Journal of Labelled Compounds and Radiopharmaceuticals

Published online 25 September 2008 in Wiley Interscience
(www.interscience.wiley.com) DOI: 10.1002/jlcr.1537

Addendum to: Synthesis of tritium-labeled bilirubin

Sir,

Latli and coworkers recently described a synthesis of tritium-labelled bilirubin by the reduction of biliverdin with sodium borotritiide.[1] They failed to note that an essentially identical, but faster and higher-yield, procedure was published in this journal by Hutchinson *et al*. in 1981[2] and a similar procedure by Ives and Gardner in 1990.[3]

Coverage of the background literature is misleadingly incomplete in other ways. For example, while noting that tritiated bilirubin has previously been prepared chemically by pyrolysis of a bilirubin derivative and biosynthetically in dogs, the authors did not mention that tritiated bilirubin, labelled in the propionic acid sidechains, has also been made by a one-pot chemical exchange procedure[4] or that rats, rather than dogs, have most frequently been used for its biosynthesis.[5] In their published procedure, it is unclear why reduction mixtures were stirred for two consecutive 12 h periods when borohydride reduction of pure biliverdin to bilirubin takes only minutes.[2,5] Such unnecessarily long reaction times may partly account for their apparently low chemical yield of labelled bilirubin, since the pigment is unstable in alkaline solutions. However, the low yield of product may also have been partly due to the use of biliverdin starting material of questionable purity; described in the vendor catalog as 80%, but possibly less.[6] Lastly, the authors fail to note that their product, being isomerically heterogeneous, is unsuitable for investigational use without further purification to remove non-IXα isomers. This has been achieved in the past by thin-layer chromatography,[3] but becomes unnecessary if isomerically pure biliverdin-IXα is used as the starting material. An advantage of the biosynthetic method is that the product, which is labelled at multiple positions compared with the single position in the borotritiide product, is isolated in crystalline form as the desired IXα isomer uncontaminated with non-IXα impurities.

There is a mistake in reference 9 of the paper; the publication year should be 1994, not 1993. And the labelled precursor used in biosynthetic methods is not 'beta-aminolevulin acid-2,3-^{3}H', as stated in the paper, but δ-aminolevulinic acid-2,3-^{3}H (or 3,5-^{3}H).[5] β-Aminolevulin(ic) acid is not a biosynthetic precursor of bilirubin.

Antony F. McDonagh, PhD, MRSC
Department of Gastroenterology
University of California, San Francisco,
San Francisco, CA 94143-0538, USA

References

[1] B. Latli, M. Hrapchak, D. Krishnamurthy, C. H. Senanayake, *J. Label. Compd. Radiopharm.* **2008**, *51*, 106–108.
[2] D. W. Hutchinson, N. M. Wilkes, H. Y. N. Au, *J. Label. Compd. Radiopharm.* **1981**, *18*, 1401–1404.
[3] N. K. Ives, R. M. Gardiner, *Ped. Res.* **1990**, *27*, 436–441.
[4] F. E. Hancock, D. W. Hutchinson, A. J. Knell, *Biochem. J.* **1976**, *157*, 511–512.
[5] A. F. McDonagh, in: *The Porphyrins*, Vol. 6, (Ed. D. Dolphin), Academic Press, **1979**, pp. 293–491.
[6] A. F. McDonagh, *Hepatology* **2005**, *41*, 680–681.

 Copyright © 2008 John Wiley & Sons, Ltd.