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THE β-IODOETHOXYL GROUP: A STABLE UNIT FOR RADIOIODINATION

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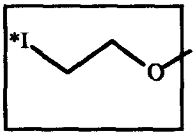
Abstract : 123-Iodine labelled 6-iodo-4-oxa-hexanoic acid, an analogue of 6-iodo-hexanoic acid, has been prepared and its radiochemical stability and *in vivo* distribution in mice evaluated. The β–iodoethoxyl group has been found to be a suitable moiety for iodine radiolabelling.

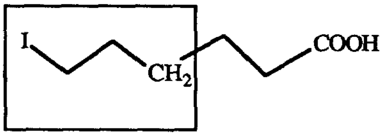
Efficiency in radioiodination processes, which are of particular importance in medical imaging applications, depends on the ease of introduction of the iodine as well as on the stability of the radiolabelled molecule thus obtained [1]. The radioactive tag thus introduced should modify the natural substrate as little as possible in terms of steric and electronic effects, so as not to interfere with biological processes. Iodoaromatic and iodovinyl units are commonly used for labelling but, not infrequently, they lack some of the above desirable features.



1

The purpose of this work is to present the advantages of a small, simple, and stable iodinated unit, the β-iodoethoxyl moiety, 1.

The unusual stability of β-iodoethyl ethers of general formula 1, was pointed out over a century ago [2,3] and later confirmed [4,5]. Our own interest in iodinated tracers of D-glucose led to the attachment of the β–iodoethoxyl moiety on different hydroxyl groups [6,7]. The advantages of the a β–iodoethoxyl unit would be most apparent however, with a substrate that could not otherwise be efficiently labelled, such as 6-iodohexanoic acid. 2 shows rapid loss of iodine after labelling, which is not surprising in that the effect of chain length on the stability of the iodine-carbon bond of such ω-iodo carboxylic acids has been well documented [8]. A direct comparison of the radiochemical stabilities of 2 and 3 (the latter is a compound in which a methylene of the former is replaced by oxygen to give a β-iodoethoxyl derivative) therefore seemed appropriate.



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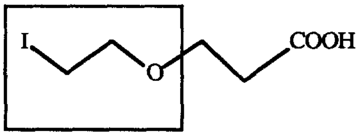
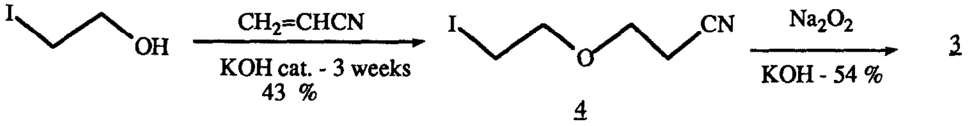


3

In that conjugate addition [9-11] of 2-iodoethanol to an acrylate was unsuccesful, we carried out the (reversible) addition to acrylonitrile to secure 4 [12] which could be purified by MPLC [13]. Alkaline oxidation of the nitrile group [14,15] then afforded the desired β-iodoethoxyl derivative 3 [16].



Radioiodine introduction could be accomplished by ^{123}I / ^{127}I isotopic exchange (Na*I / acetone, 105 °C , 20 min.) in high (> 95 %) radiochemical yield (typical activity ~ 45 MBq); the required heating reflects the stability of the carbon-iodine bond to displacement reactions, which can be attributed to the β-effect of the oxygen substituent [17]. At room temperature, no deiodination was observed, again in accordance with the chemical stability of this particular group.

Most revealing, however, of the radiochemical stability of the β-iodoethoxyl group, was the direct comparison of labelled 3 with the analog 2 lacking the β oxygen.

