Tetrahedron Letters No. 33, pp.3077-3079, 1971. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF 2-BENZAMIDO-2-MERCAPTOPROPANOIC ACID

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(Received in UK 28 June 1971; accepted in UK for publication 14 July 1971)

The epidithiopiperazine dione ring system (I) is common to a small group of fungal metabolites which are among the most virulent of poisons. The structures of sporidesmin[2], gliotoxin[2], aranotin[3], and chaetocin[4] are known and several less well characterized substances may also belong to this group[2]. Three syntheses of compounds containing the epidithiopiperazinedione ring have been reported[5-7], each proceeding via the addition of sulphur substituents to a symmetrical piperazinedione derived from two N-substituted glycine units. As part of an alternative approach to this ring system, we wish to report the synthesis of the title compound, in which the central carbon also bears a methyl substituent.

The oxazolinone (II), derived from alanine, was treated with sulphuryl chloride in 1,2-dichloroethane to give the chloro-oxazolinone (III) which was not isolated but whose identity was inferred from infrared and p.m.r. spectra. Reaction of the crude chloro compound with excess thiolacetic acid gave 4-acetylthio-4-methyl-2-phenyl-2-oxazolin-5-one (IV)[8] (75%), m.p. 116.5 - 118°. The structure was confirmed by infrared (1810, 1697 cm^{-1}) and p.m.r. spectra (five aromatic protons, methyl singlets at 1.72 and 2.27 p.p.m.). The oxazolinone (IV) formed a solid hydrochloride when treated with dry HCl in ether, and this hydrochloride was hydrolysed to the carboxylic acid (V)[8] in quantitative yield. Transesterification, to remove the S-acetyl group, was effected with aqueous methanolic HCl and the mercapto-acid (VI)[8] crystallized from chloroform as a colourless powder with m.p. 146-147° (69% yield). Protection from atmospheric oxygen was unnecessary and the mercapto-acid was quite stable to cold aqueous HCl. The structure of the 2-benzamido-2-mercaptopropanoic acid (VI) was confirmed by infrared (3300, 2600, 1725 cm^{-1}) and p.m.r. spectra (1.88 (Me), 3.8 (SH) slowly removed by D_2O, 7.4 - 8.1 p.p.m. (6 protons, one of which is slowly removed by D_2O exchange)). The methyl ester of acid (V), formed with diazomethane, was deacetylated in similar fashion to give a 75% yield of the mercapto-ester (VII)[8]. This substance was also formed in modest yield by direct reaction of the oxazolinone (IV) with methanolic HCl.

The mercapto-acid (VI) was oxidized with $FeCl_3$ in ether to a mixture of dl- and meso-forms of 2,2'-dibenzamido-2,2'-dithiodipropanoic acid (VIII)[8] which travelled as two spots in thin layer chromatography. Methylation of this mixture with diazomethane, or oxidation of the methyl ester (VII), gave the mixture of esters (IX)[8] which could be separated into two components by preparative thin layer chromatography on silica gel, eluting with chloroform. A positive identification has not been made, but the following p.m.r. data are pertinent (less mobile, more mobile): C-Me, 2.03, 2.01; O-Me, 3.81, 3.96; N-H, 7.0-7.9 (under aromatics), 8.5 p.p.m.

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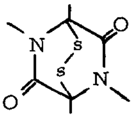
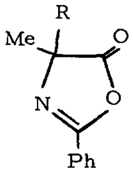
8. The formula was established either by acceptable microanalytical data or by determination of the accurate mass of the parent ion in the mass spectrometer.



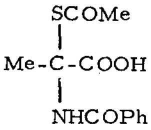
I



II : R = H

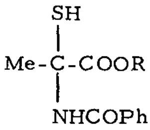
III : R = Cl

IV : R = SCOMe



$\mathrm{Me{-}}\overset{\mathrm{SCOMe}}{\underset{\mathrm{NHCOPh}}{\mathrm{C}}}\mathrm{{-}COOH}$

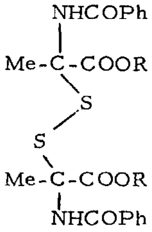
V



$\mathrm{Me{-}}\overset{\mathrm{SH}}{\underset{\mathrm{NHCOPh}}{\mathrm{C}}}\mathrm{{-}COOR}$

VI : R = H

VII : R = Me



VIII : R = H

IX : R = Me