Tetrahedron Letters No. 36, pp 3353 - 3356. 0040-4039/79/0901-3353$02.00/0

OXAZIRIDINES AND OXYGEN TRANSFER. A REVISED MECHANISM FOR THE KINETIC RESOLUTION OF 2-n-PROPYL-3-METHYL-3-iso-BUTYLOXAZIRIDINE BY BRUCINE.

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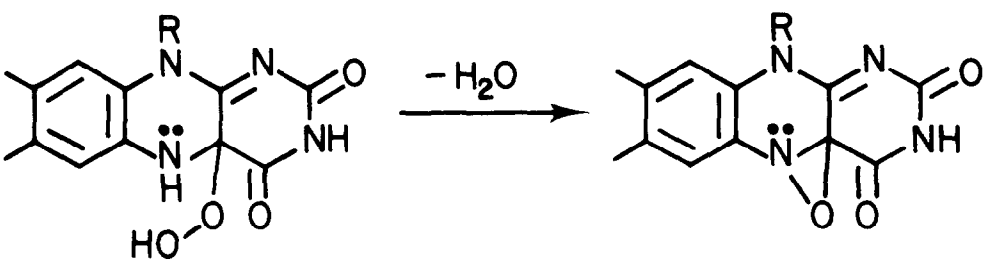
Abstract: The mechanism of kinetic resolution of an oxaziridine by brucine is re-examined. Contrary to a currently accepted report, two oxaziridines re-investigated do not transfer oxygen to the tertiary amine, brucine.

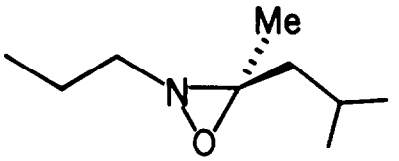
The flavin-dependent monooxygenases bind and activate molecular oxygen, ultimately transferring one oxygen atom to substrate and releasing the second as water.[1] Although flavin monooxygenations have been the object of extensive investigation, the structure of the flavin oxygenating species remains unknown. Recent work strongly implicates the 4a-hydroperoxyflavin 1 as an initial intermediate in the enzymic oxidations; this intermediate and derived species have been offered to explain the reactivity of the flavin, oxygen-transferring systems.[2a-h] Orf and Dolphin suggested[2b] the formation of flavin oxaziridine 2 from 1 and the direct transfer of oxygen from 2 to phenolates at monooxygenase active sites.



1 2

We have discussed[2h] the possible involvement of 2 in the in vivo formation of a flavin-based nitroxyl radical during phenol oxidations. The early report[3] of oxygen transfer from 2-n-propyl-3-methyl-3-iso-butyloxaziridine(3) and 2-tert-butyl-3-phenyloxaziridine (4) to brucine had prompted us to suggest that 2 functions directly in the biological, flavin-dependent conversion[4] of tertiary

amines to their N-oxides and secondary amines to the corresponding hydroxylamines. Herein we report, however, that oxaziridines 3 and 4 do not, as earlier reported, serve in the oxidation of brucine to its N-oxide. We present also a revised mechanism for the kinetic resolution of 3 by brucine.



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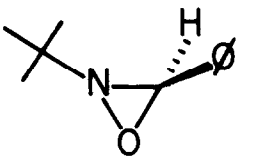

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Refluxing a methylene chloride solution of brucine and oxaziridine 3 leads to the precipitation of a white crystalline solid (mp 194°C, dec.), thought earlier[3] to be brucine N-oxide. Recovery of remaining 3 indicates preferential destruction of one antipode--after distillation and chromatography recovered 3 displays α_D^{20} - 4.34°, ℓ=1, neat.[5] Combustion analysis, ^{1}H NMR and field desorption (FD) mass spectroscopy[6] of the white crystalline precipitate shows the material to be the quaternized amine adduct of brucine and CH_2Cl_2. The material forms as well upon refluxing brucine alone in CH_2Cl_2. Similar adducts form from other tertiary amines and CH_2Cl_2.[7] Examination of the kinetic resolution reaction mixture by HPLC[8] shows no formation of brucine N-oxide. Thus, a revised mechanism for the genuine, kinetic resolution must be sought.

