THE SYNTHESIS OF ^{14}C-LABELLED 1-(4-CHLOROPHENYL)-2-METHYL-2-AMINO-PROPANE HYDROCHLORIDE (CHLORPHENTERMINE, DESOPIMON®).

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SUMMARY

The preparation of ^{14}C labelled 1-(4-chlorophenyl)-2-methyl-2-aminopropane hydrochloride is described. The radioactive carbon was introduced into the central position of the aminopropyl group in order to study the pharmacological properties and mode of action of the anorexigenic drug. The synthesis started from $Ba^{14}CO_3$, involved 3 steps, and a radiochemical yield of 23% was obtained. The chemical and radiochemical purity of the end-product was proved by thin layer chromatography and autoradiography.

INTRODUCTION.

1-(4-Chlorophenyl)-2-methyl-2-aminopropane hydrochloride was synthesized by Ferrari[1] and by Budai et al.[2]. The compound was found to possess intense anorexigenic effect. The commercial name of this pharmaceutical product is Desopimon® in Hungary. For the purpose of radioisotopic studies and pharmacological tests the ^{14}C-labelling of anorexigenic drug was performed. The ^{14}C-labelled material was prepared by the route indicated in the scheme.

The synthesis of the compound labelled in the central position of aminopropyl group was accomplished from 2-propanone-2-^{14}C (I)

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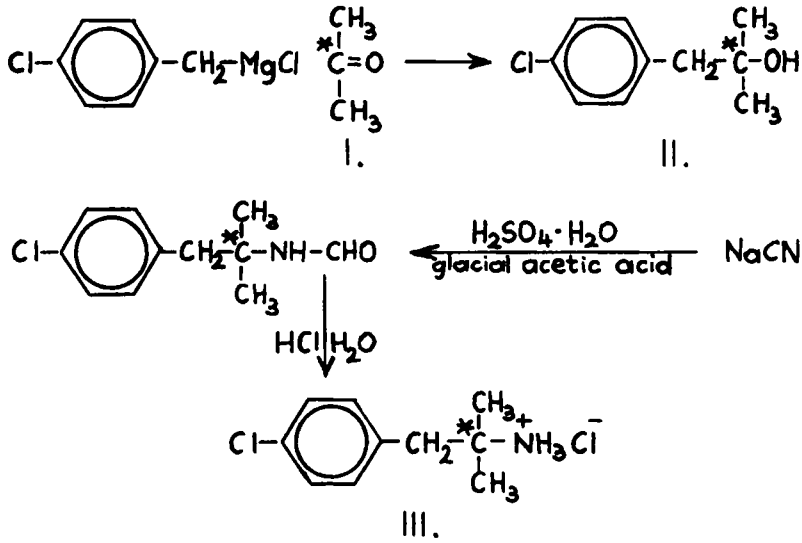
as starting material. A Grignard reagent was prepared from 4-chlorobenzyl chloride, reacted with the radioactive acetone to give 1-(4-chlorophenyl)-2-methyl-2-propanol-2-^{14}C (II). In the next step the N-formyl intermediate was prepared and reacted with hydrochloric acid to give the radioactive end-product (III). The radioactive acetone was utilized with a yield of 30% in the course of these procedures. The chemical and radiochemical purity of the end-product was checked by thin-layer chromatography. The chromatograms were evaluated radioautographically and radiometrically, using a Tri-Carb liquid scintillation spectrometer.



Scheme

The name Desopimon (R) is registered trade mark in Hungary, the property of EGYT Pharmacochemical Works. IR N° 209.728

EXPERIMENTAL.

2-Propanone-2-^{14}C (I).

Radioactive 2-propanone was synthesized by the pyrolysis of barium acetate-1-^{14}C at 500° C [3,4,5,6]: 0,435 g (7.50 mmoles) of 2-propanone-2-^{14}C, having a total activity of 37.4 mCi (86.00 mCi/g, 4.98 mCi/mmole) was prepared.

Yield: 80% based on $Ba^{14}CO_3$.

1-(4-Chlorophenyl)-2-methyl-2-propanol-2-^{14}C (II).

