NOTE

Synthesis of Isotopically Labelled 1,1'-Thiobis(2-chloroethane) and Some Related Compounds.

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SUMMARY

1,1'-Thiobis(2-hydroxyethane) has been synthesised isotopically labelled with sulphur-35, carbon-13 and deuterium. The conversion to 1,1'-thiobis(2-chloroethane) labelled with sulphur-35 and carbon-13 is described.

Keywords: 1,1'-Thiobis(2-hydroxyethane), 1,1'-Thiobis(2-chloroethane), sulphur-35, carbon-13, deuterium, synthesis.

1,1'-Thiobis(2-chloroethane) (3, mustard) is a potent vesicant and biological alkylating agent. 1,1'-Thiobis(2-hydroxyethane) (2, thiodiglycol) is the simple hydrolysis product and a putative metabolite of 3. To facilitate metabolic studies on these compounds, sulphur-35 and carbon-13 labelled forms were synthesised. In addition, to allow the formulation of satisfactory analytical protocols, deuterium labelled thiodiglycol(2) was required together with it's sulphoxide derivative (5).

The synthetic routes used to give this series of isotopically labelled compounds are shown in the Scheme. For compounds radiolabelled with sulphur-35, sodium[^{35}S]sulphide was used as the source of the radioisotope. Stable isotope labelling with carbon-13

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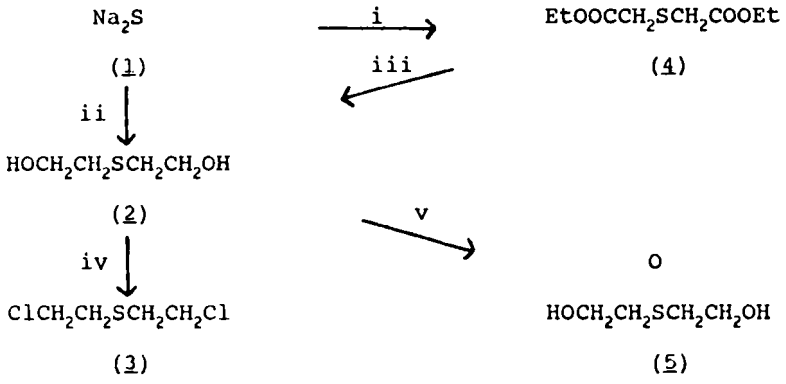
and deuterium utilised bromo[$^{13}C_2$]acetate and lithium aluminium deuteride respectively as sources of the label.



Reagents: i $BrCH_2COOEt$; ii $ClCH_2CH_2OH$; iii $LiAlH_4$; iv $SOCl_2$; v H_2O_2.

SCHEME

The synthesis of mustard(3) radiolabelled with carbon-14 has been reported previously (1). However, the use of sodium [^{35}S]sulphide at high specific activities made possible a simple synthesis of 3 using experimentally convenient procedures. Thus, the condensation of sodium[^{35}S]sulphide with 2-chloroethanol in aqueous solution at 100^0 gave after column chromatography, [^{35}S]-thiodiglycol(2) in 75% yield. Treatment of this material with thionyl chloride in dichloromethane solution gave [^{35}S]-mustard(3) in essentially quantitative yield.

For the synthesis of carbon-13 labelled (3), the use of sodium sulphide with ethyl bromo[$^{13}C_2$]acetate gave the [$^{13}C_4$]-diester(4) which on reduction with lithium aluminium hydride gave [$^{13}C_4$]-thiodiglycol(2) in 78% yield. Again, conversion to the [$^{13}C_4$]-mustard analogue(3) was quantitative. In a similar fashion, reduction of the diester(4), prepared from unlabelled starting materials, with lithium aluminium deuteride provided a convenient route to [D_4]-thiodiglycol(2) and on treatment with hydrogen peroxide, the [D_4]-sulphoxide(5).

EXPERIMENTAL.

CAUTION. 1,1'-Thiobis(2-chloroethane) (mustard, 3) is a potent vesicant and carcinogen and should be handled only by suitably qualified individuals in a well ventilated fume cupboard.

