

SYNTHESIS OF TRITIUM-LABELLED IMIPRAMINE AND DESIPRAMINE WITH HIGH SPECIFIC ACTIVITIES

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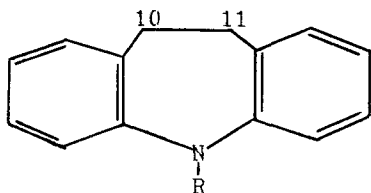
SUMMARY

[G-³H]imipramine and [G-³H]desipramine with specific activities 110-160 and 80-100 kCi/mol, respectively were synthesized by high temperature solid-phase catalytic isotope exchange with gaseous tritium.

Key words: tritiated imipramine, tritiated desipramine

INTRODUCTION

Imipramine (I) and desipramine (II) are widely used in



I R = $-(CH_2)_3N(CH_3)_2$

II R = $-(CH_2)_3NHCH_3$

practical medicine as powerful antidepressants. Their tritium-labelled analogs are used as radioligands in serotonin receptor investigations and in new potential antidepressants screening [1]. Tritiated imipramine and desipramine with high specific activities (As) are needed for these purposes.

It is known that the liquid-phase catalytic dehalogenation of 3-chloroimipramine on Pd/C in dioxan is accompanied by isotope exchange of benzyl-type hydrogen atoms in positions 10 and 11. As a result up to 20% of the incorporated activity appears in these two positions [2].

[³H]Imipramine with As 1.5 Ci/mol was obtained by liquid-phase catalytic exchange with gaseous tritium on PtO₂ [3]. An

isotope exchange with tritium-gas on PdO in methanol gave labelled imipramine and desipramine with As 14.9 and 44.9 kCi/mol, respectively [4]. In dioxan-water mixture (9:1 v/v) by a liquid-phase isotope exchange with $^3\text{H}_2$ on 10% PdO/BaSO₄ labelled desipramine was obtained with As 67 kCi/mol [5]. This product was then converted into [^3H]imipramine with As 78 kCi/mol by reductive methylation with formaldehyde and tritium in methanol using 10% PdO/BaSO₄ as catalyst.

The object of the present work was to develop a simple one-stage method of tritium incorporation into imipramine and desipramine so as to obtain products with high As

METHODS

The substrate (10 μmol) in CH₃OH (1ml) was added to 100-200 mg of catalyst. The solvent was evaporated off and the resulting dry mixture of the catalyst and substrate exposed to a tritium atmosphere at a temperature of between 50 °C and 150 °C.

HPLC on columns filled with Lichrosorb RP-18 (Merck) was used for isolation of the labelled compounds. A mixture of acetone-isopropanol-water (5:4:1 v/v), containing 0.1% of triethylamine was used as eluent for imipramine isolation, whilst an ethanol-water mixture (95:5 v/v) with addition of 0.15% of triethylamine was used for desipramine.

RESULTS AND DISCUSSION

To incorporate tritium label into imipramine and desipramine we used the solid-phase catalytic isotope exchange method which has been shown to be very efficient for various classes of organic compounds [6-8]. In experiments with solid-phase isotope exchange of imipramine we changed the nature of catalysts, the substrate-catalyst mole ratio, the reaction temperature, the duration of the

run and the pressure of the protium-tritium mixture. 5% Pd/BaSO₄, 5% PdO/Al₂O₃ and 2% PdO/SiO₂ were initially used as catalysts.

The experiments have shown that under typical conditions (gas pressure 1 atm, temperature 100-150 °C) a great deal of tritium enters the imipramine molecule not by isotope exchange but by hydrogenation of the benzene rings leading to destruction of the molecule. This was reflected in a sharp fall (up to zero) of the UV-absorption of the reaction mixture and in the appearance of more than 6 peaks of unidentified compounds in the radiochromatograms.

A series of experiments using 5% Pd/BaSO₄ and at a gas pressure of 1 atm was carried out in which the temperature was decreased from 100 to 50 °C. In this case an increase of [³H]imipramine content in the reaction mixture and a decrease of its A_s were observed simultaneously.

Rhodium catalysts turned out to be more selective than palladium ones. When the reaction was carried out on 5% Rh/Al₂O₃ at 100-110 °C over 1 h, the tritiated imipramine content in the reaction mixture was near 40%. Under milder conditions (using 0.5% Rh/Al₂O₃) an even better incorporation was achieved (up to 70%).

The optimum conditions were found to be: 10 μmol of imipramine and 100 mg of 0.5% Rh/Al₂O₃ catalyst. The mixture, after drying, was exposed to a tritium atmosphere at 100-110 °C and 0.5 atm for 1 h. Similar conditions were used for desipramine.

Isolation of the labelled compounds I and II was performed by HPLC. Both for imipramine and for desipramine fractionation of the labelled substance according to the extent of substitution was observed on the chromatographic column. For [³H]imipramine the fractions were collected with A_s 110-160 kCi/mol and for [³H]desipramine - with A_s 80-100 kCi/mol. The radiochemical purity of all the fractions was more than 95%.

Fractions of both labelled compounds with higher A_s , isolated by HPLC were less stable during storage.

^3H -NMR spectra of the tritium-labelled compounds I and II described in literature show that tritium is concentrated in the aromatic rings and in positions 10,11 [9]. A ^3H -NMR spectrum obtained by us of the labelled desipramine shows that the tritium content in the benzene rings (26%) and benzyl groups (22%) is less than in the methyl and methylene groups adjacent to the exocyclic nitrogen atom (52%).

The investigation has shown that solid-phase isotope exchange is a promising method for the synthesis of tritium-labelled polycyclic nitrogen-containing antidepressants.

REFERENCES

1. Mashkovskii M.D.- Pharmacology of antidepressants. (Russ.), Medicina, Moscow 1983
2. Evans E.A.- J.Radioanal.Chem. 64: 9 (1981)
3. Telc A., Brumfelter B., Gosztonyi T.- J.Label.Cmps. Radiopharm. 8: 13 (1972)
4. Buchman O., Pri-Bar J.- J.Label.Cmps.Radiopharm. 14: 263 (1978)
5. Fuksova K., Krulik P., Pichova D., Picha J.- Radioisotopy 29 : 178 (1988)
6. Zolotarev Ju.A., Kozik V.S., Zaitsev D.A., Dorokhova E.M., Myasoedov N.F.- Dokl. Akad. Nauk SSSR. 308: 1146 (1989)
7. Natochin Ju.V., Parnova R.G., Firsov D.L., Shakhmatova E.I., Kaminski Ju.L., Akulov G.P., Patokina N.A.- Fiziologicheskii Zhurnal (USSR) 75: 1766 (1989)
8. Akulov G.P., Snetkova E.V., Kaminski Ju.L., Kudelin B.K., Efimova V.L.- Radiokhimiya (USSR) 33: 74 (1991)
9. Evans E.A., Warrell D.C., Elvidge J.A., Jones J.R.- Handbook of Tritium NMR Spectroscopy and Applications. Wiley, Chichester, 131 (1985)

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