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Letter to the Editor

Formation of diastereomeric derivatives of 2-arylpropionic acids using L-leucinamide: the derivatization principle and its applicability

A reply

Sir,

Enantiospecific aspects of the interpretation of drug action have gained increasing interest within the past few years, reflected by an exponential increase of research papers in this field. One class of non-steroidal anti-inflammatory drugs, the 2-arylpropionic acids, attracted considerable attention, mainly because of the inversion of distomer to eutomer, which was observed for some of these compounds [1].

In 1985 Björkman [2] described a method for estimating indoprofen enantiomers using L-leucinamide (following activation with ethyl chloroformate). Using this principle with the same activation step, I was able to derivatize a series of compounds from the 2-arylpropionic acid group (benoxaprofen, carprofen, ciclopropfen, flunoxaprofen, flurbiprofen, naproxen and pirprofen, and indoprofen as control) and separate their diastereomeric derivatives. In 1987 I reported the wide applicability of the principle involved and emphasized that in general the formation of L-leucinamide derivatives of 2-arylpropionic acids is another reasonable alternative to their coupling with α-methylbenzylamine [3].

As it was possible to apply Björkman's mode of activation and coupling component for the analysis of the series of compounds, I called it "the method".

For ketoprofen [4] and very recently for e.g. flurbiprofen [5] the derivatization with L-leucinamide (after activation with ethyl chloroformate) was described. Mehvar et al. [6] used the same principle, but with trichloroethyl chloroformate instead of ethyl chloroformate for activation, for an assay method for tiaprofenic acid.

In another publication (Letter to the Editor) Mehvar and Jamali [7] reported that, using "my method", they were not able to analyze ibuprofen. We derivatized *R/S*-ibuprofen using L-leucinamide after an activation of the acid either with ethyl chloroformate [2] or with 1,1′-carbonyldiimidazole [8]. Products were formed following both these activation methods. A resolution into two peaks was

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possible on a reversed-phase column (ODS) with acetonitrile–water–phosphoric acid (50:50:0.5, v/v/v) as mobile phase. The separation factor was 1.05, the resolution factor 0.75. Thus using the general principle and in fact the same method, we were able to analyze ibuprofen. We have not used this method for tiaprofenic acid, but we were not surprised to find that some modifications like the use of trichlorethyl chloroformate [6] are necessary for the assay under certain conditions. So in fact, in my opinion "the method" should be taken as derivatization principle rather than absolutely.

In addition, L-leucinamide is not a fluorescent or UV label because of its lack of chromophores. Ibuprofen coupled to α-methylbenzylamine or S-(−)-naphthylethylamine, respectively, gave significantly higher UV responses and furthermore, since the products are more lipophilic, a better resolution by reversed-phase high-performance liquid chromatography on an ODS stationary phase. Separation is possible with a gradient elution using acetonitrile (40–60%) in 0.5% phosphoric acid. The derivatization products were also formed using carbonyldiimidazole for activation. However, here the derivatization yields were much lower in all three cases, i.e. for all the coupling components. (The enantiospecific assay of ibuprofen with S-(−)-naphthylethylamine is also subject of a report, which was published very recently [9].)

In general, different activation procedures (as formation of imidazolides, acyl chlorides, mixed anhydrides) are possible. The decision which activation procedure or which coupling component to choose has to be made on the basis of enantiomeric purity of the chiral reagents, the derivatization yield and the chromophoric and the chromatographic properties of the derivatization products.

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