

PREPARATION OF CARBON-14 LABELLED GUAZATINE (1,17-BIS-[¹⁴C]-GUANIDINO-9-AZAHEPTADECANE TRIACETATE)

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SUMMARY

1,17-Bisguanidino-9-azaheptadecane triacetate (Guazatine) has been prepared with carbon-14 labelling of the guanidine carbon atoms, by interaction of 1,17-diamino-9-azaheptadecane with S-methyl-[¹⁴C]-isothiuronium sulphate. The initial product was purified by precipitation as the carbonate which was then dissolved in aqueous acetic acid to give a 6 % solution of the triacetate, with specific activity of 20.8 $\mu\text{Ci mmol}^{-1}$.

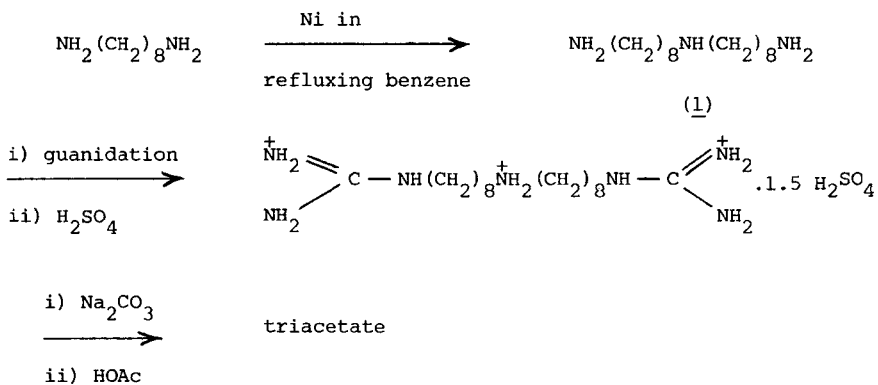
INTRODUCTION

1,17-Bisguanidino-9-azaheptadecane (Guazatine) shows activity against a range of plant pathogenic fungi⁽¹⁾ and is a component of several agricultural seed dressings used for the protection of cereal crops. For this purpose it is a valuable alternative to the highly toxic organomercurials. As part of an investigation to show that guazatine is not taken up into the leaves and stems of plants grown

from treated seeds, we have synthesised the compound with carbon-14 labelling of the guanidine carbon atoms.

DISCUSSION

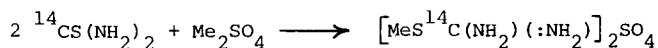
Guanidine derivatives can be prepared from the corresponding amines by interaction with a guanidating reagent such as S-methylisothiuronium sulphate, (1,2) O-methylisouronium sulphate, (3) or cyanamide. (1,4) For guazatine, the preparative route starting from 1,8-diamino-octane is shown in Scheme I.



Scheme I

The possibility of guanidation of the secondary amino group in 1,17-diamino-9-azaheptadecane (1) clearly exists (2,4) and there is evidence that this can occur to a significant extent if cyanamide is employed as the guanidating reagent. (5) With S-methylisothiuronium sulphate, however, we did not encounter this problem even when the

reagent was used in excess. The present work was therefore based on the use of S-methylisothiuronium sulphate which was prepared by a standard procedure from [¹⁴C]-thiourea (Scheme II). (6)



Scheme II

After completion of the reaction between the labelled S-methylisothiuronium sulphate and triamine (1), the 1,17-bisguanidino-9-azaheptadecane was first crystallised as the sesquisulphate. It was then purified as described by precipitation as the sesquicarbonate. Finally, the carbonate was dissolved in the calculated amount of aqueous acetic acid to give a 6 % w/v solution of the triacetate, with a specific activity of 20.8 $\mu\text{Ci mmol}^{-1}$.

EXPERIMENTAL

[¹⁴C]-Thiourea (250 μCi) was obtained from The Radiochemical Centre, Amersham, U.K., and was made up to 1.52 g with unlabelled material by dissolving it in 50 % aqueous ethanol (40 cm^3) and then removing the solvent under reduced pressure.

S-Methyl-[¹⁴C]-isothiuronium sulphate. - Dimethyl sulphate (1.49 g, 11.8 mmol) was added to [¹⁴C]-thiourea (1.52 g, 20.0 mmol, 12.5 $\mu\text{Ci mmol}^{-1}$) and water (0.7 cm^3), and the mixture was heated gently under reflux (1 h) as described. (6) The mixture was then cooled and 95 % ethanol (2 cm^3) was added to give a precipitate which was filtered off and washed with 95 % ethanol to yield the product (2.28 g, 8.20 mmol,

82 % yield), m.p. 242 - 245 °C.

