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Thermal behaviour of benzyloxycarbonyl derivatives of 2-aminoethanethiol

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Abstract

Novel benzyloxycarbonyl derivatives of 2-aminoethanethiol ($H_2NCH_2CH_2SH$, **1**) have been prepared and characterised, and their thermal behaviour studied by thermogravimetry, differential thermogravimetry and differential scanning calorimetry.

Thermal data indicate that compounds of the type $C_6H_5CH_2OC{=}OS(CH_2)_2NH_3^+X^-$ (where X is Cl^-, Br^- or I^-) melt and decarboxylate to give, predominantly, the corresponding benzyl derivative $C_6H_5CH_2S(CH_2)_2NH_3^+X^-$. Related compounds of the type $C_6H_5CH_2OC{=}OS(C_2)_2NHO{=}COCH_2C_6H_5$, $[C_6H_5CH_2OC{=}ONH(CH_2)_2S\}_2$ and $C_6H_5C{=}OS(CH_2)_2NHO{=}COCH_2C_6H_5$ showed no tendency to decarboxylate.

Keywords: Aminoethanethiol; Benzyloxycarbonyl derivative; DSC; DTG; TG

1. Introduction

The benzyloxycarbonyl moiety has been widely used as a protecting group for the thiol and amino functional groups, particularly in peptide chemistry. As part of an investigation into the reaction of both functional groups in aminoalkanethiols with benzyloxycarbonyl chloride (**2**), a reference was found which indicated that the reaction of an excess of benzyloxycarbonyl chloride (**2**) with 2-aminoethanethiol hydrochloride (**3**) gave, exclusively, *S*-benzyl-2-aminoethanethiol hydrochloride (**4**) with the loss of carbon dioxide [1] (Scheme 1).

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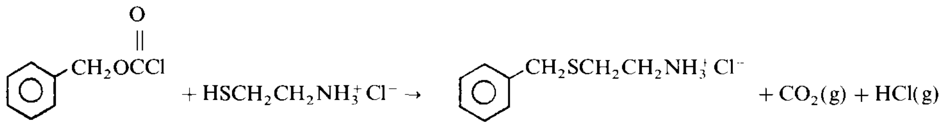
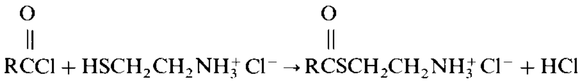


(2) (3) (4)

Scheme 1.

However, the reaction of 2-aminoethanethiol hydrochloride (**3**) with benzoyl, acetyl or octanoyl chlorides, under similar conditions, gave the expected *S*-acyl-2-aminoethanethiol hydrochlorides [2] (**5**; R = alkyl, aryl) (Scheme 2).



$$\mathrm{R\overset{\overset{O}{\|}}{C}Cl + HSCH_2CH_2NH_3^+Cl^- \rightarrow R\overset{\overset{O}{\|}}{C}SCH_2CH_2NH_3^+Cl^- + HCl}$$

(3) (5)

Scheme 2.

We report here the preparation and thermal behaviour of several benzyloxycarbonyl derivatives of 2-aminoethanethiol $H_2NCH_2CH_2SH$ (**1**).

2. Experimental

2-Aminoethanethiol hydrochloride was obtained from Robinson Brothers Limited and was used without further purification. All other reagents were obtained commercially.

2.1. Synthesis of compounds

N,S-*Dibenzyloxycarbonyl-2-aminoethanethiol (**6**)*

N,*S*-Dibenzyloxycarbonyl-2-aminoethanethiol (**6**) was prepared in a similar manner to that reported for the preparation of *N*,*S*-dibenzyloxycarbonyl cysteine [3].

2-Aminoethanethiol was generated in situ by the addition of aqueous 2 M sodium hydroxide (136 cm^3, 0.246 mol) to an aqueous solution of 2-aminoethanethiol hydrochloride (10.2 g, 0.09 mol). Benzyloxycarbonyl chloride (38.4 g, 0.225 mol) and 2 M sodium hydroxide solution (50.8 cm^3, 0.102 mol) were added concurrently to the cooled solution over 30 min. The solution was extracted with diethyl ether. Drying of the ether solution (Na_2SO_4) followed by removal of the ether and crystallisation from diethyl ether/petroleum spirit (b.p. 40–60°C) gave *N*,*S*-dibenzyloxycarbonyl-2-aminoethanethiol (**6**) (11.5 g, 37.0%, m.p. 54–55°C). The identity of the product was confirmed by elemental analysis and spectroscopic data (Table 1).

