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Discussion

Degradation product of loratadine

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Dear Sir,

The article "Stability indicating methods for the determination of loratadine in the presence of its degradation product," by N.A. El Ragehy et al. in the *Journal of Pharmaceutical and Biomedical Analysis* 28 (2002) 1041–1053, was brought to our attention by the regulatory authorities in Canada and we have attempted the synthesis of the degradation product by the method described in the article. We found that we were not able to repeat the results reported in the article and take issue with a number of points in the article.

These issues included:

1. The structures of loratadine and the hydrolysis product are drawn incorrectly. The bond between the three-ring structure and the piperidine ring is shown as a single bond in the paper and should be a double bond.
2. The structural elucidation relies only on MS and FTIR analysis. It is prudent to confirm structural assignments with complementary NMR data.
3. The experimental section of the manuscript provided no information on how the FTIR or MS analysis was conducted.
4. The MS spectrum of the degradation product does not match the proposed structure. The acid derivative of loratadine has a molecular weight of 354.8 g/mol, there is no peak in the spectrum that represents this molecular weight.

Our attempts to isolate the degradation product followed the method outlined in the article and were monitored using LC–UV–MS. Loratadine was refluxed in a 0.5 M solution of KOH in ethanol and the reaction mixture was examined by LC–UV–MS after 3 and 4 hours at reflux. After 4 hours , the reaction had converted less then 2% of the loratadine to the degradation product. The results clearly showed that there was only one peak other then loratadine in the chromatogram and therefore only one degradation product being formed. That peak is consistent in retention time and molecular weight with desloratadine. Examination of the data indicated that there was none of the acid degradation product present in the reaction mixture. It appears that after cleavage of the ester the acid degradation product was immediately undergoing decarboxylation to form desloratadine as shown in Fig. 1.

The hydrolysis product described in the paper is a carbamic acid. Wade [1] writes that carbamic acids are unstable, while Smith and March [2] show that carbamic acids will undergo the loss of CO_2 to form the amine. Perhaps the most convincing explanation for our observation is the paper by Johnson and Morrison [3], which gives the rate constant for this type of decarboxylation at $\sim 10^8\ M^{-1}\ s^{-1}$.

We repeated the hydrolysis reaction and followed it to completion (48 h). This reaction mixture was worked up and a solid sample of the hydrolysis product was isolated. The isolated material was subject to MS/MS, accurate mass MS and ^1H and ^{13}C NMR analysis. All the results were consistent with the conclusion that the isolated material was desloratadine. The MS/MS results for the isolated product were identical to those obtained under the same conditions with USP loratadine related compound A (desloratadine).

The identification of the loratadine hydrolysis product in their paper was flawed and incomplete. We believe these errors led the authors to an incorrect structure of the hydrolysis product. Our studies show that under these conditions there is only a single degradation product, the desloratadine. The intermediate acid derivative can not be isolated and will not be present in loratadine raw material or finished product.

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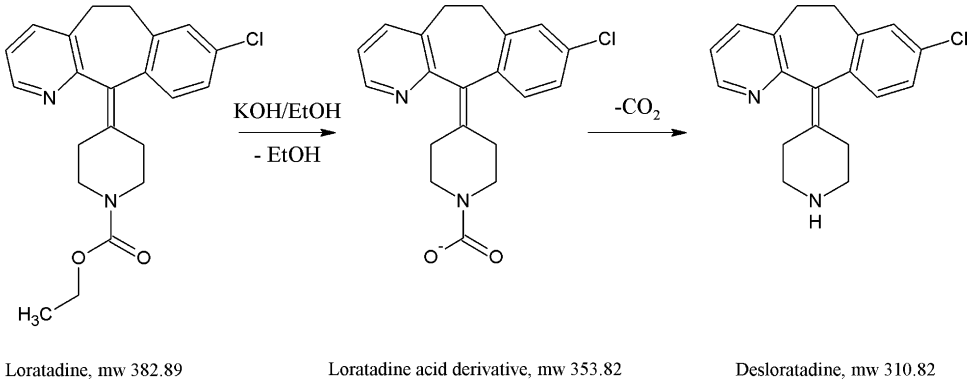

Loratadine, mw 382.89 Loratadine acid derivative, mw 353.82 Desloratadine, mw 310.82

Fig. 1. Alkali hydroslysis of loratadine.

References

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