The labelling with tritium of 2-(dimethylamino)ethanol and of some drugs containing the 2-(dimethylamino)ethyl group as a structural part

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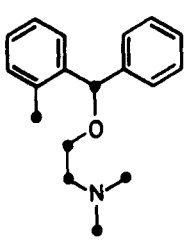
SUMMARY

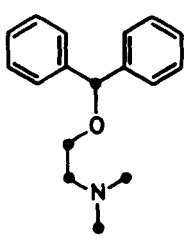
Orphenadrine hydrochloride and a related ether were labelled with tritium in the 2-(dimethylamino)-ethyl moiety, by reduction of the corresponding amides with tritiated lithium aluminium hydride (yields 72 and 51 %, resp., specific radioactivity 57,8 m C/g in both cases). Hydrolysis of one of the labelled ethers afforded tritiated 2-(dimethylamino) ethanol (yield 80 %, specific radioactivity 146 m C/g).

INTRODUCTION

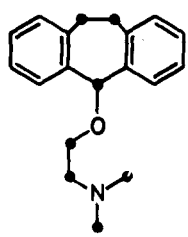
In the course of studies of the metabolic fate of orphenadrine hydrochloride [I] in the rat, we encountered substantial amounts of 2-(dimethylamino)ethanol (DMAE) among the metabolites excreted in the urine [1].



[I]



[II]



[III]

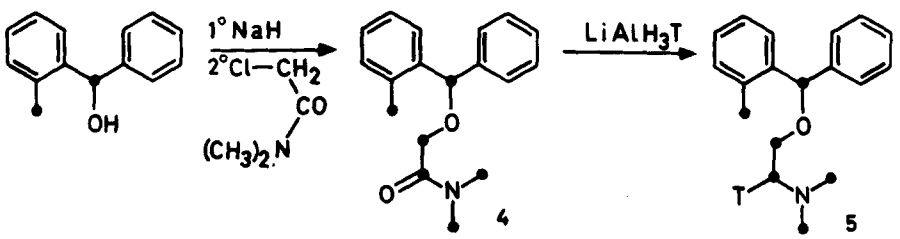
This was not unexpected, since evidence already existed for the occurrence of DMAE among the metabolites of the related diphenhydramine hydrochloride [II] [2, 3, 4].

An investigation [5] into the stability of [I] in an acid medium showed that at 37 °C and pH = 1.2 its half-life is 222 hours, which indicated that an enzymatic process might be responsible for the extent to which DMAE is formed from [I] *in vivo*.

To study the processes involved more closely, especially the quantitative aspects and localisation, we decided to synthesise [I] with a radioactive label in the DMAE-moiety.

Although the synthesis of ^{14}C-labelled DMAE had been previously reported [6, 7], we preferred tritium as a label, in view of the specific activity needed for planned autoradiographic experiments. First, a direct route *via* tritiated DMAE was envisaged in which reduction of ethyl-*N*,*N*-dimethyloxamate by means of tritiated lithium aluminium hydride was to be followed by a coupling reaction with *o*-methyl-α-phenylbenzyl alcohol. But in non-radioactive experiments we were unable to increase the yield to a satisfactory level.

This led us to circumvent this coupling reaction by synthesizing *N*,*N*-dimethyl-2-[(*o*-methyl-α-phenylbenzyl)oxylacetamide [IV] from *o*-methyl-α-phenylbenzyl alcohol and 2-chloro-*N*,*N*-dimethylacetamide and then carrying out a reduction with tritiated lithium aluminium hydride ($LiAlH_3T$ *).



This synthesis proved to be feasible; the reduction gave a yield of 72% * *.

A similar reduction with lithium aluminium hydride to prepare (non labelled) [II], had already been described [8].

After the successful labelling of [I], another 2-(dimethylamino)ethyl ether [III] of therapeutic interest, that of 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol, was labelled in a similar way, 2[(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)oxy]-*N*,*N*-dimethylacetamide affording 2-[(10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-yl)oxy]-*N*,*N*-dimethylethyl-1-t-amine. Compound [III] has a comparatively high rate of hydrolysis and use was made of this property to obtain tritiated DMAE itself.

Hydrolysis of tritiated [III] with hydrochloric acid afforded tritiated DMAE in a better yield than *via* the direct route mentioned above; moreover, the product was more easily obtained in the desired pure form.

Although seemingly round about, this route is an attractive one for the synthesis of tritiated DMAE.

* According to the manufacturer, New England Nuclear Corp., Boston, Mass., USA, this formula represents the structure of the majority of labelled molecules.

** We thank Dr. C. van der Stelt for his suggestion to use this route in the synthesis of the tritiated ether required.

The question, whether the tritiated molecules carry only one or two tritium atoms at the carbon atom involved, has been considered on the basis of existing knowledge about the reaction mechanism of this type of reduction and taking into account the specific radioactivities obtained. The conclusion was reached that not more than about 0.1% of the labelled molecules can be expected to be double-labelled.

Therefore, for the time being, the products are designated as mono-tritiated. Experiments which will allow a final decision on this issue are in progress.

