Pergamon

Tetrahedron Letters, Vol. 38, No. 3, pp. 305-308, 1997
Copyright © 1996 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02339-8

An Unexpected Oxidative Decarboxylation Reaction of Frenolicin-B

Susan D. Van Arnum* and Nancy Stepsus[1]

A Contribution from Vitamins Process Research and Development

Hoffmann-La Roche Inc., Nutley, NJ 07110, USA

and

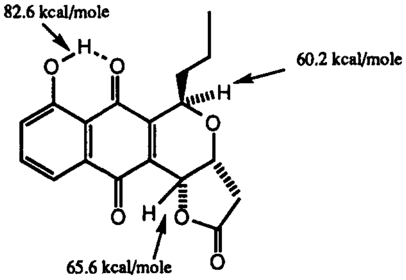
Barry K. Carpenter

A Contribution from the Department of Chemistry,

Cornell University, Ithaca, NY 14853, USA

Abstract: *In the presence of free radicals, frenolicin-B (1) undergoes an unexpected oxidative decarboxylation reaction to afford 2 in an overall yield of 51%. Theoretical calculations support the proposed mechanism.*

Assessment of drug substance chemical reactivity is an important component in the development of new pharmaceuticals. These compounds typically decompose by either hydrolytic or radical mechanisms.[2] During preformulation studies on frenolicin-B (1)[3], we were asked to characterize the free radical mediated degradation pathway for this substance. We wish to report on the results of that investigation.

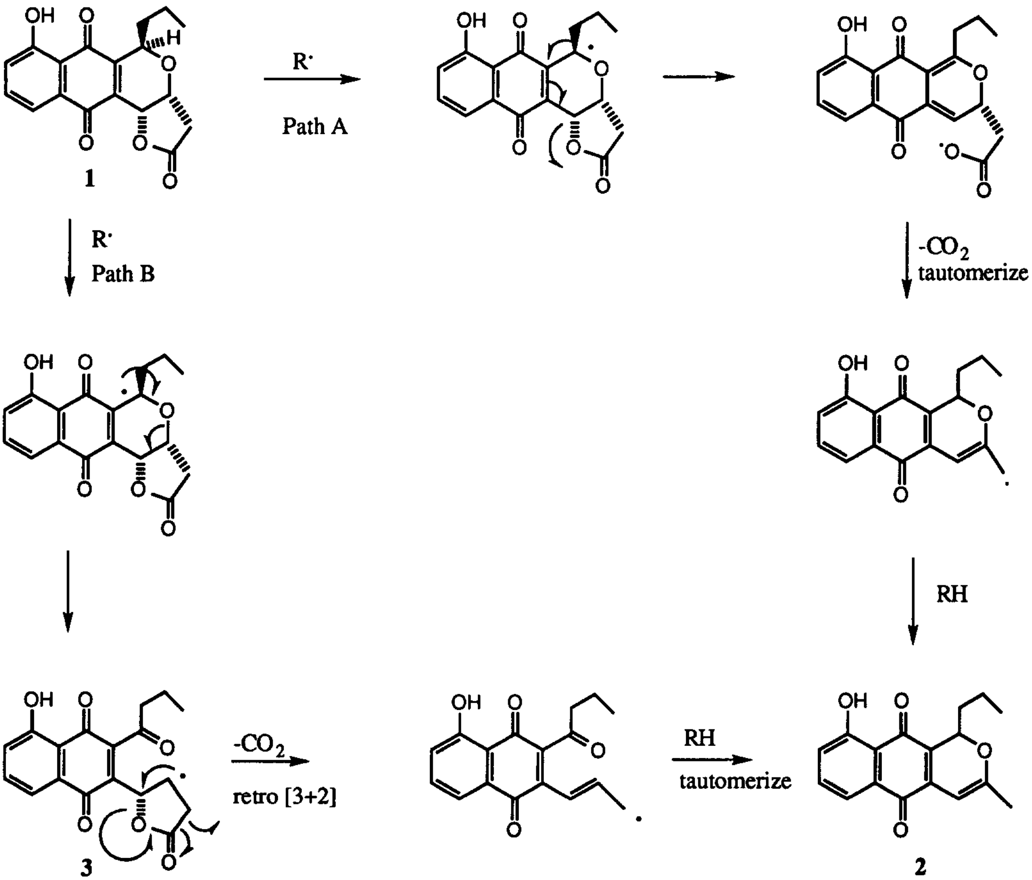


1

Figure 1

Inspection of frenolicin-B suggested that three sites may be reactive towards hydrogen abstraction as illustrated in Figure 1. Indeed, these empirical observations were supported by PM3 semiempirical MO calculations which indicated that the tertiary hydrogen α to the pyran ring oxygen has the lowest C-H bond dissociation enthalpy (BDE). Interestingly, the bond dissociation enthalpy for the phenolic O-H bond is expected to be the greatest, approximating the calculated value for 2,6-*tert* -butyl-4-methylphenol[4] and the experimentally determined value for 2,4,6-*tert*-butylphenol.[5] Although a resonance stabilized radical would result from abstraction of the phenolic hydrogen, the large BDE may be due to protection by an intramolecular hydrogen bond, in accordance with the work of Wagner on the stabilization of phenols towards hydrogen abstraction in polar solvents.[6]

