ON THE TOTAL SYNTHESIS OF (±)-FLAVIPUCINE AND ITS REARRANGEMENT TO ISOFLAVIPUCINE

John A. Findlay
Chemistry Department, University of New Brunswick, Fredericton, N.B., E3B 5A3, Canada

Abstract -- A clarification of imputed discrepancies in the literature relating to isoflavipucine is presented and the mechanism of epoxidation in the synthesis of flavipucine 1 is discussed in response to a claim of an unequivocally established elimination/addition pathway.

In 1972[1] we proposed the structure 1 for the antibiotic flavipucine and this we recently confirmed in every detail by X-ray crystallographic studies.[2] In 1974 we proposed structure 2 for isoflavipucine a remarkable isomerization product of 1.[3,4] Our discovery in 1973 of a novel high yield condensation of 4-hydroxy-6-methyl-2-pyridone 4 with isobutyl glyoxal 5 to provide 3a[3] led us to correctly forecast successful completion of our total synthesis of flavipucine using 3a as intermediate. Long after this event Wendler et al.[6] have entered the scene and did so by oxidizing the acetate of our published intermediate 3a to flavipucine. Their paper deliberately obscured the fact that we reported preparation of compound 3a much earlier.

In view of two additional articles by Wendler et al.[7,8] in which serious questions were raised about aspects of our work[3,4] on the flavipucine 1 to isoflavipucine 2 transformation, as well as our proposed mechanisms for the oxidation of the key intermediate 3a in our two-step total synthesis of (±)-flavipucine 1[10], it is necessary to bring attention to the following facts.

In an attempt to repeat our work Wendler et al. report transforming flavipucine 1 to isoflavipucine 2 by refluxing for 10 h in xylene (of unspecified quality). They concluded that our lack of success in effecting the rearrangement 1 to 2 in boiling xylene, as reported in our pioneering paper[4] on isoflavipucine, was due to too short an exposure time and incorrectly concluded that we "were led to

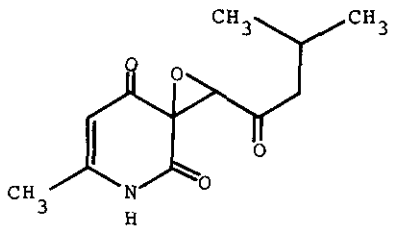
mechanistic conclusions which no longer appear tenable".[9] In our report[4] we specified the use of anhydrous xylene at 139°, since the presence of protic species would not serve to distinguish a possible radical mechanism from an ionic pathway. We have later ascertained[4] that addition of traces of water to the boiling xylene medium promotes a rapid transformation of flavipucine 1 into isoflavipucine 2 at 139°. Thus our results are not at variance with the Wendler et al. experiments and, contrary to their remarks, our mechanistic proposals incorporating ionic rather than radical intermediates are perfectly valid. Wendler's group goes on to question our observation[4] that aqueous sodium carbonate solution promotes the transformation 1 to 2. This is in view of their finding that silica gel alone (no mention of quality, solvent, yield, rate, etc. is made) catalyses the rearrangement 1 to 2 and the fact that we employed a silica gel tlc system in detecting isoflavipucine 2. Throughout our studies[1,4] we have employed silica gel in conjunction with purified solvents to separate flavipucine from isoflavipucine, both by column chromatography (often lasting several days) and by layer chromatography, and any noticeable rearrangement would not only have been detected but would have frustrated our pioneering success in first isolating and separating isoflavipucine and flavipucine from the Aspergillus flavipes cultures medium.[2] Furthermore, invariably, monitoring of our sodium carbonate catalysed (and other attempted) rearrangement reactions involved parallel tlc spotting of reaction product and flavipucine and the latter showed no detectable rearrangement under the conditions employed.[11]

As noted above, in 1973 we reported a substantial development in our efforts to effect total synthesis of (±)-flavipucine 1, namely the preparation of diol 3a by the facile condensation of the α-keto aldehyde 5 with 4-hydroxy-6-methyl-2-pyridone 4.[5] This key intermediate diol 3a was subsequently efficiently transformed by us to (±)-flavipucine 1 in a single step by treatment with tert-butyl hydroperoxide at 40-50°C and we proposed two possible mechanisms both proceeding via the peroxyketone intermediate 3c.[10] In addition we reported that diol 3a readily exchanges its sidechain hydroxyl under solvolysis conditions using alcohols to give ethers such as 3b, a discovery which prompted our exploration of the use of alkyl hydroperoxides to complete the total synthesis of (±)-flavipucine 1.

In pursuing our mechanistic proposals for these novel exchange reactions leading

to 3b and 3c, Wendler and Girotra[8] claimed to have "unequivocally" established that our suggested intermediate, the ene-trione 6 is involved in the exchange phenomena of 3a in view of their finding that refluxing 3a in tetrahydrofuran for 24 h in the presence of 1,3-diphenylisobenzofuran (DIBF) gave the corresponding Diels-Alder adduct (in unspecified yield).

It is imperative to point out that while this experiment supports the existence of the ene-trione 6 in the refluxing tetrahydrofuran/DIBF system, by no means should it be construed as unequivocal proof of its intermediacy in the exchange reactions of 3a, as claimed by Wendler and co-workers--any more than the isolation of competing elimination products in any substitution reaction proves that the latter must proceed via an elimination/addition sequence!



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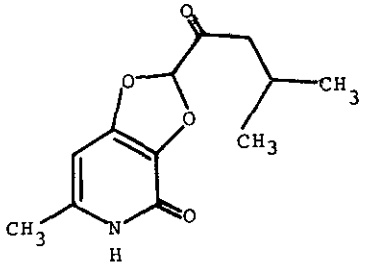

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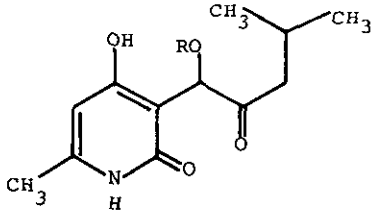
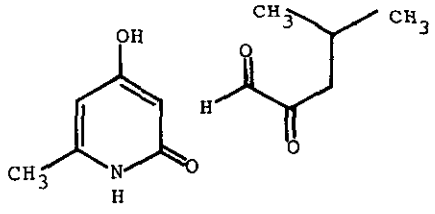


3a, R = H

3b, R = Et

3c, R = O^{t}Bu



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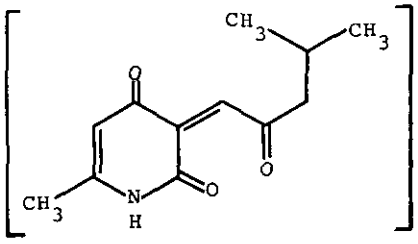

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6. N. N. Girotra, Z. S. Zelawski, and N. L. Wendler, J. Chem. Soc., Chem. Comm., 1976, 566.
7. N. N. Girotra, A. A. Patchett, and N. L. Wendler, Heterocycles, 1977, 6, 1299.
8. N. N. Girotra and N. L. Wendler, Heterocycles, 1978, 9, 417.
9. No elaboration of this criticism or alternate mechanism is offered by Wendler et al.[1]
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11. It is evidently possible that without careful control of operating parameters the rearrangement 1 to 2 may occur at a noticeable rate on a silica gel system as apparently discovered by Wendler et al.[1]

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