During chromatographic recovery of 3 from a kinetic resolution we isolated ketone 6.[9] Examination of the reaction mixture during kinetic resolution shows the formation of ketone 6 and imine 5 (Table). The resolution of 3 is effected therefore by brucine catalyzed fragmentation of the oxaziridine (Scheme). The

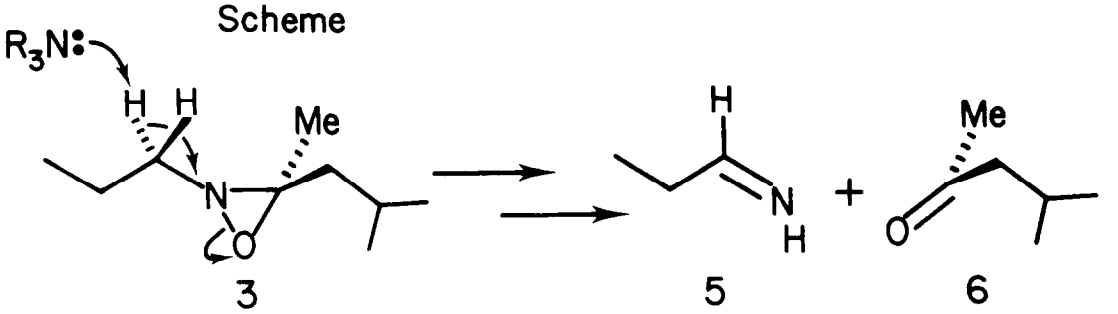
Table. Kinetic Resolution of Oxaziridine 3; Formation of Imine 5 and Ketone 6.[a]

Time Elapsed (hrs)	Percentage 3 Destroyed[b]	Percentage 5 Formed[c,d]	Percentage 6 Formed[b]
1.0	9.6-12.5	11.1-11.8[e]	10.0-11.8
4.0	33.6-34.8	28.6-30.5	30.1-33.8
10.0	52.6-55.5	23.0-25.9	49.3-50.7
16.0	62.5-68.1	14.7-18.0	59.1-62.5

[a]Range represents results of two kinetic runs, performed according to Emmons, reference 3a. [b]Determined by GLC vs. dodecane internal standard. [c]Determined by HPLC (C-18 column, 3:1, CH_3CN:H_2O) of the 2,4-dinitrophenylhydrazone derivative (2,4-DNP) vs. the 2,4-DNP of heptanal as internal standard. [d]The 2,4-DNP derivative was indistinguishable from an authentic sample by HPLC coinjection, mixture melting point and mass spectral fragmentation pattern. [e]At short reaction times 3 is converted quantitatively to 5 plus 6. Imine 5 is not stable to prolonged heating in the reaction mixture.

depicted reaction is known for oxaziridines[3] and has been used synthetically in an amine to ketone conversion.[10] Oxazirdine 4, lacking α-hydrogens is not resolved by brucine.[3] The alleged formation of brucine N-oxide from 4[3] is also incorrect; again the product formed is the brucine/CH_2Cl_2 adduct.

Scheme



3 5 6

Given the present findings, the ability of simple oxaziridines (e.g., 3 and 4) to transfer oxygen to amines must be seriously questioned. Whether or not suitably activated oxaziridines[11] (e.g., 2) will transfer oxygen to amines must be ascertained by further study.

Acknowledgement is made to the National Institutes of Health for support of this work. We thank Mr. Julian Adams for obtaining GLC/mass spectra, Professor Chris Walsh for helpful discussions, and Cathy Costello for obtaining the FD mass spectrum of the brucine-CH_2Cl_2 adduct.

References and Notes

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3. (a) Emmons, W.D. J. Am. Chem. Soc. 1957, 79, 5739. (b) See also: Emmons, W.D., Chapter IV in "The Chemistry of Heterocyclic Compounds", Vol. 19, Part I, Ed. A. Weissberger, Wiley Interscience, New York (1964).

4. See Prough, R.A.; Ziegler, D.M. Arch. Biochem. Biophys. 1977, 180, 363, and references therein.

5. Emmons (reference 3a) reports α_D^{24} - 2.80°, ℓ=1, neat and α_D^{22} - 3.94°, ℓ=1, neat for two kinetic resolutions of 3.

6. Anal., calcd. for $C_{24}H_{28}Cl_2N_2O_4 \cdot H_2O$, C, 57.95; H, 6.08; Cl, 14.26; N, 5.63; found, C, 57.66; H, 6.09; Cl, 14.07; N, 5.57. ^{1}H NMR (270 MHz, D_2O) δ (HOD) 0.73 (2H, AB q, J 9.8 Hz, $^+NCH_2Cl$). FD mass spectrum, $[R_3\overset{+}{N}-CH_2Cl\ Cl^-]^+$ parent cluster ions, m/e 478, 480, 482; $[R_3\overset{+}{N}-CH_2Cl]$ m/e 443, 445; $[R_3\overset{+}{N}-CHCl]$ m/e 442, 444; $[R_3\overset{+}{N}-CH_2]$ m/e 408; $[R_3N]^+$ m/e 394 (base peak).

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8. C-18 column, 1:1, CH_3CN: H_2O, NaOAc/HOAc buffered at pH 5.71. A control run shows brucine N-oxide to be stable to kinetic resolution reaction conditions.

9. Indistinguishable from an authentic sample by GLC coinjection and by GLC/mass spectral fragmentation pattern.

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(Received in USA 8 May 1979)