In the event, reflux of frenolicin-B in the presence of air and AIBN in methanol for two days afforded a 51% yield of racemic decarboxylated product 2[7] along with other uncharacterizable materials.[8] Our tentative mechanism, (Scheme 1) in agreement with theoretical calculations involves hydrogen abstraction at position 5 as the primary step. Two different pathways to compound 2 are possible; the feasibility of each was ascertained on the basis of theoretical calculations. PM3 calculations suggest that the activation enthalpy for direct opening of the lactone ring is approximately 46 kcal/mole (Path A) whereas the enthalpy for pyran ring opening (Path B) is calculated to be 35 kcal/mole. Although these numbers may not be useful in an absolute sense, their relative magnitudes are more meaningful. In the case of the more energtically favored path B, decarboxylation of radical 3 and hydrogen abstraction followed by ring closure would yield the observed product 2.



Scheme 1

In summary, an interesting radical-mediated oxidative decarboxylation reaction of frenolicin-B (**1**) has been described and the postulated mechanism has been supported by calculations.[9]

Acknowledgements: We wish to thank the Physical Chemistry Department of Hoffmann-La Roche and in particular, Mr. Gino Sasso for their assistance and Drs. David Burdick (Vitamins Process Research and Development) and Carole A. Bailey (Pharmaceutical Research and Development) of Hoffmann-La Roche for helpful discussions.

References and Endnotes

1. Current Address: Synthesis Development, Hoffmann-La Roche, Inc., Florence, SC 29502.

2. Wells, J. *Pharmaceutical Preformulation: The Physicochemical Properties of Drug Substances*; Halsted Press, New York, 1988.

3. Iwai, Yuzuru; Kora, Akiko; Takahashi, Yoko; Hayashi, Takako; Awaya, Juichi; Masuma, Rokurou; Oiwa, Ruiko; Omura, Satoshi. *J. Antibiot.* **1978**, *31*, 959.

4. Lucarini, M.; Pedulli, G.F.; Cipollone, M. *J. Org. Chem.* **1994**, *59*, 5063.

5a. Arnett, E.M.; Flowers, R.A. *Chem.Soc. Rev.* **1993**, 9. b. Mahoney, L.R.; Ferris, F.C.; DaRooge, M.A. *J. Am. Chem. Soc.* **1969**, *91*, 3883.

6. Wagner, D.D. M.; Lusztyk, E.; Pagé, D.; Ingold, K.U.; Mulder, P.; Laarhoven, L.J.J.; Aldrich, H.S. *J. Am. Chem. Soc.* **1995**, *117*, 8737.

7. Compound **2** had the following properties: MP 83-86°C. ^{1}H NMR (d_6-DMSO, 80°C) δ 0.92 (t, 3H, $CH_2C\underline{H_3}$), 1.46 (m, 2H, $CH_2C\underline{H_2}CH_3$) 1.92 (t, 2H, $\underline{CH_2}CH_2CH_3$) 2.00 (b, 3H, $CH{=}CC\underline{H_3}$) 5.50 (dd, 1H, $C\underline{H}O$), 5.86 (s, 1H, $CH_3C{=}C\underline{H}$) 7.29 (d, IH, Aromatic CH), 7.49 (d, 1H, Aromatic CH) 7.66 (t, 1H, Aromatic CH), 12.15 (s, 1H, OH). ^{13}C NMR (d_6-DMSO, 80°C) δ 13.04 (CH_3), 16.89 (CH_2), 19.90 (CH_3), 33.19 (CH_2), 71.94 (CH), 93.19 (CH), 114.65 (C), 118.52 (CH), 124.37 (CH), 131.08 (C), 135.41 (CH), 136.81 (C), 159.76 (C,C), 163.64 (C), 181.2 (C), 186.58 (C). IR (DRIFTS) 1668 cm^{-1} (C=O), 1643 cm^{-1} (H-bonded C=O). MS: m/z: 285 (M+H), 283 (M-H), 243 (285-C_3H_6), 241 (M-C_3H_7) UV Spectrum (Methanol) λ_{max} = 499.0 nm (ε= 5647), 265.0 nm (ε = 12,796), 209.0 nm (ε = 27,339); λ_{shl} = 423.0 nm (ε = 3449), 314.0 nm (ε = 5133). Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.70; H, 5.73. IR (DRIFTS) 1668 cm^{-1} (C=O), 1643 cm^{-1} (H-bonded C=O).

8. Interestingly, no reaction was observed under similar conditions when the decomposition was conducted in acetonitrile.

9. Further collaboration of this mechanism can from a control experiment in which the product **2** was subjected to the reaction conditions in the presence and absence of AIBN in d_4-methanol at reflux for one day. No H-D exchange was observed at position 5. This observation is consistent with the proposed mechanism. The authors are grateful for the referee's suggestion.

(*Received in USA* 19 *July* 1996; *revised* 19 *November* 1996; *accepted* 21 *November* 1996)