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Sulphur-containing Pantothenic Acid Derivatives

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The synthesis of the mercapto analogue of pantothenic acid was effected by condensation of thiopantolactone III with β-alanine. The required thiopantolactone was obtained by reduction of bis (2,2-dimethyl-3-hydroxy-3-carboxypropyl) disulphide or by debenzylation of S-benzyl-2-hydroxy-4-mercapto-3,3-dimethyl butyric acid, the latter being prepared by condensation of pantolactone with sodium benzylmercaptide in dimethylformamide.

The effect of structural variations on properties of pantothenic acid derivatives has been object of numerous investigations [1-10].

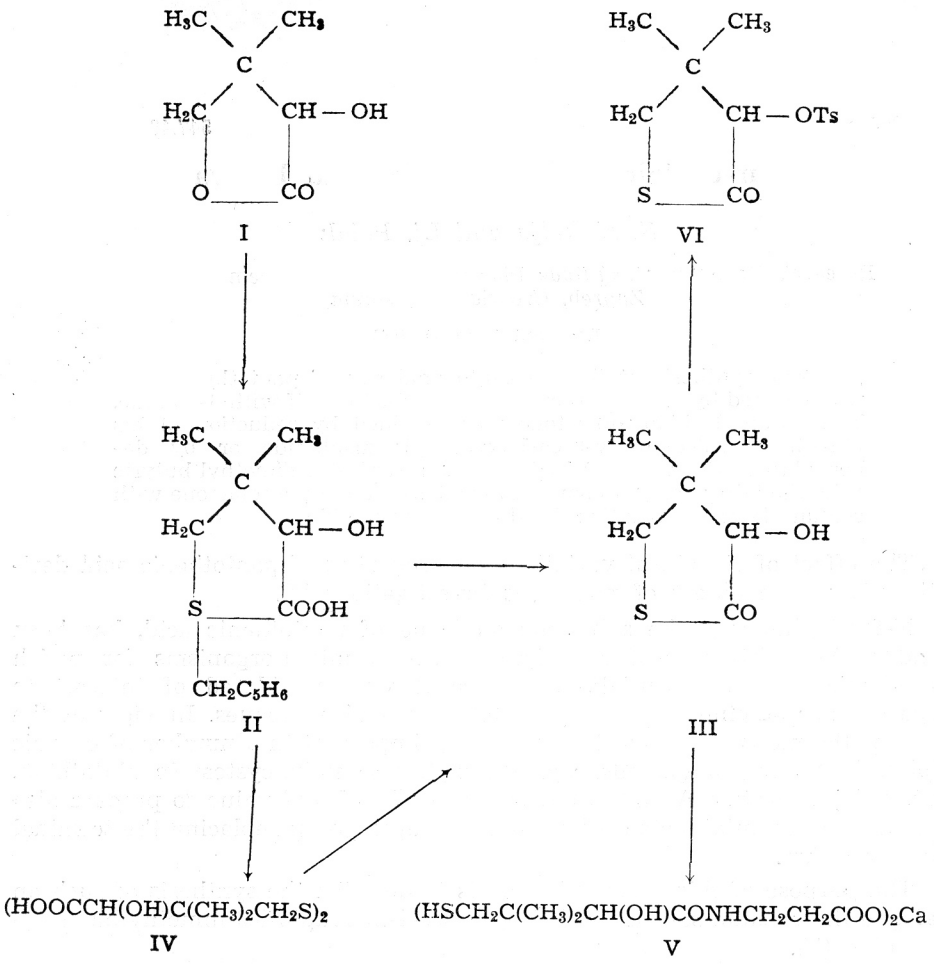
N-Pantoyltaurine, the sulphonic analogue of pantothenic acid, has been found to be a highly active antimetabolite in micro-organisms for which pantothenic acid is essential[2]. Therefore it was considered of interest to prepare other sulphur-containing pantothenic acid analogues. In view of the fact that the mercapto group is functionally important in a number of organic sulphur-containing compounds, *e. g.* cystein, homocystein, cysteamin, glutathion, pantethein, coenzyme A and other, it appeared to be of value to prepare also an analogue of pantothenic acid, with a mercapto group replacing the terminal hydroxy group.

