Journal of Labelled Compounds and Radiopharmaceuticals—Vol. XXXI, No. 10

SOLID-PHASE CATALYTIC ISOTOPE EXCHANGE OF ALKYLXANTHINES WITH GASEOUS TRITIUM

Ju.L. KAMINSKI, G.P. AKULOV, N.A. PATOKINA, S.G. ROSENBERG

V.G. Khlopin Radium Institute, St.-Petersburg, 194021, Russia
Institute of Pharmacology, Academy of Medical Sciences, Moscow,
125315, Russia

SUMMARY

The results of the synthesis of 11 different tritiated alkylxanthines by solid-phase catalytic isotope exchange are described. ^{3}H-NMR analysis of the labelled compounds shows that in contrast to liquid-phase isotope exchange the tritium label is incorporated not only in the C-8(H) position, but also in the alkyl groups. The fraction of radioactivity in an alkyl group depends on the nature and position of this group.

Key words: tritiated alkylxanthines, isotope exchange, ^{3}H-NMR.

INTRODUCTION

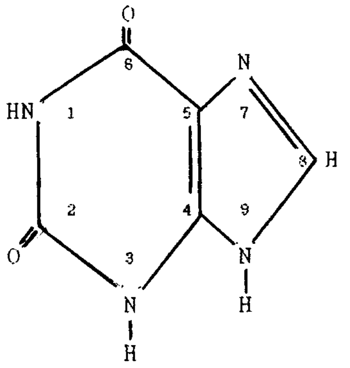
Recently catalytic isotope exchange in the solid phase at high temperatures with participation of hydrogen spillover has been widely used in the preparative chemistry of tritium-labelled compounds [1-3]. This method allows the tritium label to be included not only into those positions where it is incorporated in liquid-phase isotope exchange, but in many cases into other positions. This feature as well as the high isotopic incorporation and the avoidance of protic solvents gives the possibility of obtaining labelled compounds with very high specific activities.

In the present paper data are presented on the solid-phase isotope exchange of tritium-labelled xanthine (1) and a large

0362–4803/92/100759–04$07.00

Received 26 March, 1992
Revised 17 July, 1992

number of its alkyl-derivatives: methylxanthine (II), 3-methylxanthine (III), 7-methylxanthine (IY), 8-methylxanthine (Y), 9-methylxanthine (YI), 3-ethylxathine (YII), 3,7-dimethylxanthine (theobromine) (YIII),1,3-dimethylxanthine (theophylline) (IX), 1,3,7-trimethylxanthine (caffeine) (X) and 1-methyl-3-isobuthylxanthine (XI).



(I)

METHODS

The following conditions were used for all the compounds mentioned: 1 mg of substrate was applied as a solution on 80 mg of 5% $Pd/BaSO_4$ catalyst and after drying exposed to a tritium atmosphere at 170 °C and 0.5 atm. for 2 h. The labelled compounds were then washed from the catalyst with water (3x3 ml) and after removal of the labile tritium purified by liquid chromatography on a column (650x12 mm) with Sephadex G-50 (50 ml), using UV-absorption and radioactivity monitoring and water as an eluent. The chemical purity of the labelled alkylxanthines was controlled by measurement of the optical density of their solutions with subsequent calculation of the characteristic UV-spectrum constants. All the synthesized labelled alkylxanthines had UV-characteristics, close to those, which had been published in the literature [4]. The radiochemical purity (RCP) of the products was measured by of thin-layer chromatograthy using Silufol UV254 plates in chloroform-acetone (1:1 v/v) and isopropanol-water (9:1 v/v) and a scintillation scanning counter. For compounds I-XI RCP was more than 95%.

The distribution of tritium in the synthesized labelled compounds was ascertained by ^3H-NMR spectroscopy using a Bruker spectrometer operating at 266.8 MHz. D_2O was used as the NMR solvent.

RESULTS AND DISCUSSION

The main features of the results are summarized in the Table. Most of the alkylxanthines have specific activities (A_s) in excess of 29 kCi/mol - the maximum value for incorporation of the label in the C-8(H) position by the liquid-phase isotope exchange. An increase in A_s is observed with as the number of substituents and their chain length are increased.

The results shown allow the monomethylsubstituted xanthines II-IY and YI to be placed in order of reactivity viz. $N_1<N_7<=N_9<N_3$. For di- and tri-N-methylsubstituted xanthines the activity values are also in accordance with this sequence.

It can be noted that this sequence $N_1<N_7=N_9<N_3$ is the same for decreasing basicity of nitrogen atoms in the nonsubstituted purine [5].

The synthesized methylxanthines contain single, double and triple tritium labelled methyl groups and the CHT_2 content is a maximum in all cases.

In compounds YII and XI, which contain bulkier alkyl substituents (ethyl and isobutyl, respectively) the degree of tritium incorporation in these groups is very high and its tritium distributed throughout the substituent structure.

The present results show that the catalysis of solid phase isotope exchange with gaseous tritium at high temperatures is an effective technique for tritium label incorporation into different alkylxanthines. The specific activities of the products considerably exceed the values attainable in liquid-phase isotope exchange.

TABLE
Specific activity and intramolecular distribution of tritium ir synthesized labelled alkylxanthines

Comp. No.	Spec. activ.	Distribution of activity in positions, %					
	kCi/M	H-C$_8$	Alk-N$_1$	Alk-N$_3$	Alk-N$_7$	Alk-N$_9$	Alk-C$_8$
I	20	100	-	-	-	-	-
II	18	58	42	-	-	-	-
III	45	24	-	76	-	-	-
IY	40	35	-	-	65	-	-
Y	17	-	-	-	-	-	100
YI	24	26	-	-	-	74	-
YII	81	26	-	74	-	-	-
YIII	123	13	-	47	40	-	-
IX	124	16	35	49	-	-	-
X	203	13	12	40	35	-	-
XI	175	6	22	72	-	-	-

REFERENCES

1. Zolotarev Ju.A., Kozik V.S., Zaitsev D.A., Dorokhova E,M., Myasoedov N.F. - Dokl. Akad. Nauk SSSR. 308:1146 (1989)
2. Natochin Ju.V., Parnova R.G., Firsov D.L., Shakhmatova E.I., Kaminski Ju.L., Akulov G.P., Patokina N.A.- Fiziologicheskii Zurnal (USSR) 75:1766 (1989)
3. Akulov G.P.,Snetkova E.V., Kaminsky Ju.L., Kudelin B.K., Efimova V.L.- Radiokhimia.33:74 (1991)
4. Lister J.H.- Fused Pyrimidines..Part II: Purines. Ed. D.J.Brown, Wiley, New York (1971) 580 p
5. Read J.M., Goldstein J.H.- J.Am.Chem.Soc. 87:3440 (1965)