SYNTHESIS OF ^{14}C-LABELLED 2,4,-DIAMINO-5-PHENYLTHIAZOLE HYDROCHLORIDE (AMIPHENAZOLE)

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SUMMARY

The synthesis of 2,4-diamino-5-phenylthiazole hydrochloride labelled with carbon - 14 in the 2-position has been effected whereby the ^{14}C-label was introduced in the last step. The overall yields were 34.5% (gravimetrically) and 32.8% (radiochemically).

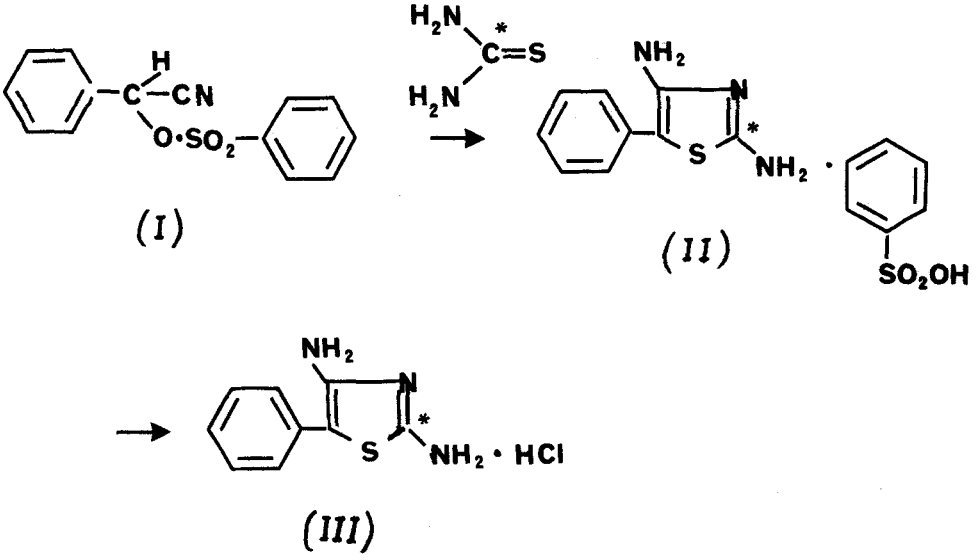
INTRODUCTION

2,4- Diamino-5-phenylthiazole (Amiphenazole) has analeptic properties [1] and has been successfully used (2,3,4,5,6,7,8,)in the management of respiratory depression caused by narcotic analgesics. Unlike N-allylnormorphine, amiphenazole does not appear to antagonise morphine and is free from undesirable side-effects [9].

Amiphenazole exhibits varying intensities of pharmacological activity dependent on the route of administration [10]. The ^{14}C-labelled compound was prepared in order to facilitate a study of its absorption, distribution and metabolism. Further, there appeared to be only scant information on the metabolic transformations of substituted thiazoles.

DISCUSSION

2,4-Diamino-5-phenylthiazole-2-^{14}C hydrochloride (III) may be readily obtained on the microscale by condensing α-benzenesulphonylbenzyl cyanide (I) with ^{14}C - thiourea using a modification of the method described by Dodson and Turner[11]. The difficulty of isolating the unstable free base from the benzenesulphonate salt (II), initially formed, was overcome by triturating (II) in acetone with hydrochloric acid and collecting the hydrochloride salt by filtration[12].



(I) (II) (III)

*denotes position of ^{14}C -label.

α-Benzenesulphonylbenzyl cyanide (I) is readily prepared by the interaction of benzaldehyde, benzenesulphonyl chloride and potassium cyanide in the cold[11].

The synthesis has the advantage of incorporating the ^{14}C-label in the final step and could be further exploited by the more recent availability of ^{35}S-thiourea.

INFRA-RED SPECTRA

The intensity of the cyanide (C≡N) absorption at 2250 cm^{-1} in α-substituted benzyl cyanides considerably depressed by an oxygenated group[13] as revealed by preparing the α-hydroxy derivative. This quenching effect

was sufficiently strong in (I) to suppress the C≡N absorption completely.

2,4 -Diamino-5-phenylthiazole hydrochloride revealed a strong, sharp band at 1640 cm^{-1}, a broader band at 1500 cm^{-1} and a sharp band of medium intensity at 1350-1340 cm^{-1} attributed to the NH δ and skeletal vibrations of the substituted thiazole ring[14]. Monosubstitution of benzene was characterized by 1070, 1050, 755 and 692 cm^{-1} C-H δ absorptions. Aromatic C-H ν absorptions were overlapped by a broad, strong "ammonium" band at 3200-2200 cm^{-1} [15,16].

EXPERIMENTAL

^{14}C-Thiourea

This was supplied as a freeze-dried sample, specific activity 21.6 mCi/m.mol by the Radiochemical centre, Amersham. Radiochemical purity was checked by dilution analysis with thiourea (101%) and by TLC in butanol/ aceticacid/ water (> 99%, m.p. 182°)
7 mg, 2mCi, was used for the synthesis.

2,4-Diamino-5-phenylthiazole-2-^{14}C benzenesulphonate (II)

α-Benzenesulphonylbenzyl cyanide (I) (0.546g, 0.001 mole; m.p. 54-56°), thiourea (0.152g, 0.001 mole, ^{14}C-thiourea diluted with thiourea m.p. 180°) and acetone (9.3 ml , dried over sodium sulphate) were shaken until solution was complete (0.5 hr). After standing at room temperature (48hr) water (2.7 ml) was added to cloudiness. Further standing (0.5°, 72hr) followed by filtration gave a crystalline product which was washed with anhydrous ether and vacuum dried (P_2O_5) (0.306g, 43.8% yield). The I.R. spectrum (KBr) and m.p. (242-244°) was identical with authentic 2,4- diamino-5-phenylthiazole benzenesulphonate.

2,4-Diamino-5-phenylthiazole-2-^{14}C hydrochloride (III)

2,4-Diamino-5-phenylthiazole benzenesulphonate (II)

(0.303g) and hydrochloric acid (0.90ml,25%) were shaken (5 min) before adding acetone (2.40ml , dried), and further shaking (1.5hr). The crystalline product was filtered,washed with acetone and vacuum dried ($CaCl_2$) (0.157g, 79.4% yield). Recrystallization from methanol/ethyl acetate gave 0.135g.

The I.R. Spectrum (KBr) and m.p. (274-276°) were identical with authentic 2,4-diamino-5-phenyl-thiazole hydrochloride (mixed m.p. 273-276°).

The specific activity, determined against a standard ^{14}C-hexadecane sample was 4.179uc/mg.
The overall yield was 34.50% (gravimetric) and 32.81% (radiochemical).

III moved as a single spot on Whatman No 1 chromatography paper and on silica gel TLC in butanol/acetic acid/water. In other solvent systems, the radioactive sample behaved like authentic "cold" 2,4-diamino-5-phenylthiazole hydrochloride and revealed several spots.

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