1,17-Diamino-9-azaheptadecane. - 1,8-Diamino-octane (200 g, 1.39 mol) was added to a freshly prepared suspension of Raney nickel (80 g)⁽⁷⁾ in benzene (1,000 cm³), from which the water had previously been removed by azeotropic distillation. The mixture was then heated under reflux (84 h), during which time ammonia (5.54 g, 0.326 mol, 47 %) was evolved. The product was separated from the residual nickel by decantation and washing with further benzene. After removal of benzene at 80 °C, the residue was distilled to yield 1,8-diamino-octane (92 g), b.p. 60 - 70 °C at 0.1 mmHg, and a fraction (37.7 g), b.p. 160 - 170 °C at 0.1 mmHg containing the required triamine (33.0 g by g.l.c.,⁽⁹⁾ 17.5 % yield). Redistillation gave a middle fraction (23.0 g), b.p. 156 - 160 °C at 0.1 mmHg, which was used for the next stage of the preparation.

Preparation of 1,17-bis-[¹⁴C]-guanidino-9-azaheptadecane as the sesquisulphate, sesquicarbonate, and triacetate. - 1,17-Diamino-9-azaheptadecane (2.04 g, 7.53 mmol), S-methyl-[¹⁴C]-isothiuronium sulphate (2.27 g, 8.17 mmol, 204 µCi), and water (4.3 cm³), were heated under reflux (1 h) whilst methanethiol which was evolved was collected in potassium permanganate traps. Sulphuric acid (2.5 cm³, 3N) was then added to the cooled mixture to give a first crop of the sesquisulphate (0.61 g) which was washed with 50 % aqueous ethanol before drying. Concentration of the mother liquor yielded a second crop (0.57 g). The combined products were dissolved in hot water (5.2 cm³) and treated with a hot solution of sodium carbonate (1.78 g) in water (5.2 cm³) to yield a precipitate which was washed with water and then dried in a desiccator to yield the sesquicarbonate (0.75 g) (Found: C, 51.1; H, 9.7; N, 22.2.

Calc. for $\text{C}_{39}\text{H}_{88}\text{N}_{14}\text{O}_9$: C, 52.2; H, 9.8; N, 21.9 %), m.p. 135 - 140 °C. ⁽¹⁰⁾

The carbonate (0.70 g) was dissolved in aqueous acetic acid (14 cm³, 2 % w/v) to give a 6 % w/v solution of 1,17-bis $[^{14}\text{C}]$ -guanidino-9-azaheptadecane triacetate (2.32 $\mu\text{Ci cm}^{-3}$; 20.8 $\mu\text{Ci mmol}^{-1}$) (Calculated activity, based on the yield of sesquicarbonate and the activity of the starting material: 2.79 $\mu\text{Ci cm}^{-3}$; 25.0 $\mu\text{Ci mmol}^{-1}$).

ACKNOWLEDGEMENT

We thank Mr. J.M.Bull for assistance with radioactivity measurements.

REFERENCES

1. Evans Medical Ltd., Brit. Patent 1, 114, 155 (1968).
2. Phillips, R. and Clarke, H.T., J. Amer. Chem. Soc., 45, 1755 (1923).
3. Taylor, G.R., Wilkinson, P.A., Dyke, W.J.C., and Badcock, G.G. (Evans Medical Ltd.), Brit. Patent 1, 294, 927 (1972).
4. Werner, E.A. and Bell, J., J. Chem. Soc., 1790 (1922).
5. Bjorklund, J.A.C., and Reuterhall, A.R. (Kemanord AB), Ger. Offen. 2, 647, 915 (1977).
6. Org. Synth., Coll. Vol. 2, 411 (1943).
7. Org. Synth., Coll. Vol. 3, 181 (1955).
8. Kindler, K., Melamed, G., and Mathies, D., Ann., 23, 644 (1961).
9. Lynch, V.P., Environmental Quality and Safety, Suppl. Vol. III, ed. Coulston, F. and Korte, F., Thieme, Stuttgart, p. 124 (1975).
10. A similar experiment using a 100 % excess of unlabelled S-methylisothio-uronium sulphate with four hours heating yielded a similar product (Found: C, 52.5; H, 10.1; N, 21.8 %).