The Grignard solution was prepared from 0.212 g (8.75 mmoles) of magnesium turnings and 1.368 g (8.50 mmoles) of 4-chlorobenzyl chloride in 20 ml of absolute ether. The stirred reaction mixture was refluxed for 2 hours in dry nitrogen atmosphere and 0.435 g (7.50 mmoles, 37.4 mCi, 86.00 mCi/g, 4.98 mCi/mmole) of 2-propanone-2-^{14}C in 10 ml of dry ether was added dropwise, with stirring, at 20°C. After stirring for one hour at 40°C in nitrogen atmosphere, a solution of ammonium chloride (0.75 g in 15 ml of water) was added to decompose the complex. The precipitate dissolved and the mixture separated into two phases. After separation the aqueous layer was extracted with 3 x 10 ml of ether, the combined extracts were washed with 3 x 10 ml of water and dried over megnesium sulphate overnight. The solvent was removed under atmospheric pressure and the pale yellow oily residue was purified by fractionation in vacuum.

Yield: 1.111 g (6.01 mmoles), 80.1% based on I.

B.p. 85°/0.3 mm, M.p. 39°C.

1-(4-Chlorophenyl)-2-methyl-2-aminopropane-2-^{14}C hydrochloride (III).

A mixture of 0.294 g (6.01 mmoles) of sodium cyanide and 0.67 ml of glacial acetic acid was stirred at -5°C and a mixture of 0.67 ml of glacial acetic acid and 0.78 ml of sulphuric acid monohydrate was added dropwise. To this formylating agent 1.111 g (6.01 mmoles) of II was added over a period of 30 min., with continuous stirring. After

addition the reaction mixture was stirred for a further 2 hours at 70°C allowed to stand overnight at room temperature, and 4 ml of water was added with stirring and cooling. The solution was made alkaline with 2 N sodium hydroxide (pH 8) and extracted with 3 x 20 ml of benzene. After separation the combined organic phases were washed with 3 x 10 ml of water, dried over magnesium sulphate overnight and concentrated under vacuum to yield 1.028 g (4.85 mmoles) of a brown oil. According to the experience obtained in earlier experiments with inactive material, this crude 1-(4-chlorophenyl)-2-methyl-2-formyl-propane-2-^{14}C may be used in the following step without purification. To the brown oily product a mixture of 5 ml of ethanol, 1 ml of water and 1 ml of conc. hydrochloric acid (dens.1.19) was added. The reaction mixture was refluxed on an oil bath at 120°C for 4 hours and set aside at room temperature overnight. The mixture was evaporated under reduced pressure, the solid residue was dissolved in 20 ml of water and allowed to stand at 80°C for 30 min. The solution was cooled to room temperature, extracted with 2 x 10 ml of chloroform and the aqueous layer decolorized with charcoal. The solvent was removed under vacuum and the crude solid product was recrystallized from a 1 : 1 mixture of acetone and ethanol (1.5 ml).

Yield: 0.457 g (2.08 mmoles), 34.6% based on II, m.p. 233°C.
Radiochemical yield: 10.68 mCi (23.39 mCi/g, 5.16 mCi/mmole), 22.8% based on $Ba^{14}CO_3$.

Chromatographic determinations.

Adsorbent: Kieselgel G. Solvent: n-butanol : acetic acid : water= 40 : 10 : 5. Sample mass: 20 µg. Detection: Dragendorff's reagent. Autoradiogram: contact exposure on a Forte-type X-ray film for 24 hours. Rf: 0.68.

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REFERENCES

1. Ferrari, G. - Ger. Pat., 1,187,242 (1965).
2. Budai, Z., Benkó, P., Pallos, L., Márton, L., Nagy, F. and Kiss, Cs. - Hung. Pat., 159.521 (1968).
3. Dauben, W. G. and Vaughan, C. W. - J. Amer. Chem. Soc. 75 : 4651 (1953).
4. Grosse, A. V. and Weinhouse, S. - Science, 104 : 2704 (1946).
5. Logan, A. V. and Murray, J. - J. Amer. Chem. Soc. 74 : 2436 (1952).
6. Murray A. and Williams D. L. - "Organic Syntheses with Isotopes", Interscience Publishers, Inc., N. Y., 1958, p. 34.