S-*Benzyloxycarbonyl-2-aminoethanethiol hydrobromide (**7**)*

N,*S*-Dibenzyloxycarbonyl-2-aminoethanethiol (**6**; 2.1 g, 0.0061 mol) was dissolved in a solution of 2 M hydrogen bromide in acetic acid (18 cm^3, 0.036 mol) [4].

Table 1
Results of elemental analysis

Compound		Analytical data found (theoretical)					
		% C		% H		% N	
$C_6H_5CH_2OC{=}OSCH_2CH_2NHC{=}OOCH_2C_6H_5$	(**6**)	62.48	(62.60)	5.59	(5.50)	4.05	(4.05)
$C_6H_5CH_2OC{=}OSCH_2CH_2NH_3^+Br^-$	(**7**)	40.87	(41.11)	4.80	(4.83)	4.84	(4.79)
$C_6H_5CH_2OC{=}OSCH_2CH_2NH_3^+Cl^-$	(**8**)	48.60	(48.48)	5.65	(5.70)	5.79	(5.65)
$C_6H_5CH_2OC{=}OSCH_2CH_2NH_3^+I^-$	(**9**)	36.03	(35.40)	4.20	(4.16)	4.17	(4.13)
$[C_6H_5CH_2OC{=}ONHCH_2CH_2S]_2$	(**10**)	Identity confirmed from Ref. [5]					
$C_6H_5C{=}OSCH_2CH_2NHC{=}OOCH_2C_6H_5$	(**11**)	64.90	(64.74)	5.74	(5.43)	4.50	(4.44)

After 25 min at room temperature the product was precipitated by the addition of diethyl ether. Crystallisation from ethanol/diethyl ether gave *S*-benzyloxycarbonyl-2-aminoethanethiol hydrobromide as a white powder (1.4 g, 77.8%, m.p. 165–166°C (decomp.)). The identity of the product was confirmed by elemental analysis and spectroscopic data (Table 1).

S-*Benzyloxycarbonyl-2-aminoethanethiol hydrochloride* (**8**)

S-Benzyloxycarbonyl-2-aminoethanethiol hydrobromide (**7**; 4 g, 0.014 mol) was dissolved in water (50 cm^3) and to it was added sodium hydrogen carbonate (2 g, 0.024 mol) dissolved in water (25 cm^3). The resultant free base (*S*-benzyloxycarbonyl-2-aminoethanethiol) was extracted into diethyl ether and the ether solution was dried (Na_2SO_4). Saturation of the ether solution with hydrogen chloride gas gave *S*-benzyloxycarbonyl-2-aminoethanethiol hydrochloride (**8**) which crystallised from ethanol as white leaflets (1.2 g, 35.4%, m.p. 176–177°C (decomp.)). The identity of the product was determined by elemental analysis and spectroscopic data (Table 1).

S-*Benzyloxycarbonyl-2-aminoethanethiol hydroiodide* (**9**)

S-Benzyloxycarbonyl-2-aminoethanethiol hydrobromide (**7**; 2 g, 0.007 mol) was dissolved in water (25 cm^3) and 47% w/v hydriodic acid (5 cm^3, 0.018 mol) was added. A white solid precipitated which was crystallised from ethanol/petroleum spirit (b.p. 40–60°C) to give *S*-benzyloxycarbonyl-2-aminoethanethiol hydroiodide (**9**; 1.9 g, 81.9%, m.p. 140–141°C (decomp.)). The identity of the product was confirmed by spectroscopic data and elemental analysis (Table 1).

*Bis-(*N,N′*-dibenzyloxycarbonyl-2-aminoethane) disulphide* (**10**)

N,*S*-Dibenzyloxycarbonyl-2-aminoethanethiol (**6**; 2.1 g, 0.0061 mol) was dissolved in 0.1 M sodium methoxide in methanol (100 cm^3, 0.01 mol), under nitrogen, and stirred for four hours at room temperature [4]. 0.1 M sodium hydroxide solution (300 cm^3, 0.03 mol) was added and the resultant solution was washed twice with diethyl ether (2 × 25 cm^3). 0.05 M iodine solution (60 cm^3) was added dropwise to the solution, and a solid gradually precipitated which was isolated and crystallised from ethanol to give bis-(*N*,*N*′-dibenzyloxycarbonyl-2-aminoethane) disulphide (**10**; 1.1 g, 42.8%, m.p. 125.5–126.6°C). The melting point and IR spectrum of the product were identical to those of the product prepared by Bradley [5].

