MECHANISM OF EPOXIDATION IN THE SYNTHESIS OF FLAVIPUCINE. THE EXCHANGE REACTION OF ITS PRECURSORS

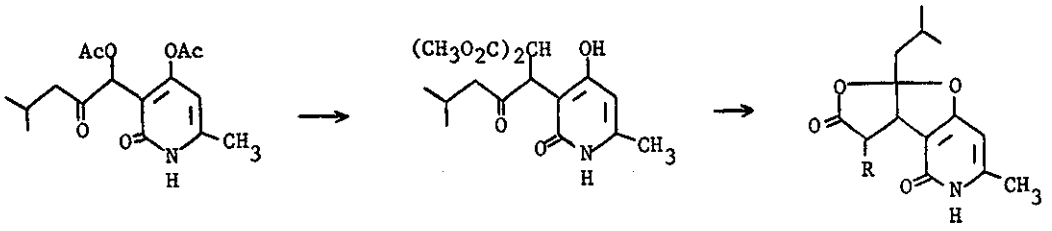
Narindar N. Girotra and Norman L. Wendler

Merck Sharp & Dohme Research Laboratories
Division of Merck & Co., Inc.
P. O. Box 2000, Rahway, New Jersey 07065

An elimination-addition pathway has been established for the mechanism of the epoxidation reaction leading to flavipucine as well as the exchange reactions in general of its precursors.

In the synthesis of the antibiotic flavipucine 6[1], the important observation was recorded that the precursor diol diacetate 1 is exceedingly susceptible to exchange of its side-chain acetoxyl function. Thus treatment of 1 with methoxide,[1] amines[2] or nucleophiles in general proceeded smoothly with substitution of the side-chain acetoxyl group by the corresponding anionic species. The ease of this exchange reaction is demonstrated in particular by the formation of new carbon to carbon bonds at this site. Thus a solution of the diacetate 1 in tetrahydrofuran at 25° on treatment with 3 equivalents of sodium methyl malonate at 25° was converted smoothly and essentially quantitatively to the derived malonate 2 [mp ca 120°; ir ($CHCl_3$) 2.60-4.60, 5.78 and 6.14μ; λ_{max}^{MeOH} 285 nm (ε, 6960); nmr ($CDCl_3$) δ6.00 (s, 5-H), 4.92, 4.45 (each d, J = 11 Hz, -CO-CH-CH(CO_2CH_3)$_2$) 3.73, 3.53 (each s, -CH(CO_2CH_3)$_2$) and 2.27 (s, 6-CH_3); M^+ 353]. The latter was subsequently converted in refluxing toluene to the tricyclic ester 3 (M^+ 321) and thence (aq. NaCl-DMF/130°) to the tricyclic lactone acetal 3a [mp 218-220°; ir ($CHCl_3$) 2.60-4.50, 5.58 and 6.02μ; λ_{max}^{MeOH} 289 nm (ε, 6924), nmr ($CDCl_3$) δ5.88 (s, 5-H),

3.87 (broad t, J = ca 6 Hz, $-CH_2-\underset{|}{CH}-\underset{|}{C}=$), 2.98 (broad d, J = ca 6 Hz, $-CO-CH_2-\underset{|}{CH}-$), 2.33 (s, 6-$CH_3$) and 1.03 (d, J = ca 6 Hz, $-CH(CH_3)_2$); M^+ 263; Calcd. for $C_{14}H_{17}O_4N$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.68; H, 6.46; N, 5.36].[7]