The purpose of this communication is to describe the synthesis of such an analogue the calcium salt of DL-*N*-(2-hydroxy-4-mercapto-3,3-dimethylbutyryl)-β-alanine (V).

The required starting material *S*-benzyl-2-hydroxy-4-mercapto-3,3-dimethylbutyric acid (II), was prepared by condensation of pantolactone I with sodium benzylmercaptide in dimethylformamide. It could be isolated as a pale yellow oil. For identification purpose, the methyl ester of II was prepared.

Compound II was debenzylated with sodium in liquid ammonia and subsequently treated with hydrochloric acid to give thiopantolactone III. The latter compound was also obtained from bis (2,2-dimethyl-3-hydroxy-3-carboxypropyl) disulphide (IV), which was prepared from II by reduction with sodium in liquid ammonia followed by oxidation. Since the thiopantolactone III was an oil, it was characterized by reaction with tosyl chloride in pyridine to give the crystalline O-tosyl derivate VI.

Condensation of thiopantolactone III with β-alanine in the presence of diethyl amine in methanol according to the procedure reported by E. H. Wilson *et al.*[11] yielded the ω-mercapto analogue of pantothenic acid, which by addition of calcium oxide afforded the calcium salt V. This salt is markedly hygroscopic under atmospheric conditions.



EXPERIMENTAL

All melting and boiling points are uncorrected.

S-*Benzyl-2-hydroxy-4-mercapto-3,3-dimethylbutyric acid* (II)

To 200 ml. of absolute methanol was added 24.15 g. (1.05 mole) of sodium. When all of the sodium had reacted 130 g. (1.05 mole) of benzylmercaptane was added and the excess of methanol removed under reduced pressure. To the remaining sodium benzylmercaptide was added 80 ml. of dry benzene, the solvent evaporated and the solution of 130 g. (1 mole) of pantolactone in 500 ml. of dimethylformamide added to the powdered salt. The mixture was heated in an oil bath at 130—135° for 4 hours and allowed to stand at room temperature overnight. Next morning the solvent was distilled off under reduced pressure. The resulting oily product was dissolved in 300 ml. of water, the solution extracted with ether and the ethereal extract discarded. The aqueous solution was acidified with 100 ml. of concentrated hydrochloric acid, the oily product dissolved in ether, the layers separated and the aqueous layer extracted twice with 100 ml. of ether. After drying and distilling off the solvent a pale yellow viscous oil remained. The yield of crude product was 195 g. (76%). The analytical sample was distilled at 148—153° at 4.5×10^{-3} mm.

Anal. $C_{13}H_{18}O_3S$ (254.27) calc'd.: C 61.40; H 7.14%
found : C 61.14; H 6.85%

Methyl S-benzyl-2-hydroxy-4-mercapto-3,3-dimethylbutyrate

An ethereal solution of diazomethane prepared from 10 g. of nitrosomethylurea was gradually added to a solution of 5.08 g. (0.02 mole) of II in 20 ml. of ether while strirring and cooling. After standing for one hour the solvent and excess of diazomethane were evaporated under reduced pressure. The oily residue was dissolved in 30 ml. of ether, the solution washed twice with 10% sodium hydroxide solution, then with water and dried with anhyd. sodium sulphate. After removing the solvent the oily product (5 g.) distilled at 145—148°/0.7 mm.

Anal. $C_{14}H_{20}O_3S$ (268.30) calc'd.: C 62.67; H 7.56%
found : C 62.68; H 7.27%

Bis (2,2-dimethyl-3-hydroxy-3-carboxypropyl) disulphide (IV)

A solution of 19 g. (0.075 mole) of S-benzyl-2-hydroxy-4-mercapto-3,3-dimethylbutyric acid in 20 ml. of ether was added to about 50 ml. of liquid ammonia. The mixture was stirred and sodium added in small portions until the blue colour finally persisted for at least 10 minutes. The excess of sodium was decomposed by addition of a few crystals of ammonium chloride. The ammonia was evaporated from the open flask at room temperature overnight. The residue was dissolved in 100 ml. of water, the solution extracted twice with 50 ml. of ether and the ether extract discarded. The aqueous solution was acidified with 25 ml. of concentrated hydrochloric acid, extracted with five 50 ml. portions of ether, the ethereal extracts washed with water and dried over anhyd. sodium sulphate. When the solvent was evaporated, the viscous residue solidified upon standing; yield 10.5 g. (87%), m.p. 100—102°. Recrystallization from benzene gave pure disulphide melting at 105—106°.