N-*Benzyloxycarbonyl*-S-*benzoyl-2-aminoethanethiol* (**11**)

N,*S*-Dibenzyloxycarbonyl-2-aminoethanethiol (**6**) was treated with 0.1 M sodium methoxide in methanol as described in the preparation of bis-(*N*,*N*′-dibenzyloxycarbonyl-2-aminoethane) disulphide (**10**).

Benzoyl chloride (2.1 g, 0.015 mol) was added (in place of iodine) with shaking. An oil formed which was extracted into diethyl ether. After drying (Na_2SO_4) and removal of ether, the residue was crystallised from diethyl ether/petroleum spirit (b.p. 40–60°C) to give *N*-benzyloxycarbonyl-*S*-benzoyl-2-aminoethanethiol (**11**; 0.4 g, 21.1%, m.p. 76.6–77°C). The identity of the product was determined by spectroscopic data and elemental analysis (Table 1).

2.2. *Analysis of compounds*

Results of the elemental analysis are shown in Table 1.

All compounds were also analysed by ^1H and ^{13}C NMR spectroscopy, and IR spectroscopy, the results of which are available on request.

2.3. *Instrumentation*

Elemental analysis was performed by C.H.N. Analysis Ltd., South Wigston, Leicester, UK.

Mass spectra were recorded on a Hewlett-Packard 5995 GC mass spectrometer.

All thermogravimetric and differential thermogravimetric work was carried out using a Mettler M3 Balance, and differential scanning calorimetry was carried out using a Mettler DSC 20 Standard Cell.

The thermal data obtained were processed using a Mettler TC10A T.A. Processor and were recorded using a Print Swiss Matrix Printer in conjunction with a Zenith Data System Computer.

Thermal analyses were carried out under a dynamic atmosphere of nitrogen.

3. Results and discussion

All compounds were initially analysed by DSC (Table 2). Benzyloxycarbonyl derivatives were sealed inside a standard aluminium pan with a perforated lid, which was compared to an identical, but empty, pan and lid. Samples were typically heated from 50 to 220°C at 10°C min^{-1}. Temperatures above 220°C were not employed since all the compounds either boiled or totally decomposed above this point.

3.1. *Results of DSC*

N,*S*-Dibenzyloxycarbonyl-2-aminoethanethiol (**6**), bis-(*N*,*N*′-dibenzyloxycarbonyl-2-aminoethane) disulphide (**10**) and *N*-benzyloxycarbonyl-*S*-benzoyl-2-amino-

Table 2
Results of differential scanning calorimetry

Compound			Peak	Type	Start temperature in °C	Peak temperature in °C	End temperature in °C	Enthalpy change in kJ mol^{-1}
$C_6H_5CH_2OC{=}OSCH_2CH_2NHC{=}OOCH_2C_6H_5$	(**6**)	(a)	1st	Endothermic	43.3	53.7	65.3	29.88
		(b)	1st	Endothermic	43.1	53.6	65.4	30.14
$C_6H_5CH_2OC{=}OSCH_2CH_2NH_3^+Br^-$	(**7**)	(a)	1st	Endothermic	148.3	167.9	171.0	16.88
			2nd	Exothermic	171.0	173.0	178.3	
		(b)	1st	Endothermic	140.7	166.4	169.0	17.89
			2nd	Exothermic	169.0	171.5	176.7	
$C_6H_5CH_2OC{=}OSCH_2NH_3^+Cl^-$	(**8**)	(a)	1st	Endothermic	165.0	177.1	196.7	53.55
		(b)	1st	Endothermic	163.7	177.1	197.0	55.14
$C_6H_5CH_2OC{=}OSCH_2CH_2NH_3^+I^-$	(**9**)	(a)	1st	Endothermic	133.3	148.0	150.0	14.73
			2nd	Exothermic	150.0	152.0	158.3	
		(b)	1st	Endothermic	135.0	147.9	150.1	13.56
			2nd	Exothermic	150.1	152.0	158.3	
$[C_6H_5CH_2OC{=}ONHCH_2CH_2S]_2$	(**10**)	(a)	1st	Endothermic	112.7	123.3	135.3	55.05
		(b)	1st	Endothermic	113.0	123.4	136.0	55.97
$C_6H_5C{=}OSCH_2CH_2NHC{=}OOCH_2C_6H_5$	(**11**)	(a)	1st	Endothermic	65.0	75.9	87.4	33.39
		(b)	1st	Endothermic	65.0	75.9	86.7	33.31