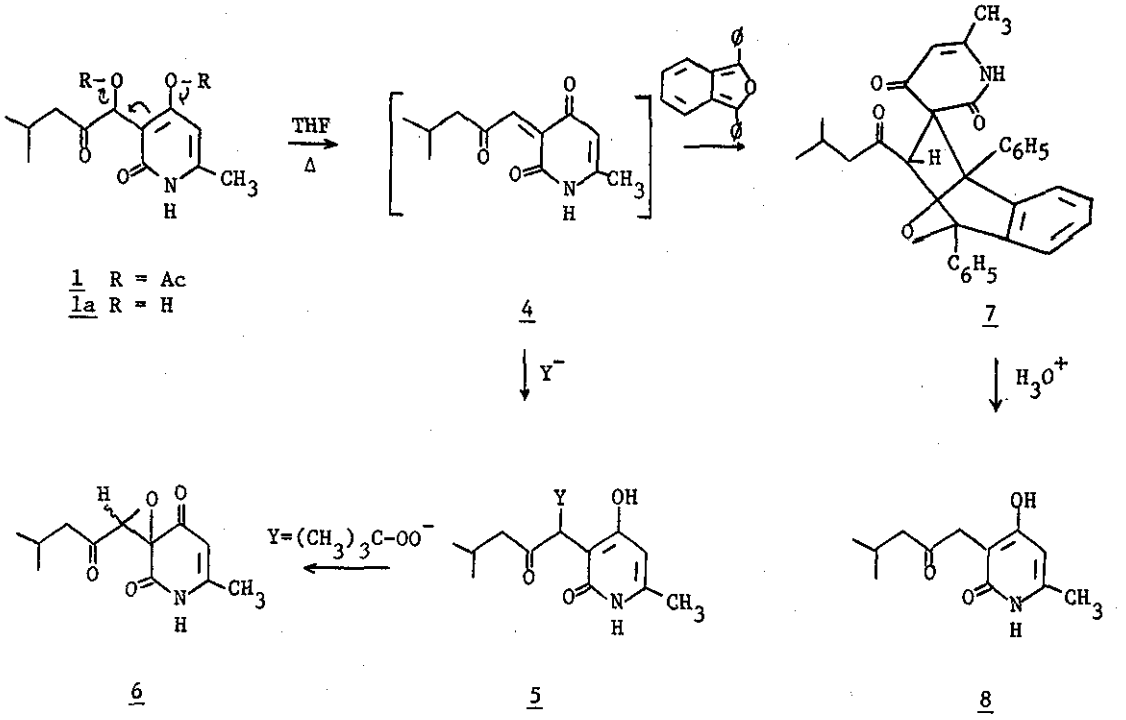


1 2 3 R = CO_2CH_3 3a R = H

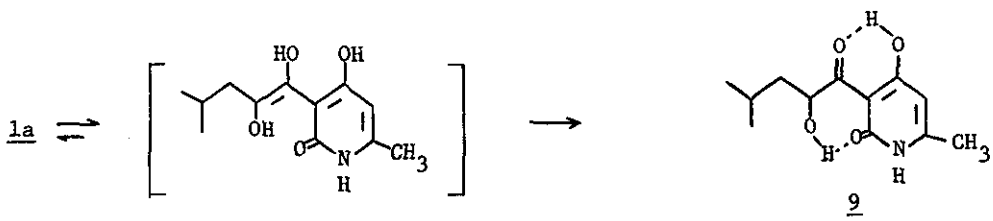
In the instance of the synthesis of flavipucine 6 itself, the tertiary butyl peroxide anion provides the exchanging nucleophile. These observations strongly suggested a process of successive elimination to an enetrione (1 → 4) followed by Michael addition of the corresponding anionic component (4 → 5)[7] as proposed earlier.[1] The intermediate formation of the enetrione 4, moreover, was further supported by the mass spectrum of the diol 1a which exhibits a significant peak at 221 (M^+ -18). Findlay et al[3] in a recent repetition of our synthetic experience in which, however, they employed the free diol 1a instead of the diacetate 1, suggested that the side-chain group exchange might arise by direct nucleophilic displacement of the oxygen functionality itself, a process seemingly without precedent per se.

We now wish to report evidence which unequivocally establishes the intermediate formation of the enetrione 4 in the transformations involving this exchange phenomenon. Although all attempts thus far to isolate 4 have been contravened by the latter's inordinate reactivity, this compound could, nonetheless, be trapped as a Diels-Alder adduct with 1,3-diphenylisobenzofuran. Thus an equimolecular mixture of diol 1a and DIBF in tetrahydrofuran was refluxed for 24 hrs to provide the adduct 7,[4] isolated by chromatography on silica gel [mp 201-4°; ir ($CHCl_3$) 2.70-4.30, 5.86, 6.10 and 6.16μ; nmr (CD_3SOCD_3) δ7.50 (m,

