Tetrahedron Vol. 35, pp. 1315 to 1316
© Pergamon Press Ltd., 1979. Printed in Great Britain

0040-4020/79/0515-1315/\$02.00/0

A SYNTHESIS OF α-AMINOSULPHONIC ACIDS

SUCHATA JINACHITRA† and A. J. MACLEOD*
Department of Chemistry, Queen Elizabeth College, University of London, Campden Hill Road, London W8 7AH, England

(*Received in UK* 18 *October* 1978)

Abstract—The α-aminosulphonic acid analogues of cysteine and methionine were prepared by sulphonation of the appropriate amines at their α-C atom using Sulfan. It is essential that moisture is excluded at all stages.

The sulphonic acid analogues of cysteine and methionine were prepared as potential antitumour agents. Some activity has been described for a number of cysteine[1–5] and methionine[6] derivatives, and the possibility of unnatural α-aminosulphonic acids behaving as antimetabolites for the natural aminocarboxylic acid analogues has long been recognized.[7] Although many such α-aminosulphonic acids have been prepared (and tested for biological activity), those of the natural sulphur-containing amino acids described here have not.

Aromatic sulphonic acids have been more widely studied than the aliphatic series, and many methods of preparation have been adequately reviewed.[8,9] The aliphatic acids have usually been obtained by oxidation of thiols.[10] With regard specifically to the α-aminosulphonic acids, again the aromatic series is well known but although aliphatic examples were quoted as long ago as 1899,[11] they have not been greatly studied since then. Their general method of preparation was developed by McIlwain in 1942[12] and simply involves reaction between ammonia and the bisulphite addition compound of the appropriate aldehyde (that is, a hydroxysulphonate). Many aliphatic α-aminosulphonic acids and derivatives have been prepared by this basic procedure,[13] and although slight modifications have been suggested[14,15] it remains the standard preparative method for these compounds. However, in this project all attempts to convert the readily prepared bisulphite addition compound of 3-(methylthio)propanal into the α-aminosulphonic acid analogue of methionine failed, either using the basic method or any of its modifications. In validation of the method we were nevertheless able to obtain without difficulty good yields of 2-aminobutane-1-sulphonic acid from butanal.

Other reported methods of preparation of aliphatic sulphonic acids also failed, including attempts to oxidise α-aminothiols. A procedure beginning with methionine itself was also unsuccessful. However, sulphonation of the appropriate amine at the α-C atom in a one step reaction did provide the required product. This method is a new approach to the synthesis of α-aminosulphonic acids. In this way 1-amino-3-(methylthio)propane was converted into the sulphonic acid analogue of methionine and 1-amino-2-(methylthio)ethane into the corresponding analogue of cysteine. Initially the sulphonating agent employed was fuming sulphuric acid in the form of oleum containing 65% sulphur trioxide, and dry chloroform was used as solvent. The reaction had to be carried out at low temperature and freshly distilled amine and solvent were necessary for success, as well as a dry inert atmosphere throughout reaction and work-up. Ultimately a superior sulphonating agent for this reaction was discovered, namely Sulfan (Hardmen & Holden Ltd.) which is the γ-form of sulphur trioxide stabilized by the addition of a small amount of high b.p. materials. Moisture is a strong catalyst for Sulfan polymerization and thus the reagent and reaction system must be kept completely dry at all times. Sulfan is best used as a vapour so the stabilizer remains behind as a liquid residue. The most satisfactory method for reaction was to liberate the sulphonating agent by passing a stream of dry nitrogen over the surface of Sulfan heated to 30–32° (equilibrium m.p. of the straight chain β-polymer of sulphur trioxide is 32.5°) in a vaporizer flask which had an outlet connected to the reaction flask in which was contained the appropriate freshly distilled amine dissolved in dry ether.