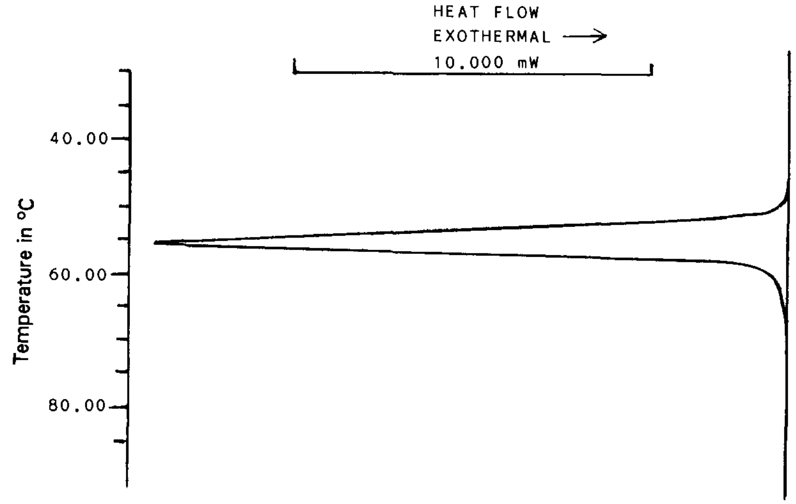


Fig. 1. DSC of *N*,*S*-dibenzyloxycarbonyl-2-aminoethanethiol (**6**).

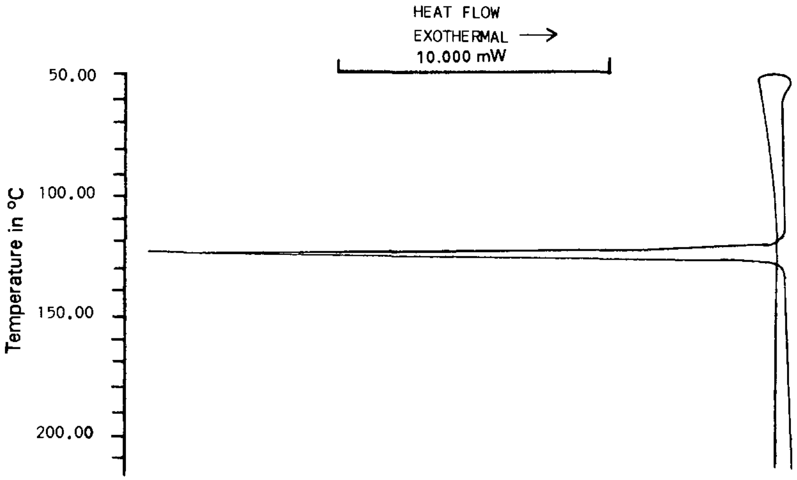


Fig. 2. DSC of bis-(*N*,*N*′-dibenzyloxycarbonyl-2-aminoethane) disulphide (**10**).

ethanethiol (**11**) showed only one exotherm, corresponding to the melting point of the compound (Figs. 1–3).

However, *S*-benzyloxycarbonyl-2-aminoethanethiol hydrobromide (**7**) and hydroiodide (**9**) showed the expected endotherm corresponding to the melting point followed immediately by an exotherm (Figs. 4 and 5).

S-Benzyloxycarbonyl-2-aminoethanethiol hydrochloride (**8**) showed the expected endotherm on melting followed by several endotherms and exotherms which were attributed to the total decomposition of the molecule (Fig. 6).

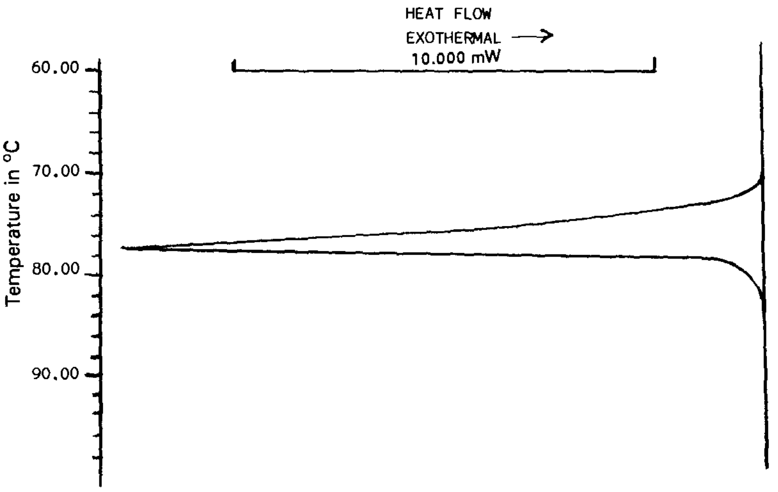


Fig. 3. DSC of *N*-benzyloxycarbonyl-*S*-benzoyl-2-aminoethanethiol (**11**).