EXPERIMENTAL *

Determination of radioactivity

The radioactivities were determined with the aid of a Tri-Carb Liquid Scintillation Spectrometer 314 EX. Specific radioactivities were calculated by comparing the measured radioactivities to that of a hexadecane-1-2-t standard (Radiochemical Centre, Amersham, England), measured under the same conditions. Radioactivity on thin-layer chromatograms was localised by scanning the plates with a Berthold Dünnschicht-Scanner.

N,N-*Dimethyl-2-*[(o-*methyl-*α-*phenylbenzyl*)*oxy*]*acetamide* [IV]

To 4 g (0.02 mole) of *o*-methyl-α-phenylbenzyl alcohol and 2.4 g (0.02 mole) of 2-chloro-*N*,*N*-dimethylacetamide, dissolved in 50 ml of ether, 1 g of 50% sodium hydride in an oily suspension was added, portionwise. The mixture was left for 2 hours and then refluxed for 1 hour with stirring. After cooling, the excess of sodium hydride was decomposed with water and the reaction mixture extracted with ether. After drying, filtration and removal of the ether by distillation an oil was obtained, which was dissolved in petroleum ether (b.p. 60-80°C). On cooling, the desired compound was obtained in the crystalline form. Yield : 3.5 g (62%). Melting point : 63-65°C.

Found : C76.3; H7.6; N5.0

Calc. for $C_{18}H_{21}NO_2$ (283.4) : C76.30; H7.47; N4.94.

The structure was confirmed with the aid of NMR spectroscopy.

2-[(*10,11-Dihydro-5*H-*dibenzo*[a,d]*cyclohepten-5-yl*)*oxy*]-N,N-*dimethylacetamide*

This compound was synthesised in an analogous manner, by replacing *o*-methyl-α-phenylbenzyl alcohol by an equivalent amount of 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ol.

Yield : 4.9 g (83%). Melting point : 83-85°C.

Found : C77.1; H7.1; N4.6;

Calc. for $C_{19}H_{21}NO_2$ (295.4) : C77.26; H7.17; N4.74.

* With the assistance of W.J. Heus and W.J.F. Klopper.

N,N-*Dimethyl-2-*[(o-*methyl-α-phenylbenzyl)oxy]ethyl-1-t-amine hydrochloride* [V]

To 1.5 g (5 mmole) of *N,N*-dimethyl-2-[(*o*-methyl-α-phenylbenzyl)oxy] acetamide, dissolved in 25 ml of dry ether, 200 mg in total of $LiAlH_4$ + $LiAlH_3T$ (5.3 mmole) were added according to the following dosage scheme :

a) 25 mg (0.66 mmole) of $LiAlH_4$ at once;

b) 43 mg (1.14 mmole) of $LiAlH_3T$ (100 mC) after 1 hour of stirring and refluxing;

c) 132 mg (3.50 mmole) of $LiAlH_4$ after 3 hours of stirring and refluxing.

After the addition was completed, refluxing was continued over night, after which the mixture was decomposed with water and filtered. The ethereal solution was separated and dried; after removal of the ether the residue was taken up in a few ml of alcohol and the solution was adjusted to pH = 5.4 with alcoholic hydrogen chloride. Next, ether was added to the point where, after shaking, some turbidity just persisted. The solution was then cooled to let the product crystallise.

Yield : 1.10 g (72%) *. Melting point : 160-162°C.

Specific radioactivity : 57.8 mC/g.

2-[(*10,11-Dihydro-5*H-*dibenzo*[a,d]*cyclohepten-5-yloxy*]-N,N-*dimethylethyl-1-t-amine hydrochloride*

This compound was synthesised as described for the tritiated orphenadrine hydrochloride. In this case 1.47 g (5 mmole) of the corresponding amide was reduced.

Yield : 0.81 g (51%) *. Melting point : 167-169°C.

Specific radioactivity : 57.8 mC/g.

*2-(Dimethylamino)ethanol-1-*t *hydrochloride*

0.49 g (1.5 mmole) of 2-[(10,11-dihydro-5*H*-dibenzo[*a,d*]cyclohepten-5-yl)oxy]-*N,N*-dimethylethyl-1-t-amine hydrochloride, dissolved in 10 ml of ether, was stirred for 3 hours with 5 ml of hydrochloric acid 0.1 *N*. The ethereal layer was separated and the aqueous layer adjusted to pH = 5.8 with 1 *N* sodium hydroxide. For further (metabolic) research the 2-(dimethylamino)ethanol-1-t was not isolated from this solution.

Identity, chemical and radiochemical purity were checked by thin-layer chromatography. The presence of a few per cent of the starting compound was demonstrated but this was acceptable for our purpose. The concentration of the solution was calculated by comparing its radioactivity to that of a solution of the starting material of a known concentration.

Yield : 0.15 g (80%). Specific radioactivity : 146 mC/g.

* The identities of the compounds were confirmed by thin-layer chromatography using different solvent systems. This also showed the products to be chemically and radiochemically pure.

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