Spectral and analytical data presented here confirm the assigned structures of the two sulphonic acids. The IR spectra of both show strong bands in the region of 3400 and at 1620 cm^{-1} due to N–H stretching and bending respectively; the sulphonic acid absorption is recognised as broad bands at 1150 and 1060 cm^{-1} for the cysteine analogue and at 1200 and 1085 cm^{-1} for the methionine analogue. In the mass spectrometer both compounds undergo very ready α-cleavage with the elimination of SO_3 such that molecular ion peaks are not observed and the spectra are effectively those of the corresponding amines; all features can be explained on this basis and metastable ion peaks are observed for main fragmentations. Accurate mass measurements on the amine parent ion peaks at m/e 105 and 91 for the two compounds confirmed their atomic composition. In the case of the methionine analogue, a small peak was observed in the spectrum at m/e 137 and accurate mass measurement showed this to correspond to $C_3H_7NO_3S$ due to the elimination of methanethiol from the molecular ion. This peak therefore confirms the presence of the retained sulphonic acid group in the molecule, and it would not be unexpected for the corresponding fragment ion for the lower homologue to be too unstable for detection.

The only doubt concerning the structures could arise from the position of the sulphonic acid group within the molecules, but ^1H NMR spectroscopy shows the compounds to be α-aminosulphonic acids and not the corresponding β-amino derivatives. Against the latter structure for the methionine analogue is the absence of two doublets due to two methylene groups and a quintet due to a methine group in the NMR spectrum, and although similar splittings might be expected in the case of the two cysteine sulphonic acid possibilities, integration values rule against the β-amino structure. Similar reasoning

---

†Present address: Department of Chemistry, Chulalongkorn University, Bangkok, Thailand.

precludes the γ-amino derivative as a possibility for the methionine analogue.

EXPERIMENTAL

IR spectra were recorded on a Pye-Unicam SP 200 instrument; ^{1}H NMR spectra on a Perkin–Elmer R 10 operating at 60 MHz; and mass spectra on an AE1 MS 902 operating at 70 eV. Microanalyses were performed by the Alfred Bernhardt Laboratory, Germany. All m.ps. are uncorrected.

1-*Chloro*-2-(*methylthio*)*ethane*. Prepared in 80% yield from 2-(methylthio)ethanol as described in Organic Syntheses,[16] b.p. 55–6°/30 mm (lit.[16] b.p. 55°/30 mm).

N-2-(*methylthio*)*ethylphthalimide*. 1-Chloro-2-(methylthio)ethane (50 g, 0.45 mol) and potassium phthalimide (84 g, 0.455 mol) in 1 l DMF were refluxed 1.5 hr with stirring, $CHCl_3$(100 ml) was added to the cooled soln and it was then poured into water. The aqueous layer was extracted with 3 × 50 ml $CHCl_3$. The solvent was removed from the combined dried $CHCl_3$ extracts and the residue was recrystallized (EtOH) to give 63.7 g (64%) of the colourless crystalline product, m.p. 89° (lit.[17] m.p. 88°).

1-*Amino*-2-(*methylthio*)*ethane*. N-2-(methylthio)ethylphthalimide (63 g, 0.285 mol) was refluxed 17 hr with 50% KOH aq (800 ml). The mixture was cooled, extracted with diethyl ether and the extract dried over KOH pellets. The ether was removed and the residue distilled to give 18 g (69%) of the required product as a colourless liquid, b.p. 48–50°/25 mm (lit.[18] b.p. 145–147°/760 mm); IR (Nujol) 3380, 1595, 1390, 1325 cm^{-1}. (Found: C, 39.36; H, 9.96; N, 15.57; S, 35.27. Calc. for C_3H_9NS: C, 39.56; H, 9.89; N, 15.38; S, 35.16%).

1-*Amino*-2-(*methylthio*)*ethane*-1-*sulphonic acid*. 1-Amino-2-(methylthio)ethane (0.5 g, 0.0055 mol) in dry diethyl ether (10 ml) was placed in a 2-necked reaction flask equipped with inlet gas tube and outlet protected by a drying tube. The soln was stirred magnetically. An excess of approx 1 ml Sulfan (stabilized liquid SO_3, Hardman and Holden, Ltd., Colles Hill, Manchester) was placed in a 3-necked vaporiser flask equipped with stirrer and connected to the reaction flask. A flow of dry N_2 through the vaporiser flask was commenced immediately, and the Sulfan was then warmed over a small flame to a temp. of 30–32°.