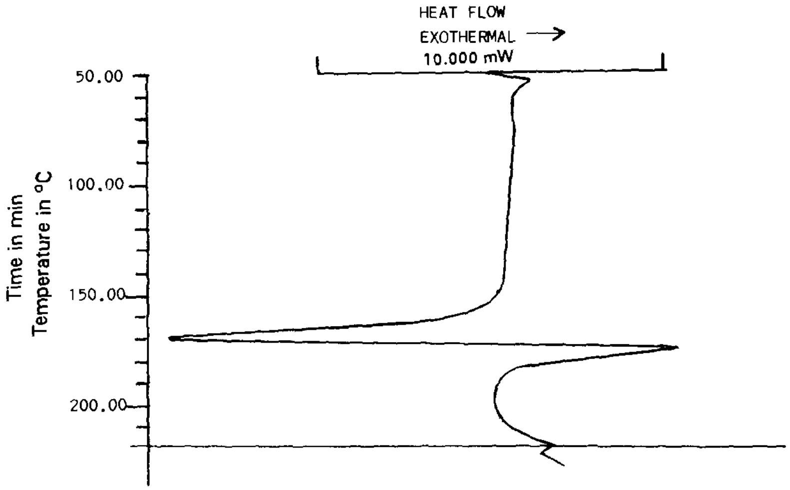


Fig. 4. DSC of *S*-benzyloxycarbonyl-2-aminoethanethiol hydrobromide (**7**).

The three salts were analysed by thermogravimetry and differential thermogravimetry (Table 3). Generally, 5–10 mg of sample was weighed into a porcelain crucible and heated from 50 to 220°C at 10°C min^{-1} under a dynamic nitrogen atmosphere.

3.2. Results of TG and DTG

Each salt showed a single weight loss before total decomposition occurred (Figs. 7–9). In the case of *S*-benzyloxycarbonyl-2-aminoethanethiol hydrochloride (**8**),

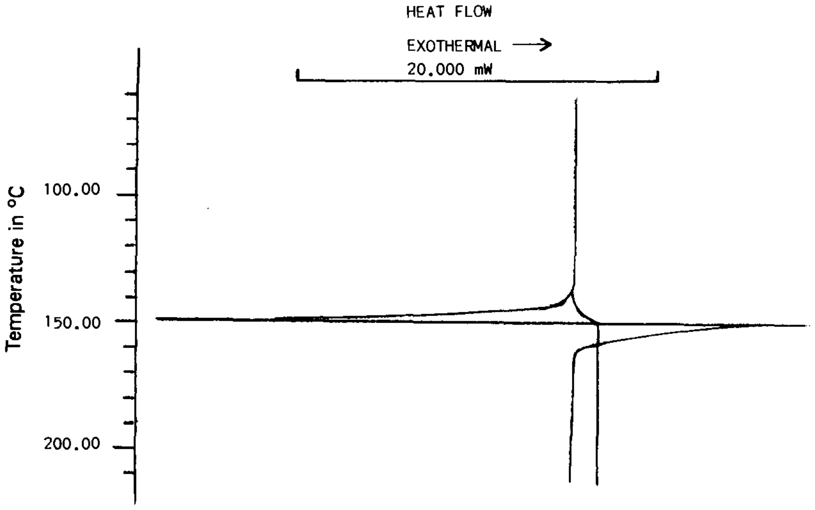


Fig. 5. DSC of *S*-benzyloxycarbonyl-2-aminoethanethiol hydroiodide (**9**).

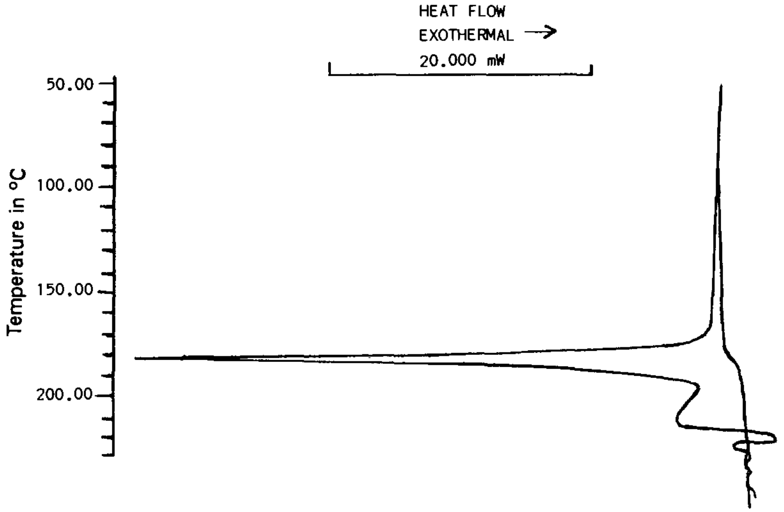


Fig. 6. DSC of *S*-benzyloxycarbonyl-2-aminoethanethiol hydrochloride (**8**).

the first weight loss step was followed immediately by total decomposition. This was expected from the DSC result which indicated that decomposition followed the melting point.

