adjusted to 9, and excess benzylmercaptan was extracted with ether. The solution was acidified and the (*R*)-(+)-*S*-benzyl-thiolactic acid was extracted with ether. The yield of crude acid after evaporation of the ether was 12.4 g as a light yellow oil, $[\alpha]_D^{25} = +251°$ ($c = 5.3$, 96 % ethanol). Part of the acid was passed through a column of silica gel with benzene-cyclohexane (1:1). The solution of the eluted acid was evaporated *in vacuo* to leave a colourless crystalline compound. M.p. 72–82°, $[\alpha]_D^{25} = +250°$ ($c = 0.5$, 96 % ethanol). Lit.[11] m.p. for racemic acid 78–79°. (Found: Equiv. wt. 197.5. Calc. for $C_{10}H_{12}O_2S$: Equiv. wt. 196.3).

Its NMR spectrum in chloroform consists of a doublet at δ 1.38 (CH_3), a quartet at δ 3.28 (CH), a singlet at δ 3.87 (CH_2) and a singlet at δ 7.28 (C_6H_5), and a singlet at δ 10.6 (COOH).

(R)-(+)-*Dithiodilactic acid (X).* Crude (*R*)-(+)-*S*-benzyl-thiolactic acid, 9.8 g (0.05 mole), was dissolved in 500 ml of liquid ammonia. Small pieces of sodium were added with stirring until the blue colour remained for 15 min. Ammonium chloride was then added in small portions until the blue colour disappeared. The ammonia was evaporated and the residue dissolved in 500 ml of water. The pH of the solution was adjusted to 9, and the solution was cooled in an ice bath. A few drops of a ferric chloride solution were added, and air was led through the solution until the dark blue colour disappeared.

The pH of the solution was then lowered to 1, and the (*R*)-(+)-dithiodilactic acid was extracted with benzene (3×150 ml). The benzene solution was treated with activated carbon, dried over magnesium sulphate, and evaporated, yielding 4.2 g (80 %) of (*R*)-(+)-dithiodilactic acid, m.p. 109–117°, $[\alpha]_D^{25} = +267°$ ($c = 3.2$, water). (Lit.[10] values for optically pure (+)-dithiodilactic acid: m.p. 120–121°, $[\alpha]_D^{45} = +417°$ ($c = 2.1$, water)). (Found: Equiv. wt. 106.0. Calc. for $C_6H_{10}O_4S_2$: Equiv. wt. 105.2).

Its NMR spectrum in acetone-d_4 consisted of a doublet at δ 1.49 and a quartet at δ 3.72 in the intensity ratio of 3:1.

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REFERENCES

1. Claeson, G. *Arkiv Kemi* **30** (1968) 277.
2. Hope, D. B. and Humphries, J. F. *J. Chem. Soc.* **1964** 869.
3. Greenstein, J. P. and Winitz, M. *Chemistry of the Amino Acids*, Wiley, New York 1961, Vol. 3, p. 2657.
4. Snow, M. L., Dombro, R. S. and Ressler, C. *J. Org. Chem.* **32** (1967) 246.
5. Brewster, P., Hughes, E. D., Ingold, C. K. and Rao, P. A. D. S. *Nature* **166** (1950) 178.
6. Brewster, P., Hiron, F., Hughes, E. D., Ingold, C. K. and Rao, P. A. D. S. *Nature* **166** (1950) 179.
7. Gould, E. S. *Mechanism and Structure in Organic Chemistry*, Holt, Rinehart and Winston, New York 1962, p. 565.
8. Claeson, G. and Jonsson, H.-G. *Arkiv Kemi* **26** (1966) 247.
9. Fredga, A. *Svensk Kem. Tidskr.* **67** (1955) 343.
10. Bernton, A. *Beiträge zur Kenntnis der optisch aktiven Thiomilchsäuren, ihrer Mercaptide und Disulfide*, Diss., Lund 1932, p. 94.
11. Owen, L. N. and Sultanbawa, M. U. S. *J. Chem. Soc.* **1949** 3109, 3112.

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