aromatic Hs), 5.85 (s, 5-H), 5.20 (s, -$\overset{1'}{C}$H-CO-) and 2.03 (s, 6-CH_3); M^+ 491, forms a monosilyl[6] derivative M^+ 563; Calcd. for $C_{32}H_{29}O_4N$: C, 78.18; H, 5.95; N, 2.85. Found: C, 78.16; H, 5.94; N, 2.67]. Hydrolysis of adduct 7 in dilute aq. HCl-THF afforded o-dibenzoylbenzene, mp 145-146°, together with the ketone 8[7] [mp 196-198°; ir (Nujol) 2.70-4.80, 5.83, 6.10 and 6.18μ; nmr (CD_3OD) δ5.90 (s, 5-H), 3.53 (s, 1'-Hs), 2.22 (s, 6-CH_3) and 0.92 (d, J = 6 Hz, $CH(\underline{CH_3})_2$); M^+ 223; Calcd. for $C_{12}H_{17}O_3N$: C, 64.55; H, 7.68; N, 6.27. Found: C, 64.31; H, 7.67; N, 6.28]. λ_{max}^{MeOH} 284 nm (ε, 7460).



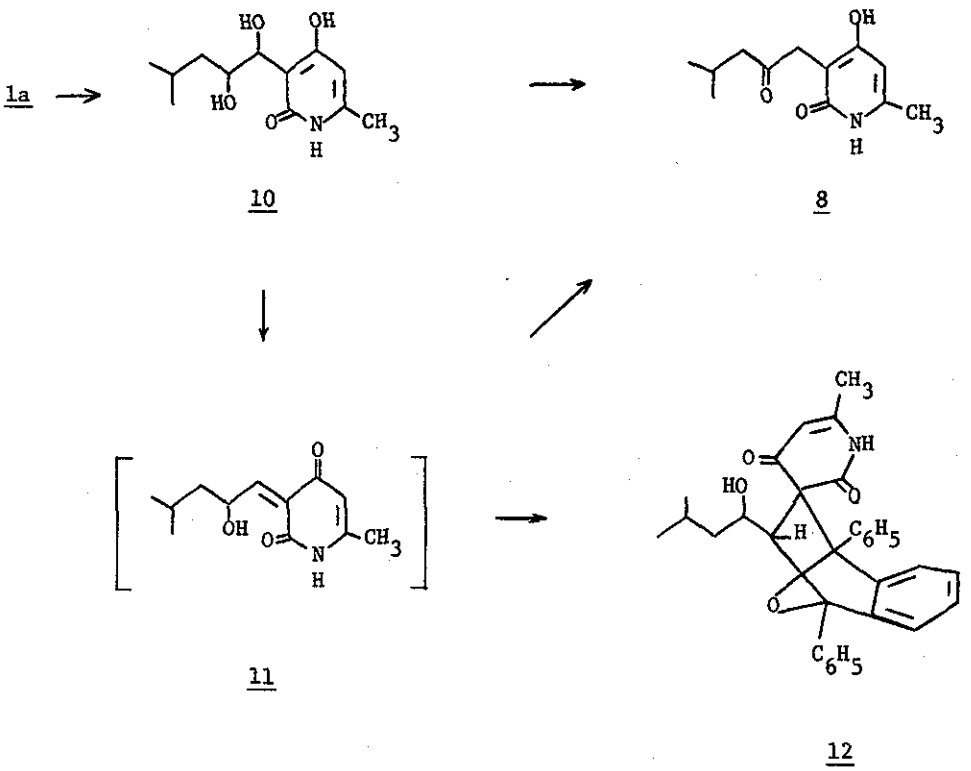
In the course of events it was observed that the diol 1a in addition to providing the intermediate enetrione 4 also sustains isomerization in part to the stable, crystalline isomeric hydroxy ketone 9 [mp 174-76°; ir ($CHCl_3$) 2.60-4.30, 6.05 and 6.15μ; λ_{max}^{MeOH} 328 nm (ε, 11580), 268 (3180) and 230 (11630); nmr ($CDCl_3$) δ5.92 (s, 5-H), 5.10 (m, 2′-H, transforms to a d of d on exchange with CD_3OD), 4.50 (d, J = 8 Hz, 2′-OH, exchanges with CD_3OD), 2.32 (s, 6-CH_3), 1.00 and 0.96 (each d, J = 6.5 Hz, $CH(CH_3)2$); M^+ 239; Calcd. for $C_{12}H_{17}O_4N$: C, 60.24; H, 7.16; N, 5.84; Found: C, 59.90; H, 7.14; N, 5.64]. This hydroxy ketone 9 moreover becomes the predominant product when the diol 1a in tetrahydrofuran is treated with 1,4-diazobicyclo[2.2.2]octane (DABCO) at 25°. The latter is apparently the consequence of enolization directed to the side-chain carbonyl with subsequent reketonization in the opposite sense. This isomeric ketone exhibited typical uv absorption essentially identical with that of 3-acetyl-4-hydroxy-6-methylpyridone.[5] The ir exhibited no well defined hydroxyl but rather a high degree of hydrogen-bonding suggestive of a chelated pseudo-tricyclic structure.



