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Synthesis of 5-Amino[*carboxyl*-^{14}C]salicylic Acid

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SUMMARY

Improvements have been made to the synthesis of 5-aminosalicylic acid (5-ASA) in order to make it applicable for the small-scale synthesis of 5-amino[*carboxyl*-^{14}C]salicylic acid.

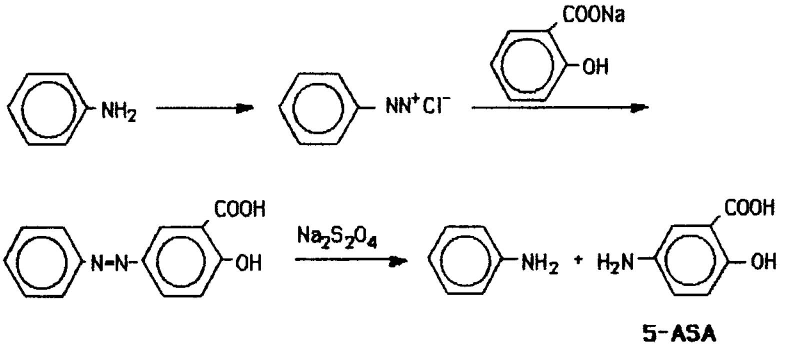
keywords: 5-ASA, 5-aminosalicylic acid, 5-amino[*carboxyl*-^{14}C]salicylic acid

INTRODUCTION

It has been convincingly demonstrated that 5-aminosalicylic acid (5-ASA) is the active metabolite of salicylazosulphapyridine (SASP, Sulphasalazine), which is currently used in the treatment of ulcerative colitis and Crohn's disease [1,2]. A series of 5-ASA derivatives has recently been developed as alternatives to the SASP treatment. However, the fate of the 5-ASA in the human organism is not clear [1].

The present paper describes the synthesis of ^{14}C-labelled 5-ASA, as a part of a comprehensive study to elucidate the fate of 5-ASA in the organism.

The synthesis of 5-ASA from readily available starting materials, i.e. salicylic acid and aniline, is well known (cf. scheme 1) [3].



Scheme 1

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However, operating with small quantities, it appeared necessary to improve the above procedure in order to obtain adequate yields of 5-ASA.

METHOD

Redistilled aniline (0.20 ml; 2.19 mmol) was dissolved in 2.1M hydrochloric acid (2.50 ml). Sodium nitrite (0.17 g; 2.46 mmol), dissolved in water (1.0 ml) was added rapidly (stirring) at 0-5°C (note 1). After completion the reaction mixture was stirred for 10 min at 0°C. [Carboxyl-^{14}C]salicylic acid (63.61 mg; 0.46 mmol) (Amersham International plc, Specific Activity 2.04 GBq/mmol) and salicylic acid (250 mg) were dissolved under nitrogen at 0°C in 1.8 M sodium hydroxide (4 ml) (note 2). Under vigorous stirring the phenyldiazonium chloride solution was added (0-5°C) in one portion. pH was ajusted to 8-9 , if necessary, with sodium hydroxide, and the reaction mixture was left at 0°C for 1.5 h (note 3). Following addition of 50% sodium hydroxide (1.5 ml) the reaction mixture was heated to 80°C and small portions of sodium dithionite (total appr. 2.5 g, note 4) were added until the solution was decolourised. After cooling to ambient temperature the reaction mixture was extracted with 3 x 20 ml diethyl ether. Remaining ether was removed from the aqueous phase under reduced pressure. The aqueous phase was acidified with stirring at 0°C to pH 4.1 with concentrated hydrochloric acid, whereby the 5-ASA precipitated. Liberated sulphur dioxide was removed under reduced pressure. 5-ASA was isolated by filtration and subsequently washed with water (x3), acetone (x2) and diethyl ether (x1) and dried *in vacuo*. Yield: 250 mg (75%). mp 279-80°C. The product was purified by reprecipitation in the following way: The dried 5-ASA (250 mg) were suspended in an EDTA/sodium pyrosulfite solution (15 ml) (note 5) and brought into solution by addition of the necessary volume of 1.8 M hydrochloric acid. A few crystals of sodium dithionite were added and pH was ajusted to 4 by the addition of 1 M sodium hydroxide. 5-ASA precipitated at 0°C as a slightly yellow product. The product was isolated by filtration and subsequently washed with water, acetone and diethyl ether (note 6). Yield 200 mg (60%). mp 280-81°C (note 7). The specific activity of the product was determined to be 0.33 GBq/mmol. The purity of of the product, verified by mass spectrometry was better than 99%. The content of free salicylic acid was demonstrated to be less than 1%.

NOTES

note 1: approximately three times the usual volumes of hydrochloric acid and water were used to dissolve aniline and sodium nitrite, respectively. The relative high dilution appers crucial in order to secure an effective stirring, and, hence, to obtain an uniform reaction throughout the mixture.

note 2: approximately four times the usual volume of sodium hydroxide was used.

note 3: The reaction mixture should be left for no longer the 1.5 h in contrast to the 5-6 h previously suggested [3].

note 4: The necessary amount of sodium dithionite is calculated only with difficulty, due to the lability of this compound. Thus, small portions should be added to decolorise the solution.

note 5: 250 mg sodium-EDTA and 1750 mg sodium pyrosulfite per litre.

note 6: Since pure 5-ASA is only very slightly soluble in water, acetone and ether, the volumes used for washing are not critical.

note 7: The melting point cannot be used as the sole criterion of purity as 5-ASA decomposes upon heating.

REFERENCES

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