General Procedures. T.l.c. was performed by upward irrigation of microscope slides coated with Merck silica gel 60 G and column chromatography with Merck silica gel, particle size 0.063-0.200 mm, in the same solvent as used for t.l.c. The plates were developed with iodine vapour. H.p.l.c. was carried out using a Gilson system (Anachem) controlled by an IBM PS\2 computer using Gilson 715 HPLC System Controller Software (Version 1.0). A Packard Trace II 7150 Radioactivity Monitor fitted with a heterogeneous flow cell assembly was used for in-line radiochemical detection. The identity of radiolabelled compounds was inferred by full spectroscopic analysis (n.m.r., i.r. and m.s.) of products obtained under comparable experimental conditions using unlabelled reactants and were homogeneous by t.l.c., h.p.l.c. and g.c analysis. N.m.r. spectra were obtained on a Jeol GSX 400 instrument in deuteriochloroform solution and mass spectra on a VG Micromass 7070 spectrometer. Sodiu m[^{35}S]sulphide was obtained from Amersham International p.l.c. Ethyl bromo[$^{13}C_2$]acetate and lithium aluminium deuteride were purchased from Aldrich Chemical Company Ltd.

1,1'-[^{35}S]-Thiobis(2-hydroxyethane)(2). 2-chloroethanol (161 mg., 2 mmol) in water (1.0 ml.) was added to a solution of anhydrous sodium[^{35}S]sulphide (36 mg., 0.46 mmol, 10mCi) and "cold" sodium sulphide nonahydrate (130 mg., 0.54 mmol) in water (2.0 ml.). The solution was heated at 100^0 for 1h. and then evaporated to dryness under reduced pressure. The residue (salt plus product) was chromatographed over silica eluting with benzene-ether-ethanol,

9:1:1, to give [^{35}S]-(2) as a colourless oil (90 mg., 74%), homogeneous by h.p.l.c. analysis (with respect to both uv and radiochemical detectors) using a Dynamax phenyl bonded-phase column (4.6 mm. i.d. x 25 cm.) eluted with water only at a flow rate of 1.0 ml./min. The retention time was 10.05 min. The specific activity was 10.4 mCi/mmol.

1,1'-[^{35}S]-Thiobis(2-chloroethane)(3). A solution of [^{35}S]-thiodiglycol(2), (90 mg., 0.73 mmol) in dichloromethane (4 ml.) was treated with thionyl chloride (0.3 ml.). The mixture was allowed to stand at room temperature for 1h. and then evaporated to dryness. The residue was distilled " bulb-to-bulb" in a Kuglrohr apparatus under reduced pressure to give [^{35}S]-(3) as a colourless oil (116 mg. 99%). The sample was homogeneous by g.c. analysis (15M. x 0.313 mm. i.d. fused silica column coated with 1μm DB-1 at 300^0, f.i.d. detector) and h.p.l.c. analysis (Dynamax C-18 bonded-phase column, 4.6 mm. x 25 cm. eluted with acetonitrile-water, 70:30 at a flow rate of 1.0 ml./min. using both uv and radiochemical detectors. The retention time was 6.1 min.).

Diethyl 2,2'-thiobis[$^{13}C_4$]acetate(4). Ethyl bromo[$^{13}C_2$]acetate (1.0 g., 5.9 mmol) was added to a solution of sodium sulphide nonahydrate (0.72 g., 3.0 mmol) and the mixture stirred and boiled under reflux for 1h. The mixture was cooled, filtered (to remove solid sodium bromide) and evaporated under reduced pressure. Chromatography of the residue over silica with petrol-ethyl acetate, 9:1 gave [$^{13}C_4$]-(4) as a colourless homogeneous oil (0.47 g., 75%). δ_H 1.30(6H, t, $^3J_{HH}$=7.0 Hz., $OCH_2\underline{CH}_3$), 3.40(4H, m, $^1J_{CH}$=141, $^2J_{CH}$=5.5 and $^3J_{CH}$=5.0 Hz, $S\underline{CH}_2$) and 4.2(4H, q of d, $^3J_{HH}$=7.0 and $^3J_{CH}$=3.0 Hz, $O\underline{CH}_2CH_3$). δ_C 14.1($CH_2\underline{CH}_3$), 33.6(d, $^1J_{CC}$=62 Hz., $S\underline{CH}_2$) and 169.8(d, $^1J_{CC}$=62 Hz.,C=O).

