REBUTTAL TO COMMENTS MADE BY P. POTIER REGARDING OUR ARTICLE IN "HETEROCYCLES" AND ENTITLED "STUDIES ON THE SYNTHESIS OF BIS-INDOLE ALKALOIDS. XIII. A SYNTHESIS OF CATHARINE." BY J.P. KUTNEY, J. BALSEVICH AND B.R. WORTH.

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The comments by P. Potier as they relate to our work in the above-mentioned article are not supported by scientific fact since this author does not have any evidence as to when and how experiments were conducted in our laboratory. His implication that we rushed into print with the above article after the article by N. Langlois and P. Potier, J. Chem. Soc., Chem. Commun., 102 (1978) on leurosine appeared, is completely false. We find it distasteful to pursue this matter in this fashion and only wish to make our rebuttal as it is based on real fact and not conjecture. The following comments will hopefully clarify our position and will reveal to the scientific community that our experiments in the above and related areas represent independent investigations.

1. The publication by Langlois and Potier, as noted above, appeared in the February 1978 issue. Our article was submitted to the editorial office of Heterocycles on February 7, 1978 and received in that office on February 14, 1978. Bearing in mind that Chemical Communications published by the Chemical Society, London is sent to our institution by sea mail it was clearly impossible for us to be aware of the experiments published by the above authors. In point of fact, we did not have any information of such results until several months after our article had been submitted.

2. Secondly, our synthesis of catharine as detailed in the Heterocycles article (Heterocycles, 9, 493 (1978)) represents only a small portion of a long series of investigations involving oxidative transformations within the bisindole area. The first publication in this area appeared in 1976.

J.P. Kutney, J. Balsevich, G.H. Bokelman, T. Hibino, I. Itoh and A.H. Ratcliffe, Heterocycles 4, 997 (1976). Studies on the Synthesis of Bisindole Alkaloids III. The Synthesis of Leurosine and 3'-Hydroxyvinblastine.

The experiments described therein represent our studies with oxygen and t-butyl hydroperoxide as reagents in this area and reveal the first synthesis of leurosine.

The next publication in this series, also published in 1976, is as follows.

J.P. Kutney, J. Balsevich and G.H. Bokelman, Heterocycles 4, 1377 (1976). Studies on the Synthesis of Bisindole Alkaloids VI. Novel Lactam Derivatives in the Vinblastine Series.

In this publication we report the isolation of an oxidation product (structure XII) and tentatively assigned the name, 5'-oxoleurosine to this product.

The detailed experiments in the above series were submitted to the editorial office of Can. J. Chem. in June, 1977 and published as follows.

J.P. Kutney, J. Balsevich, G.H. Bokelman, T. Hibino, T. Honda, I. Itoh, A.H. Ratcliffe and B.R. Worth, Can. J. Chem., 56, 62 (1978). Total synthesis of indole and dihydroindole alkaloids XII. Selective functionalization of various bisindoles. Efficient syntheses of leurosine and related bisindole alkaloid derivatives.

As our experiments continued in this and other areas it was essential to make appropriate comparisons of our synthetic substances with natural alkaloids (catharine, vinamidine, vincathicine, carosine etc.) kindly supplied by Dr. Gordon Svoboda, Eli Lilly Company. During these studies it was realized that 5'-oxoleurosine is in fact catharine as documented in our publication on the synthesis of catharine.

Two years after our initial publications in this area we now find the Langlois and Potier publication appearing in Chemical Communications and to which Potier now refers in his comments.

3. Our own suspicions about the "artefact" nature of leurosine, catharine, vinamidine etc. were evaluated in the laboratory by the use of cell-free extracts of Catharanthus roseus and the various results have recently appeared in the following.

K.L. Stuart, J.P. Kutney and B.R. Worth, Heterocycles, 9, 1015 (1978). Studies on the Synthesis of Bisindole Alkaloids XIV. Enzyme Catalyzed Formation of Leurosine.

K.L. Stuart, J.P. Kutney, T. Honda and B.R. Worth, Heterocycles, 9, 1391 (1978). Studies on the Biosynthesis of Bisindole Alkaloids. The Final Stages in Biosynthesis of Vinblastine, Leurosine and Catharine.

K.L. Stuart, J.P. Kutney, T. Honda and B.R. Worth, Heterocycles, 9, 1419 (1978). Intermediacy of 3',4'-Dehydrovinblastine in the Biosynthesis of Vinblastine-type Alkaloids.

Conclusions

In 1976, our group studied the oxidation of 3',4'-dehydrovinblastine and isolated leurosine, 5'-oxoleurosine etc. The latter product has been shown to be catharine in more recent studies (1977).

In 1978, our group has shown that leurosine and catharine are not artefacts as claimed by others but are in fact obtained from 3',4'-dehydrovinblastine.

Finally the last paragraph of Potier's "comment" suggests that syntheses of biologically inactive compounds should not be published in preliminary form but rather as footnotes. We hasten to add that on this basis many fine synthetic achievements would remain unpublished.

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