9

Reduction of the diol 1a, on the other hand, with sodium borohydride in aqueous solution followed by acidification (NaH_2PO_4), yielded a labile triol 10 (no side-chain C=O in ir) which was readily transformed (e.g., on silica gel, in DMSO, hot THF) to the ketone 8 (see earlier). The formation of 8 from 10 should logically arise via the hydroxy enedione 11 - in analogy with the transformation 1 → 4 - followed by tautomerization to 8. This pathway was again established by trapping 11 as its Diels-Alder adduct with 1,3-diphenylisobenzofuran to give 12[4] [mp 209-11°; ir (Nujol) 2.80-4.40, 6.04 and 6.14μ; nmr ($CDCl_3$)

δ7.33 (m, aromatic Hs), 5.58 (s, 5-H), 4.45 (d, J = 5 Hz, -CH-CH(OH)-), 3.83 (m, -CH(OH)-, 2.13 (s, 6-CH_3), 10.73 (broad, NH, exchanges with CD_3OD) and 10.43 (s, -CH(OH)-, exchanges); M^+ 493; forms a disilyl[6] derivative M^+ 637].



REFERENCES AND NOTES

1. N. N. Girotra, Z. S. Zelawski and N. L. Wendler, Chem. Comm. (J. Chem. Soc.), 566 (1976).

2. Reaction of 1 with various alcohols containing 3 eq. of the corresponding alkoxide at 25° afforded 5 (Y = OCH_3).[1] Similar treatment of 1 with amines in THF gave 5 [Y = NH-$C(CH_3)_3$: ill-defined mp; ir ($CHCl_3$) 2.60-4.50, 5.88 and 6.17μ; nmr ($CDCl_3$) δ5.63 (s, 5-H), 4.95 (s, 1'-H), 2.24 (s, 6-CH_3), 1.14 (s, $C(CH_3)_3$) and 0.88 and 0.82 (each d, J = 6 Hz, -$CH(CH_3)_2$); M^+ 294; 221 [294-73 ($tBuNH_2$)]; Calcd. for $C_{16}H_{26}O_3N_2$: C, 65.28; H, 8.90; N, 9.52. Found: C, 65.08; H, 9.05; N, 9.34]. The behavior of 1 bears a certain analogy to gramine, although transformations of the latter require more drastic conditions.

3. J. A. Findlay, J. Wah Hung Tam and J. Krepinsky, Synthetic Communications, 149 (1977).

4. Relative configuration of adduct not known.

5. S. Seto, H. Sasaki and K. Ogura, Bull. Chem. Soc. Japan, 39, 281 (1966).

6. Prepared with N,O-bis-(trimethylsilyl)trifluoroacetamide in dimethylformamide at 25°.

7. Assignment of the 2-pyridone structure to this and other compounds in this series is based on the corresponding uv absorption spectra. In this regard 4-pyridone in solution (pH 7) exhibits a λ_{max} 253 nm some 40 nm less than the principal band of 2-pyridone. For a discussion of this point see: N. N. Girotra, A. A. Patchett and N. L. Wendler, This Journal, 6, 1299 (1977); also A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," The MacMillan Co., New York, 1964, p. 178, 182.

Received, 12th December, 1977