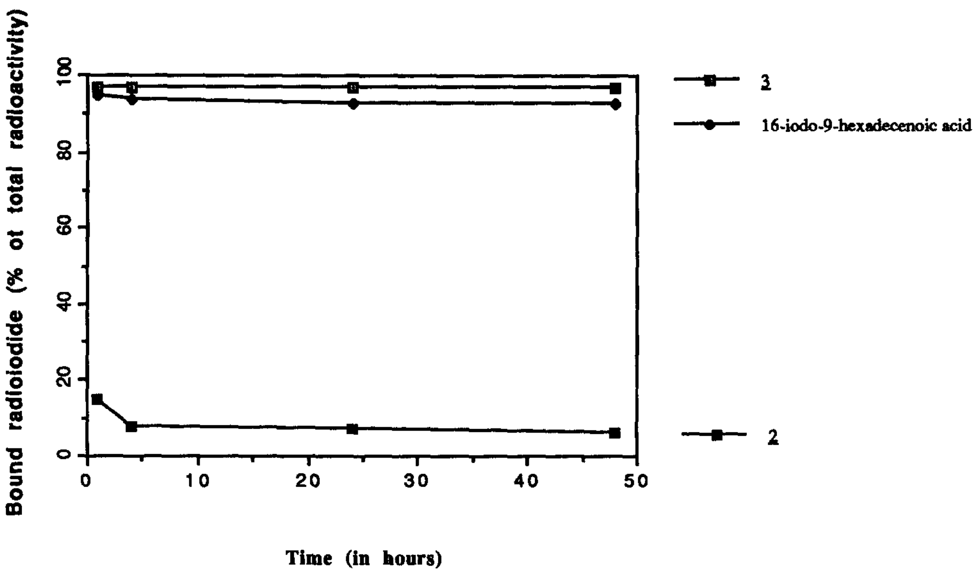


Figure : Comparison of stabilities of radiolabelled 2 (data taken from ref. 8) and 3 in 6 % HSA[18] .

As shown in the figure, no significant deiodination of 3 was observed (< 5 % after 2 days), which contrasts sharply with the results obtained (> 85 % after 1 hour) with 6-iodohexanoic acid 2 under identical conditions [8,18]. Furthermore, 3 is of a similar stability as 16-iodo-9-hexadecenoic acid [8].

Time	Heart	Liver	Lungs	Kydneys	Brain
15 sec.	17.8 ± 1.5	2.3 ± 0.9	18.4 ± 2.8	8.6 ± 1.4	5.5 ± 1.7
30 sec.	7.9 ± 2.1	5.5 ± 0.3	12.6 ± 3.0	8.8 ± 1.0	5.1 ± 0.4
1 min.	6.2 ± 1.2	7.8 ± 0.6	12.0 ± 1.9	9.0 ± 0.4	4.7 ± 1.2
2 min.	5.3 ± 0.3	8.5 ± 1.7	10.9 ± 1.3	11.3 ± 1.6	4.1 ± 0.6
5 min.	4.2 ± 0.3	9.9 ± 0.6	8.8 ± 0.8	13.2 ± 0.6	2.4 ± 0.2
10 min.	3.2 ± 0.4	7.1 ± 1.0	6.5 ± 0.4	12.7 ± 2.8	1.6 ± 0.2

Table : Biodistribution of ^{123}I labelled 3 in mice (the values, expressed in percents of injected dose per gram of organ, are the means of three experiments).

Compound 3, stable under physiological conditions, can be viewed as a lower fatty acid homolog and a study of its biodistribution in mice was felt to be of interest. The accompanying table presents the amount of radioactivity observed in various tissues observed with time. It is of interest to note that levels in organs such as the brain [19] are not negligeable.

The comparison of 2 and 3 would seem to indicate considerable potential for the the β-iodoethoxyl unit in labelling, particularly since the introduction of radioactive iodine isotopes into this stable unit is carried out by a simple isotopic exchange reaction. The incorporation of 1 into other biomolecules should prove to be of interest and is presently being carried out in our laboratory.

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12: 4 : oil; ^1H nmr (200 MHz - $CDCl_3$): multiplets at 2.5 ($C\underline{H}_2CN$), 3.2($C\underline{H}_2I$) and 3.6 ppm($C\underline{H}_2O$); ^{13}C nmr (50 MHz - $CDCl_3$): 3.5(CH_2I), 18.9 ($\underline{C}H_2CN$), 65.1 and 71.4 ($\underline{C}H_2\,O\,\underline{C}H_2$), 118.1(CN).

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16. 3 : m.p.: 72-3 °C; ^1H nmr (200 MHz - $CDCl_3$): multiplets at 2.3 ($C\underline{H}_2COOH$), 3.0 ($C\underline{H}_2I$) and 3.6 ($C\underline{H}OC\underline{H}_2$), 6.1 and 6.4 ppm (exch. protons); ^{13}C nmr (50 MHz - $CDCl_3$) : 3.6 ($\underline{C}H_2I$), 35.4 ($\underline{C}H_2CO$), 65.5 and 70.4 ($\underline{C}H_2O\underline{C}H_2$), 173.3 (CO).

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