As shown in Table 3, there is a discrepancy between the expected weight loss, assuming all the carbon dioxide is evolved from the molecule, and the actual weight loss. The discrepancy was greatest for *S*-benzyloxycarbonyl-2-aminoethanethiol hydrochloride (**8**). Both thermochemical techniques suggested that for this com-

Table 3
Results of thermogravimetric analysis

Compound			Start temperature in °C	Peak temperature in °C	End temperature in °C	Weight loss in %	Theoretical weight loss if carbon dioxide evolved in %
$C_6H_5CH_2OC{=}OSCH_2CH_2NH_3^+Br^-$	(**7**)	(a)	135.5	165.5	183.0	22.65	15.05
		(b)	137.5	165.5	183.0	23.19	
$C_6H_5CH_2OC{=}OSCH_2CH_2NH_3^+Cl^-$	(**8**)	(a)	141.0	177.0	198.5	38.05	17.76
		(b)	137.5	176.5	200.5	37.95	
$C_6H_5CH_2OC{=}OSCH_2CH_2NH_3^+I^-$	(**9**)	(a)	134.0	149.0	166.0	19.50	12.97
		(b)	130.5	150.0	165.5	18.95	

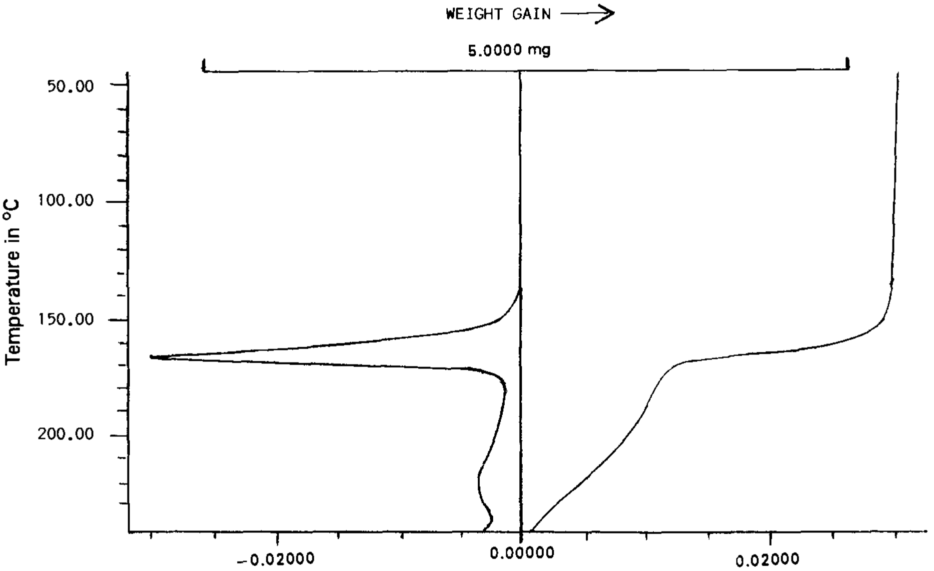


Fig. 7. TG and DTG of *S*-benzyloxycarbonyl-2-aminoethanethiol hydrobromide (**7**).