As sulphonation proceeded a white ppt was formed in the flask. When the solid just began to deposit on the glass wall, the gas line was disconnected and the flask was stoppered. The mixture was stirred for a further 5 min under N_2 to complete reaction, and then the product was filtered at the pump in a dry box under dry N_2. It was washed several times with dry ether, allowed to dry, and stored carefully under N_2 in a sealed tube due to its hygroscopic nature. The product was thus obtained in 48% yield (0.45 g) as a white crystalline solid, m.p. 63–4°; IR (Nujol) 3450, 2900, 2100, 1620, 1560, 1390, 1325, 1150, 1060 cm^{-1}; ^{1}H NMR (TFA) δ 4.4 (quart, 1 H), 2.95 (d, 2 H), 2.2 (s, 3 H); mass spectrum 91(69), 74(2), 61(21), 47(17), 44(12), 30(100), 28(30). (Found: C, 21.26; H, 5.43; N, 8.28; S, 37.25. Calc. for $C_3H_9NO_3S_2$: C, 21.05; H, 5.26; N, 8.19; S, 37.43%).

1-*Amino*-3-(*methylthio*)*propane*-1-*sulphonic acid*. This was prepared exactly as the lower homologue above from 1-amino-3-(methylthio)propane (0.5 g, 0.0048 mol) and Sulfan (~1 ml), and was thus obtained in 71% yield (0.63 g) as a white crystalline hygroscopic solid, m.p. 48°; IR (Nujol) 3400, 2900, 2080, 1620, 1545, 1385, 1330, 1200, 1085 cm^{-1}; ^{1}H NMR (TFA) δ 4.4 (quart, 1 H), 3.45 (t, 2 H), 2.75 (quart, 2 H), 2.2 (s, 3H); mass spectrum, 137(1), 105(50), 88(85), 75(8), 74(33), 61(55), 57(60), 47(28), 44(13), 41(12), 30(100), 28(30). (Found: C, 25.75; H, 6.06; N, 7.54; S, 34.53. Calc. for $C_4H_{11}NO_3S_2$: C, 25.95; H, 5.95; N, 7.57; S, 34.59%).

Acknowledgement—We are grateful to the Cancer Research Campaign for a grant supporting this project.

REFERENCES

[1] T. A. Martin, J. R. Corrigan and C. W. Waller, *J. Org. Chem.* **30**, 2839 (1965).

[2] T. A. Martin, D. H. Causey and J. R. Corrigan, *J. Med. Chem.* **11**, 625 (1968).

[3] W. A. Zygmunt and T. A. Martin, *Ibid.* **11**, 623 (1968).

[4] R. H. Adamson, *Nature* **217**, 751 (1968).

[5] Kwang-Yuen, Zee-Cheng and C. C. Cheng, *J. Med. Chem.* **13**, 414 (1970).

[6] R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole and J. R. Vaughan, Jr., *J. Am. Chem. Soc.* **67**, 290 (1945).

[7] H. McIlwain, *Br. J. Exptl Path.* **22**, 148 (1941).

[8] E. E. Gilbert, *Synthesis* **1**, 3 (1969).

[9] S. R. Sandler and W. Karo, *Organic Functional Group Preparations*, p. 506. Academic Press, New York (1968).

[10] W. G. Filby, R. D. Penzhorn and K. Gunther, *J. Org. Chem.* **38**, 4070 (1973).

[11] R. A. Worstall, *J. Am. Chem. Soc.* **21**, 246 (1899).

[12] H. McIlwain, *J. Chem. Soc.* 75 (1941).

[13] L. Neelakantan and W. H. Hartung, *J. Org. Chem.* **24**, 1943 (1959).

[14] M. Frankel and P. Moses, *Tetrahedron* **9**, 289 (1960).

[15] J. Hennes and L. Jackson, *U.S. Pat. No.* 3009950 (Nov. 1961).

[16] W. R. Kirner and W. Windus, *Organic Syntheses* Col. Vol. II, p. 136.

[17] P. Karrer, E. Scheitlin and H. Siegrist, *Helv. Chim. Acta* **53**, 1237 (1950).

[18] H. M. Woodburn and B. G. Pautler, *J. Org. Chem.* **19**, 863 (1954).