Anal. $C_{12}H_{22}O_6S_2$ (326.20) calc'd.: C 44.17; H 6.80%
found : C 44.38; H 7.09%

2-Hydroxy-3,3-dimethylbutyrothiolactone (III)

A. From II. — S-Benzyl-2-hydroxy-4-mercapto-3,3-dimethylbutyric acid (50.8 g., 0.2 mole) was reduced with sodium in about 400 ml. of liquid ammonia as described previously. After removing the ammonia by evaporation, the flask was flushed out several times with pure nitrogen, 400 ml. of concentrated hydrochloric acid was added and the mixture heated during 50 minutes on a steam bath. After standing overnight the solution was extracted with five 90 ml. portions of ether, the extracts washed and dried over anhyd. sodium sulphate. The solvent was removed under reduced pressure and the oily residue (20 g., 68%) distilled at 110°/14 mm.

Anal. $C_6H_{10}O_2S$ (146.14) calc'd.: C 49.31; H 6.90%
found : C 49.58; H 6.81%

B. From IV. — Compound III was also prepared from 3.26 g. (0.01 mole) bis (2,2-dimethyl-3-hydroxy-3-carboxypropyl) disulphide as described previously under A. The yield of crude product was 2.6 g. (80%), b.p. 110°/14 mm.

O-p-Toluensulphonyl-2-hydroxy-3,3-dimethylbutyrothiolactone (VI)

Thiopantolactone (3 g., 0.02 mole) was tosylated following the procedure described by J. Barnett *et al.*[7]. There was obtained 5.5 g. of a crude product melting at 67—68°. After crystallization from 5 ml. of methanol 4.8 g. (80%) of colourless needles were obtained, m.p. 76—78°. A sample for analysis was recrystallized from the same solvent, m.p. 77—78°.

Anal. $C_{16}H_{16}O_4S_2$ (300.26) calc'd.: C 52.00; H 5.37%
found : C 52.28; H 5.32%

Calcium salt of N-(2-hydroxy-4-mercapto-3,3-dimethylbutyryl)-β-alanine (V)

A mixture of 7.3 g. (0.05 mole) of thiopantolactone III, 4.5 g. (0.05 mole) of β-alanine, 12.5 ml. of absolute methanol and 6.25 ml. (0.06 mole) of diethylamine

was placed in a 100 ml. three-necked flask equipped with a mechanical strirrer, thermometer and a reflux condeser. The mixture was refluxed while stirring for eight hours under an atmosphere of nitrogen. The excess of diethylamine and the methanol were distilled off at atmospheric pressure until the internal temperature reached 92°. The residue was held at 80—90° for 30 minutes, and then dissolved in 15 ml. of absolute methanol, cooled to room temperature and 1.55 g. (0.027 mole) of calcium oxide was added. The mixture was stirred at 30—35° during 3 hours and the solution freed by filtration of a small amount of brown coloured precipitate. The filtrate was evaporated to dryness under reduced pressure and the residue dissolved in 50 ml. of absolute methanol. This solution was added dropwise with vigorous stirring to 400 ml. of dry acetone, the precipitated product filtered off and dried *in vacuo*. The colourless micro-crystalline powder of calcium thiopantothenate weighted 7.3 g. (60%).

Anal. $C_{18}H_{32}O_8N_2S_2Ca$ (508.66) calc'd.: C.42.50; H 6.34%
found : C 42.54; H 6.11%

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IZVOD

Spojevi pantotenske kiseline koji sadrže sumpor

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Kondenzacijom tiopantolaktona (III) sa β-alaninom pripravljen je merkapto analog pantotenske kiseline. Tiopantolakton III pripravljen je redukcijom bis (2,2-dimetil-3-hidroksi-3-karboksipropil) disulfida, ili debenzilacijom S-benzil-2--hidroksi-4-merkapto-3,3-dimetil maslačne kiseline, koja je pripravljena iz pantolaktona sa natrijevim benzilmerkaptidom u dimetilformamidu.

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