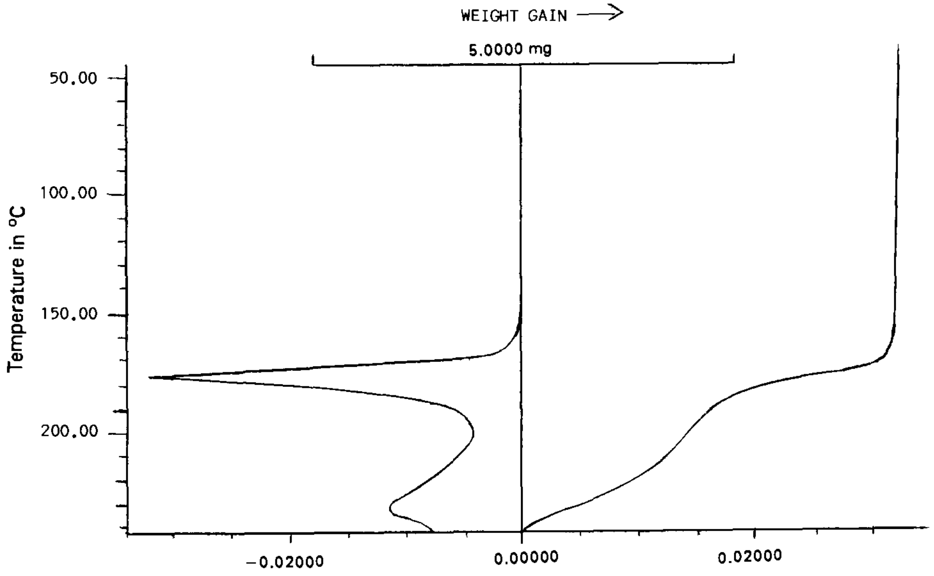


Fig. 8. TG and DTG of *S*-benzyloxycarbonyl-2-aminoethanethiol hydrochloride (**8**).

pound the temperature difference between the initial weight loss step and total decomposition was small. This could explain the large discrepancy between theoretical and actual weight loss figures as, at decomposition, various other volatile compounds as well as carbon dioxide are evolved.

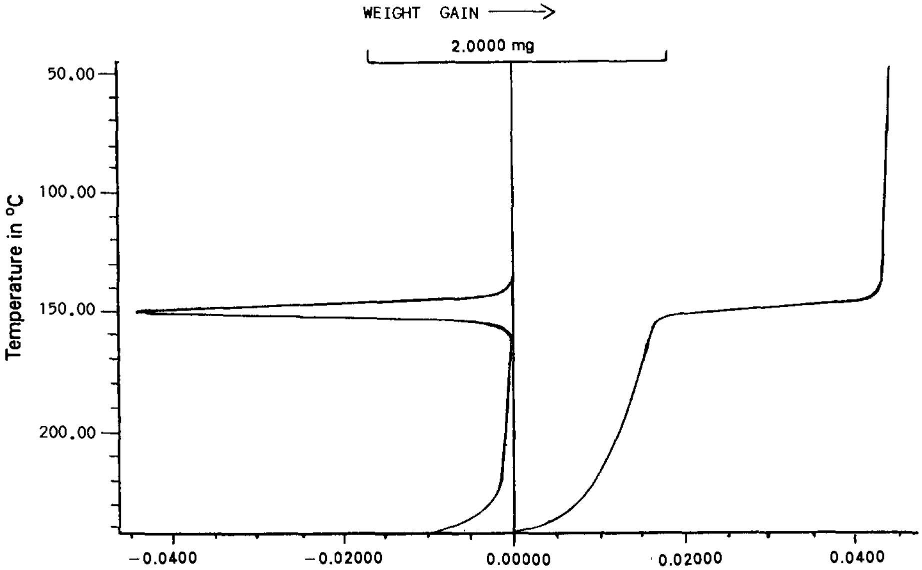


Fig. 9. TG and DTG of *S*-benzyloxycarbonyl-2-aminoethanethiol hydroiodide (**9**).

In order to determine the product(s) of the thermal decomposition of the *S*-benzyloxycarbonyl-2-aminoethanethiol salts, *S*-benzyloxycarbonyl-2-aminoethanethiol hydroiodide (**9**) was studied in detail. This compound was chosen as the DSC results indicated that the melting and decarboxylation temperatures (in the range approximately 130–160°C) were well removed from the temperature of complete decomposition (200°C).

S-Benzyloxycarbonyl-2-aminoethanethiol hydroiodide was sealed inside a sample vial fitted with a rubber septum. The sample was heated to 175°C in an oil bath for 5 min. The gas in the vial was sampled using a syringe and injected into the column of the GC/MS instrument.

