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Reply

Re: Discussion on "Stability indicating methods for the determination of loratadine in the presence of its degradation product" [N.A. El Ragehy et al., J. Pharma. Biomed. Anal. 28 (2002) 1041–1053]

Actually the work done in this paper was carried out about five years ago, thus it took some time to memorize and check back again. Here are the main points:

1- Yes, it is obvious that the structure of loratadine is missing the double bond between the three rings and the piperidine ring. It was a structure drawing mistake and we apologize for.
2- The MS and IR spectra were not run at our institute. They were carried out in the laboratories of College of Science, Cairo University; that is why it was not easy to check how the analyses were carried out.
3- We relied on MS and IR to help in elucidation of the structure of the reaction product since both charts showed evidence to our suggestion. This was performed keeping in mind that the main aim of the paper is to analyze loratadine itself in the presence of the isolated hydrolysis product, not to synthesize the product, i.e. we shall not work on the product, either pharmacologically or toxicologically, it was just a suggestion or an expectation for the structure of this product. However, we need to clarify the following points to show on which basis our suggestion was based.

i- The parent peak in the MS of the isolated degradation product – as shown in the published article – lies at *m/e* (352) which is nearly equal to the M.W. of the acid derivative of the drug, not to the M.W. after removal of CO_2 (310).
ii- The IR spectrum of the degradation product shows a broad band at 3200–4000 cm^{-1} which is attributed to the presence of the OH group of the carboxylic group of the acid derivative expected.
iii- In our work, the drug was refluxed for only 4 h, then the reaction was stopped by acidification. In the Canadian procedure, they kept the hydrolysis reaction on reflux for 48 h (2 days) which may be considered drastic conditions, leading to a decarboxylation step.
iv- We referred to the given reference in the comments; *Organic Chemistry* by Wade Jr. page 990, there is nothing mentioned that "carbamic acids are unstable" as copied by the authors. It is stated that carbamic acid itself is unstable. Our product is a carbamic acid analogue or derivative, not the acid itself. If our product is unstable so why did it take them 2 days to change to the decarboxylated derivative? Solomons and Fryhle [1] mentioned that "carbamates tend to be nicely crystalline solids and are useful derivatives for identification of alcohols." Thus, it can be explained why the reaction product in our procedure (after 4 h reflux) was a carbamic acid (carbamate) derivative.
v- From an organic point of view, it may be assumed that decarboxylation took them 2 days to take place since upon decarboxylation, the N of the NH group of desloratadine, will carry a −ve charge, which needs to be stabilized through resonance. There could be no resonance with the piperidene ring which lacks unsaturation. Since there is no unsaturation in the piperidine ring, so the COOH can still remain stable as under our conditions (4 h hydrolysis).

Reference

[1] Solomons & Fryhle Organic Chemistry, eighth ed., John Wiley & Sons. Inc., 2004, p. 876.

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