1,1'-Thiobis(2-hydroxy[$^{13}C_4$]ethane)(2). A solution of [$^{13}C_4$]-(4) (178 mg., 0.86 mmol) in anhydrous ether (5 ml.) was added to a stirred suspension of lithium aluminium hydride (100 mg., 2.7 mmol) in anhydrous ether (5 ml.). The reaction mixture was stirred at room temperature for 1h. when the excess lithium aluminium hydride was destroyed by the cautious addition of a small amount of water. Anhydrous magnesium sulphate was added to the mixture which was filtered. The inorganic solids were washed with further portions of ether. The combined organic extracts were concentrated and the residue chromatographed over silica with chloroform-methanol, 19:1, to afford [$^{13}C_4$]-(2) as a homogeneous colourless oil (82 mg., 78%). δ_H 2.75(4H, m, $^1J_{CH}$=138, $^2J_{CH}$=4.5, $^3J_{HH}$=5.9 and $^3J_{CH}$=2.9 Hz., C$\underline{H}_2$S), 2.85(2H, s, CH$_2$O$\underline{H}$) and 3.75(4H, d of t, $^1J_{CH}$=144, $^3J_{HH}$=5.9 and $^2J_{CH}$=1.8 Hz., C$\underline{H}_2$OH). δ_C 35.14(d, $^1J_{CC}$=39 Hz., $\underline{C}H_2$S) and 61.32(d, $^1J_{CC}$=39 Hz., $\underline{C}H_2$OH).

1,1'-Thiobis(2-chloro[$^{13}C_4$]ethane)(3). As described above, [$^{13}C_4$]-thiodiglycol(2) (70 mg., 0.55 mmol) in dichloromethane (3 ml.) with thionyl chloride (0.25 ml.) gave [$^{13}C_4$]-(3) (95 mg., 100%) as a colourless homogeneous oil. δ_H 2.99(4H, m, $^1J_{CH}$=142, $^3J_{HH}$=8.0, $^2J_{CH}$=4.5 and $^3J_{CH}$=3 Hz., C$\underline{H}_2$S) and 3.65(4H, t of d, $^1J_{CH}$=152, $^3J_{HH}$=8.0 and $^2J_{CH}$=3.9 Hz., C$\underline{H}_2$Cl). δ_C 34.68(m ,$^1J_{CH}$=142, $^1J_{CC}$=38 and $^2J_{CH}$=3.9 Hz.,$\underline{C}H_2$S) and 43.2(t of d, $^1J_{CH}$=152,$^1J_{CC}$=38 and $^2J_{CH}$=4.5 Hz., $\underline{C}H_2$Cl).

1,1'-Thiobis(2-hydroxy[2,2-D_2]ethane)(2). As above, reduction of unlabelled diester(4) (1.8 g.,8.7 mmol) in dry ether (25 ml.) with lithium aluminium deuteride (1.0 g., 27 mmol) in dry ether (25 ml.) gave tetradeuterio-(2) (0.85 g., 71%) as a colourless oil. δ_H 2.7(s , SC$\underline{H}_2$) and 3.6(s, CH$_2$O$\underline{H}$) δ_C 34.8(s, $\underline{C}H_2$S) and 60.4(q, $^1J_{CD}$=22 Hz.,$\underline{C}D_2$OH). δ_D 3.7(s, CD$_2$OH).

1,1'-Sulphinylbis[2-hydroxy[2,2-D_2]ethane](5). A solution of tetradeuterio-(2) (126 mg., 1.0 mmol) in water (2 ml.) was treated with hydrogen peroxide (60% solution, 0.1 ml.). The mixture was kept at room temperature and the course of the reaction monitored by h.p.l.c. (Dynamax phenyl bonded-phase column eluting with water) until no starting material was present (ca. 1.5 h.). The water was removed under reduced pressure and the white residue recrystallised from a small volume of isopropanol to afford the tetradeuterio-sulphoxide(5) as a white solid (101 mg., 71%), m.p. 113°. δ_H 3.07 and 3.14(ABq, $^2J_{HH}$=13.8 Hz.,C$\underline{H}_2$). δ_C 56.59(t,$^1J_{CH}$=139.8 Hz.,C$\underline{H}_2$) and 56.78(quintet of d.,$^1J_{CD}$=22.4 and $^2J_{CH}$=6.4 Hz.,$\underline{C}D_2$). δ_D 3.97(s, C$\underline{D}_2$). (Spectra were determined in D_2O solution).

REFERENCES.

1. Ott D.G., Reisfeld M.J. and Whaley T.W., Synth. Appl. Isot. Labelled Comp., Proc. 2nd Int. Symp., 1985, R.R. Muccino (Ed), Pub., Elsevier, Amsterdam, 1986, 409-414.