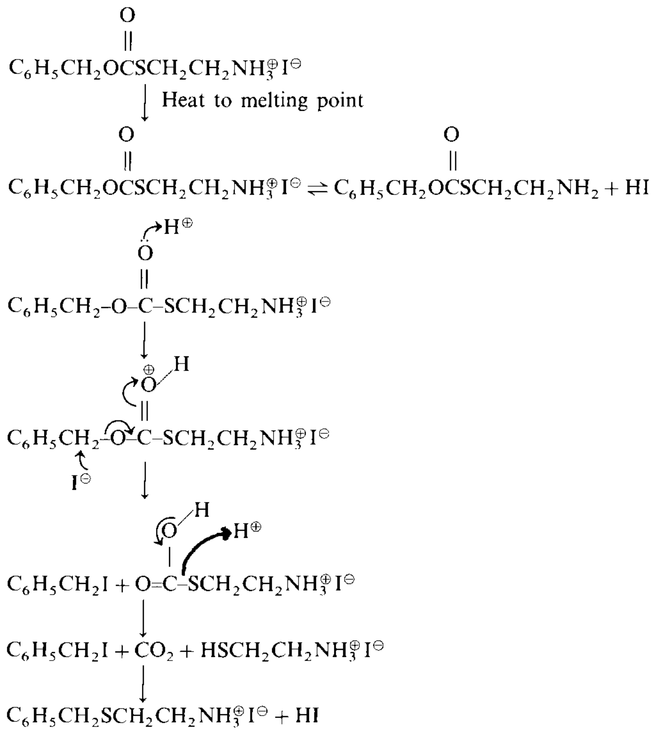
Comparison of the spectrum obtained with a spectrum of an injected air sample indicated a high concentration of a gas with a mass no. of 44 in the gas from the vial. There were no other significant differences between the spectra. This confirmed that carbon dioxide was evolved when *S*-benzyloxycarbonyl-2-aminoethanethiol hydroiodide (**9**) was heated to its melting point.

The residue left in the vial was treated with an excess of aqueous 2 M sodium hydroxide and extracted with chloroform. A sample of the chloroform solution was then injected onto the column of the GC/MS instrument.

Two components eluted with a peak area ratio of 96:4% (uncorrected GC figure). The minor component had a molecular ion of 108 and could not be identified. The major component had a molecular ion of 167.

An authentic sample of *S*-benzyl-2-aminoethanethiol hydroiodide (**12**) was treated and analysed in a similar manner to the residue, and was identified as the major component from the thermal decomposition of *S*-benzyloxycarbonyl-2-aminoethanethiol hydroiodide (**9**).

Based on the thermal data, the mechanism shown in Scheme 3 is proposed for the thermally induced decarboxylation of *S*-benzyloxycarbonyl-2-aminoethanethiol hydroiodide (**9**) to *S*-benzyl-2-aminoethanethiol hydroiodide (**12**).



Scheme 3.

3.3. Results of MS

Further supporting evidence for the proposed mechanism was found in the mass spectrum of *S*-benzyloxycarbonyl-2-aminoethanethiol hydroiodide (**9**). An ion was observed at *m*/*z* 218, which corresponds to the relative molecular mass of benzyl iodide.

It is assumed that identical reactions take place in the case of *S*-benzyloxycarbonyl-2-aminoethanethiol hydrobromide (**7**) and the corresponding hydrochloride (**8**).

The mass spectrum of *S*-benzyloxycarbonyl-2-aminoethanethiol hydrobromide (**7**) contains two ions of equal intensity at *m*/*z* 170 and 172, corresponding to the relative molecular mass of benzyl bromide.

The mass spectrum of *S*-benzyloxycarbonyl-2-aminoethanethiol hydrochloride (**8**) was expected to contain ions at *m/z* 126 and 128 in the abundance ratio of 3:1, which would be due to benzyl chloride. No such ions were present in the spectrum. However, when a sample of the compound was injected into the zone of the GC/MS instrument at a temperature of 250°C (above the decomposition temperature of the compound), a major component eluted from the GC column which was identified as benzyl chloride.

The discrepancy between theoretical and actual weight loss is explained by the loss of some of the associated benzyl halide at the temperature at which the decomposition takes place. This would explain why this discrepancy is greatest for *S*-benzyloxycarbonyl-2-aminoethanethiol hydrochloride (**8**), which melts and decarboxylates over the temperature range 160–190°C, near to the boiling point of benzyl chloride (177–181°C). Therefore, when thermal decarboxylation takes place, the loss of benzyl chloride is likely to be significant, resulting in the unusually high weight loss observed with this compound.

References

[1] W.O. Foye, R.N. Durall and J. Mickles, J. Pharm. Sci., 51 (1962) 168.
[2] Massachusetts College of Pharmacy, US Patent 3,328,442, 1967.
[3] A. Berger, J. Noguchi and E. Katchalski, J. Am. Chem. Soc., 78 (1956) 4483.
[4] L. Zerval, I. Photaki and N. Ghelis, J. Am. Chem. Soc., 85 (1963) 1337.
[5] P.R. Bradley, Reactions of 2-Mercaptoethylamine, Dissertation, Wolverhampton Polytechnic, June 1981.